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BOOK OF **ABSTRACTS**

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Finding the sweet spot of stimulus length of remote conditioning maneuvers

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Content:

Introduction:
Although the mechanical stimulus of brief, repetitive cycles of ischemia/reperfusion (I/R) remote from the heart (remote ischemic conditioning, RIC) reduces I/R-injury in experimental settings, its translation to patients with acute myocardial infarction remains still inconsistent. Thousands of articles have been published on RIC, however its stimulus length as a determinant of stimulus efficiency remain largely overlooked and among factors discussed for the heterogeneous outcomes, the stimulus itself is rarely questioned. Whittaker and Przyklenk hypothesized the phenomenon of "hyperconditioning" as consequence of multiple conditioning episodes. The nowadays mostly used RIC stimulus length was selected empirically, retained over time and has so far never been re-evaluated. In addition, auricular tragus stimulation (ATS), a newly identified remote stimulus, was never assessed in a stimulus length dependent manner before. Systemic signal transmission from the remote side to the heart causally involves humoral cardioprotective factors. We used this fact to estimate the cardioprotective potential of the respective maneuver by evaluating the protective potential of these humoral factors.
Methodology:
Blood from young, healthy volunteers (n=4/2 m/f) was drawn before and 60' after RIC [10, 30 and 60 min (1-, 3- or 6×5'/5') upper-arm I/R] or ATS [10', 30' and 60' (200µs x 30Hz, 5/5s on/off)], plasma separated and dialysate prepared. Isolated adult rat cardiomyocytes were either incubated with buffer or plasma-dialysate for 30' before being subjected to hypoxia/reoxygenation (H/R) (30'/5'), respectively. Cardiomyocyte viability was calculated as percentage of rod-shaped cardiomyocytes relative to the total number of cardiomyocytes, to assess the cardioprotective potential as cardiomyocyte preservation after H/R.
Results:
After H/R, cardiomyocyte viability did not differ between cells incubated with before-plasma-dialysates. In contrast, plasma-dialysates collected after 10' RIC showed no preserved cardiomyocyte viability. 60' of RIC showed a tendency in increase in preserved cardiomyocytes. The highest preservation of cardiomyocyte viability was after 30 minutes of RIC as well as ATS.
Conclusion:
In healthy volunteers, both remote stimuli release the most humoral cardioprotective factors after 30' stimulus. These data may help to identify the strongest cardioprotective remote stimulus in patients.

DEVELOPMENT OF NOVEL RHODANINE-BASED INHIBITORS OF MATRIX METALLOPROTEINASE-2 FOR CARDIOPROTECTION

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Content:

We previously showed that newly developed imidazole carboxylic acid- and thiazole carboxylic acid-based drug candidates moderately inhibit matrix metalloproteinase-2 (MMP-2) activity, thereby achieving cardioprotection in a rat model of acute myocardial infarction (AMI). However, these candidates lost their efficacy when hyperlipidemia was present as an AMI comorbidity. Therefore, we tested rhodanine-based compounds for selective and moderate inhibition of MMP-2.

Newly synthesized rhodanine-based structures were subjected to in silico molecular docking to 8H78, the newest catalytic domain structure of MMP-2. Twenty drug candidates with the best docking scores were selected for further evaluation.

Gelatin zymography was performed to assess the in vitro MMP-2 inhibitory potency of the compounds. Heart homogenates from young adult control rats were loaded onto 8%-SDS-polyacrylamide gels containing 2 mg/mL gelatin as substrate to measure biologically active MMP-2 enzyme activity. Ilomastat was used as a positive control, as a potent hydroxamate-type, non-selective MMP inhibitor. Gel pieces were incubated at 37°C for 40 h in the presence of the candidates at 10 micromolar or ilomastat at 10 nanomolar. Dimethyl sulfoxide served for vehicle.

Docking scores ranged from -5.32 to -7.23. MMP-2 activity was detected in all rat myocardial samples at 568±34 arbitrary units (AU). Ilomastat at 10 nM achieved over 90% inhibition of MMP-2 activity (23.3±4.2 AU, $p<0.001$ vs vehicle). Two of the 20 drug candidates achieved a moderate but significant reduction in MMP-2 activity at 10 micromolar (15.2% and 26.7%, respectively, $p<0.05$ vs vehicle), representing the most potent rhodanine-based compounds.

Concentration-response analysis based on gelatin zymography yielded IC50 values of 179.5 µM for Compound 795 and 71.12 µM for Compound 802, demonstrating their functional inhibitory potency on MMP-2. These novel rhodanine-based compounds could be promising lead candidates for anti-ischemic cardioprotection showing higher potency with Compound 802. Further experiments are planned to test their potency to increase cell viability on isolated cardiac myocytes subjected to simulated ischemia/reperfusion injury.

Chronic amiodarone treatment modifies electrophysiological response to IKr block in human failing ventricular myocardium

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Content:

Introduction

Amiodarone (AMIO) is a widely used antiarrhythmic agent effective against ventricular and supraventricular arrhythmias. Despite extensive clinical use, its cellular antiarrhythmic mechanisms remain incompletely understood. Although extracardiac toxicity is a concern, AMIO exhibits a low proarrhythmic potential compared to other antiarrhythmics. This study investigated the cellular electrophysiological effects of chronic AMIO therapy in end-stage heart failure (HF) patients using human left ventricular tissue, comparing responses to IKr inhibition with tissues from non-AMIO-treated HF patients and non diseased donor hearts.

Methodology

Left ventricular tissue slices were obtained from explanted hearts of end-stage HF patients treated or not treated with chronic AMIO, and from non diseased donor hearts. Conventional microelectrode recordings were performed to assess action potential duration (APD),responses to 50 nM dofetilide (DOF; an IKr blocker), and the frequency dependence of the maximal upstroke velocity (Vmax)

Results

Both AMIO- treated and non-AMIO-treated HF tissues exhibited significantly prolonged APD compared to donor samples (donor: 364.95 ± 11.61 msn; HF non AMIO treated: 455.87 ± 12.53 ms; HF AMIO treated: 528.58 ± 22.93 ms), and the two failing hearts are significantly different from each other. Upon application of 50 nM DOF, donor and HF+AMIO samples
showed moderate APD prolongation (donor: +21%; HF AMIO treated: +37%) without early after depolarizations (EADs). In contrast, HF non-AMIO treated samples developed EADs and failed repolarization. Furthermore, chronic AMIO treatment induced a marked use-dependent depression of Vmax, which was absent in donor and HF non-AMIO treated groups.

Conclusion

Chronic amiodarone therapy in heart failure patients induces a pronounced use-dependent reduction in the Vmax, a phenomenon not observed in donor hearts or in HF patients without amiodarone treatment. This distinctive electrophysiological modulation may contribute to the drug's low proarrhythmic potential and therapeutic efficacy in the failing human heart. These findings highlight a potentially protective mechanism of chronic amiodarone administration and needs further mechanistic and clinical investigation.

IMMORTELLE ESSENTIAL OIL- ENRICHED HYDROGEL ATTENUATES OXIDATIVE DAMAGE AND INFLAMMATORY RESPONSE IN DIABETIC WOUNDS

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Content:

Introduction: Helichrysum italicum (immortelle) essential oil has attracted increasing attention because of its antioxidant, anti-inflammatory, and antimicrobial activities, suggesting its potential as a therapeutic agent for chronic wounds.

Nevertheless, experimental evidence supporting its efficacy in diabetic wound healing remains insufficient. The present study aimed to develop a hydrogel containing immortelle essential oil and investigate its effects on oxidative stress and inflammatory processes in a diabetic rat wound model.

Methodology: Full-thickness excision wounds (2 × 2 cm) were created on the dorsal skin of thirty-two streptozotocin-induced diabetic Wistar albino rats. The animals were randomly assigned to four groups: untreated control (CTRL), hydrogel base, 0.5% immortelle essential oil hydrogel, and 1% silver sulfadiazine. Treatments were applied topically once daily for 21 days. Wound tissues were then collected for biochemical analysis of oxidative stress (TBARS), antioxidant defense (CAT, SOD, and GSH), and inflammatory cytokines (TNF-α, IL-6, and IL-10) using ELISA.

Results: Treatment with the immortelle essential oil hydrogel significantly enhanced the activity of endogenous antioxidant enzymes and reduced lipid peroxidation compared with the untreated and vehicle-treated groups. In addition, the hydrogel markedly decreased the concentrations of the pro-inflammatory cytokines TNF-α and IL-6, while increasing the level of the anti-inflammatory cytokine IL-10, indicating attenuation of the inflammatory response within the wound microenvironment.

Conclusion: Topical administration of an immortelle hydrogel effectively improved the redox status and regulated inflammatory mediators in diabetic wound tissue, suggesting that this formulation may represent a promising therapeutic strategy for enhancing diabetic wound repair.

Translating basic science into novel strategies for risk prediction and management in inherited arrhythmias

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Content:

Inherited arrhythmias and sudden cardiac death may arise secondary to mutations in a large variety of genes encoding ion channels, ion transporters and structural proteins. Although the clinical, genetic and biophysical characteristics of most of these disorders have been extensively studied, progress in development of novel risk prediction and treatment strategies has remained limited. Phenotype severity and disease penetrance is often highly variable, and may be modulated by age, sex, genetic modifiers, co-morbidities, and environmental factors. Genome wide association studies are increasingly
employed with the aim of ultimately developing polygenic risk scores. Nevertheless, increased mechanistic insight into the underlying disease pathways, both within and beyond the cardiomyocyte, is essential for identification of patients at high risk for sudden cardiac death, and for development of novel therapeutic targets. To achieve this, we employ a multi-
disciplinary approach combining clinical and genetic data with genomics, bioinformatics and functional mechanistic studies in human and animal disease models – focusing not only on the heart and cardiomyocyte, but also on the autonomic nervous system.

Mitochondrial Transplantation Restores Cardiac Function Through Nrf2-Mediated Mitochondrial Protection

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Content:

Introduction: Mitochondrial dysfunction contributes to cardiac injury through impaired bioenergetics, excessive reactive oxygen species (ROS), disturbed Ca2+ homeostasis, and altered mitochondrial dynamics. Mitochondrial transplantation (MTT) has emerged as a regenerative strategy to restore mitochondrial function in damaged myocardium. Here, we investigated whether the protective effects of MTT are mediated, at least in part, through activation of the Nrf2/Keap1 redox-signaling pathway.

Methodology: Functional mitochondria were isolated from healthy donor cells and evaluated before transplantation. MTT was studied in doxorubicin-induced cardiac injury and ischemia–reperfusion models using cellular, ex vivo, and in vivo approaches. Mitochondrial membrane potential, ROS, intracellular Ca2+, mitochondrial dynamics, apoptosis-related proteins, Nrf2/Keap1 signaling, and cardiac contractile function were assessed. To examine the role of Nrf2, experiments were additionally performed in the presence of the Nrf2 inhibitor ML385.

Results: MTT improved mitochondrial and cardiac function under pathological conditions. Transplantation reduced excessive ROS, improved mitochondrial membrane potential and Ca2+ homeostasis, and modulated proteins involved in mitochondrial dynamics and apoptosis. MTT increased Nrf2 protein levels and decreased Keap1 expression, indicating activation of the Nrf2 pathway. Importantly, pharmacological inhibition of Nrf2 attenuated the beneficial effects of MTT on mitochondrial membrane potential and oxidative stress, supporting a functional role for Nrf2 signaling in mitochondrial rescue. Ex vivo and in vivo experiments further demonstrated recovery of cardiac contractile performance following MTT. Conclusion: MTT protects the injured heart through coordinated restoration of mitochondrial homeostasis and activation of Nrf2-dependent antioxidant signaling. These findings identify Nrf2 as a potential mechanistic link between transplanted mitochondria and cardiac protection and support MTT as a promising therapeutic strategy for myocardial injury and heart failure.

Can We Protect Diabetic Heart with Quercetin?

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Content:

Compared to a healthy, non-diabetic heart, the diabetic heart is characterized by several metabolically driven morphological and functional changes, including cardiac hypertrophy and fibrosis, ventricular remodeling, and microvascular dysfunction, which lead to diastolic dysfunction and, potentially, reduced systolic function. Over time, diabetic cardiomyopathy (DCM) may develop, leading 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, for example, 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) exhibited significant cardioprotective effects in preventing damage caused by ischemia-reperfusion (I/R) in healthy hearts without diabetes. The aim of this study was to evaluate the cardioprotective potential of quercetin in diabetic hearts, both in terms of preventing the development of DCM and protecting against I/R injury when diabetes is 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 in vivo cardioprotective effects in T2DM by preventing the development of diastolic dysfunction and cardiac fibrosis; however, it is not effective in preventing I/R injury in diabetic hearts. In conclusion, QCT may potentially prevent the development of DCM; however, diabetes and aging may reduce or even abolish the anti-ischemic effects of QCT.

Protective Effects of Urolithin A Against Isoprenaline-Induced Cellular Injury in Fibroblast and Cardiomyoblast Cell Models

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Content:

Introduction

Chronic heart failure is a progressive clinical syndrome in which adverse cardiac remodeling and myocardial fibrosis contribute substantially to the deterioration of cardiac function. Fibrosis is a progressive pathological process resulting from aberrant remodeling of the extracellular matrix and alterations in resident tissue cells, which may occur as a consequence of aging, tissue injury, or various diseases, ultimately leading to excessive scar formation and organ dysfunction. Targeting fibrosis progression and its suppression may present an effective therapeutic strategy for heart failure. The current study investigated the effects of different concentrations of urolithin A, combined with isoprenaline, across varying exposure periods on the proliferation and morphology of MRC-5 and H9c2 cells.

Methodology

The MTT assay was performed to assess cell viability and cytotoxic effects following treatment. Effects of the treatments and interference of co-treatments on morphological features were assessed using phase-contrast microscopy. Cells were treated with ISO (1, 5, 10, 15, and 20 μM), equimolar UA, or a combination, followed by additional 24- and 48-hour incubation periods. The control group was defined as cells with 100% viability, and cell viability was compared with that of the untreated control.

Results

The results indicated that isoprenaline (10 μM) increased the cell viability and metabolic activity of MRC-5 cells throughout the exposure period, whereas co-treatment with urolithin Ainhibited fibroblast proliferation and induced morphological changes. However, isoprenaline (1 μM) inhibited the proliferative capacity of H9c2 cells, with the inhibitory effect increasing in a dose- and time-dependent manner. On the other hand, urolithin Aexhibited a protective effect in these cells when co-treated with isoprenaline, attenuating its harmful effects. Furthermore, the cells appeared healthy under the phase-contrast microscope, as in the untreated control.

Conclusion

These findings suggest potential relevance of urolithin Afor the modulation of fibrotic remodeling and protection against cardiac injury, but further preclinical and clinical investigation is warranted.

FABP2 and PPARG gene polymorphisms in patients with acute myocardial infarction

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Content:

Introduction: Fatty acid-binding protein 2 (FABP2) is involved in intestinal fatty acid absorption and transport and its polymorphisms have been associated with altered lipid metabolism and insulin resistance. Peroxisome proliferator-activated receptor gamma (PPARG) is a transcription factor involved in adipocyte differentiation, lipid storage, glucose homeostasis and insulin sensitivity. As both genes are involved in metabolic pathways relevant to atherosclerosis, this study investigated the associations of FABP2 and PPARG polymorphisms with clinical and biochemical characteristics in patients with acute myocardial infarction (AMI).

Methodology: We analyzed genetic and available clinical data from 152 patients with AMI. Genotyping of FABP2 rs1799883 and PPARG rs1801282 was performed using real-time PCR (qPCR) with TaqMan assays. Chi-square and Student's t-tests were used for statistical analysis, and Hardy-Weinberg equilibrium (HWE) was assessed for both polymorphisms. Results: The mean age of patients was 62.5 years, and 72.4% were male. FABP2 genotype frequencies were 45.4% for CC, 47.4% for CT and 7.2% for TT, with a T allele frequency of 30.9%, and were consistent with HWE (p=0.18). PPARG genotype frequencies were 67.1% for CC, 30.9% for CG, and 2.0% for GG, with a G allele frequency of 17.4%, and were also consistent with HWE (p=0.36). LDL cholesterol tended to be higher among FABP2 T-allele carriers than among CC homozygotes, although the difference did not reach statistical significance (p=0.073). PPARG G-allele carriers were significantly older than CC homozygotes at the time of AMI (p=0.030). No significant associations were observed between either polymorphism and BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, or blood pressure.

Conclusion: Among patients with AMI, LDL cholesterol tended to be higher in FABP2 T-allele carriers than in CC homozygotes ($p = 0.073$), whereas PPARG G-allele carriers were significantly older than CC homozygotes at the time of AMI ($p = 0.030$). These findings suggest that FABP2 and PPARG polymorphisms may be related to metabolic characteristics relevant to cardiovascular disease. However, in the absence of a control group, their potential contribution to AMI susceptibility cannot be determined. Larger case-control studies are needed to further investigate these associations.

Hyperleptinemia is involved in obesity-associated elevation of endogenous NO synthase inhibitor ADMA: Implications for cardiovascular diseases

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Content:

Intruduction. Leptin is the adipose tissue hormone which regulates food intake and energy expenditure. Plasma leptin concentration is increased in obese individuals and hyperleptinemia is involved in the pathogenesis of obesity-associated cardiovascular diseases. Previously, we have demonstrated that experimental hyperleptinemia decreases the expression of paraoxonase 1 (PON1), the enzyme which hydrolyzes homocysteine thiolactone (HTL), and increases N-homocysteinylation of plasma proteins, but functional implications of these effects are unclear. The present aims were to examine: (1) the effect of leptin on endogenous NO synthase inhibitor, ADMA, and its metabolizing enzyme, DDAH, (2) role of HTL in the regulation of DDAH-ADMApathway, (3) role of endogenous hyperleptinemia in obesity-associated abnormalities of DDAH-ADMApathway by using specific leptin receptor antagonist.
Methodology. 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 lower plasma PON1 activity toward HTL, increased protein N-homocysteinylation, higher ADMAconcentration and reduced DDAH activity despite unchanged enzyme expression. In vitro, HTL, but not homocysteine, reduced the activity of DDAH which was accompanied by time- and concentration-dependent N-homocysteinylation of the enzyme. PEG-SLRAadministered to obese rats did not improve adiposity or metabolic profile but increased PON1 activity, reduced DDAH N-homocysteinylation and increased enzyme activity as well as reduced ADMAconcentration. Both hyperleptinjemia and obesity impaired NO-dependent acetylcholine-induced relaxation of aortic rings but endothelial dysfunction was only partially improved by PEG-SLRA.
Conclusions. Obesity is associated with N-homocysteinylation and partial inactivation of DDAH which results in accumulation of ADMA. This effect is mediated by chronic hyperleptinemia. However, endothelial dysfunction associated with obesity is only partially accounted for by abnormalities of DDAH-ADMA-NO synthase pathway.

INVESTIGATING THE ARRHYTHMOGENIC EFFECT OF ACTION POTENTIAL ALTERNANS IN HUMAN HEART FAILURE

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Content:

Heart failure (HF) is a complex, progressive disease characterized by structural and electrical remodeling of the heart, significantly increasing the risk of ventricular fibrillation (VF). However, prior to the onset of VF, a potentially reversible phenomenon known as alternans may develop. Action potential (AP) alternans refers to beat-to-beat oscillations in AP duration, leading to repolarization inhomogeneity. As no specific pharmacological intervention currently exists to prevent alternans, this study investigated the effects of the selective Na^+/Ca^{2+} exchanger (NCX) inhibitor ORM-10962(ORM) on alternans formation in failing and non-failing human hearts.

Tissue samples from failing and non-failing human hearts were used. APs were recorded using conventional microelectrode technique in ventricular preparations. Electrical mapping was used to measure APs from midmyocardial (M) slices. The level of fibrosis and the perinexus width was also investigated. In silico modelling was conducted. SERCA protein expression was measured.

In HF samples, AP duration (APD) alternans was significantly larger than in non-failing hearts. In several cases, pronounced amplitude alternans were observed in left ventricular HF preparations, predominantly at higher pacing rates. These further increased APD alternans magnitude and led to a 2:1 conduction block. Treatment with 1 μM ORM shortened APD in HF samples, reduced APD alternans magnitude, and shifted the onset of amplitude alternans and conduction block to higher pacing rates. In silico modelling showed an anti-alternans effect of SERCAimprovement and INaL inhibition. ORM significantly decreased the conductance velocity alternans measured from M-slices. We observed higher fibrosis scores in older HF hearts, as well as progressive widening of the perinexus. No significant differences were observed between SERCAexpressions between groups.

Electrical remodeling in HF markedly increases APD alternans, which appears to worsen with age, likely due to age-dependent fibrosis and widening perinexus. Notably, failing hearts may develop amplitude alternans at higher heart rates, further amplifying APD alternans. The underlying mechanism may involve impaired recovery of the sodium current.

Selective NCX inhibition attenuates alternans in the failing human heart, likely through APD shortening and its effects on Ca2+ handling. This therapeutic potential could be further enhanced by concomitant SERCAactivation and INaL inhibition.

Preliminary Antihypertensive and Cardioprotective Effects of Geranium robertianum L. Methanolic Extract in Spontaneously Hypertensive Rats

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Content:

Background: Geranium robertianum L. (Herb Robert) is a traditional medicinal plant with reported cardiovascular properties, but its antihypertensive potential has not been extensively investigated. This study evaluated the effects of its methanolic extract, alone and in combination with captopril, on blood pressure, cardiac structure/function, and aortic morphology in spontaneously hypertensive rats (SHR).

Methods: SHR were allocated into five groups: untreated SHR, normotensive WKY controls, extract-treated (250 mg/kg, oral gavage in 0.5% NaCMC), captopril-treated (13.5 mg/kg), and combination (extract + captopril), administered daily for 28 days. This abstract presents preliminary findings from the three treatment groups.

Results: Baseline systolic blood pressure averaged 158 mmHg across groups. After 28 days, systolic pressure decreased in all treatment groups: captopril (124 mmHg), combination (126 mmHg), and extract alone (131 mmHg), indicating genuine antihypertensive activity of Geranium robertianum L., particularly when combined with a standard therapeutic agent. Echocardiography showed preserved systolic function (EF, FS) in all groups, consistent with a compensated hypertensive phenotype. Interventricular septal and posterior wall thickness increased from baseline in all groups, with the smallest increase in the combination group, followed by captopril and extract alone. LV diastolic diameter and end-diastolic volume decreased from baseline in all groups, consistent with concentric hypertrophic adaptation to sustained pressure overload. Morphometric analysis of the aortic tunica media showed a thinner, more compact structure in the extract group (52.5 μm) and combination group (54.3 μm) compared with captopril alone (66.8 μm), with a correspondingly smaller diameter of smooth muscle fibers, suggesting a beneficial effect of the extract on vascular structure independent of its effect on blood pressure.

Conclusion: These preliminary results suggest that Geranium robertianum L. has genuine antihypertensive and vasculoprotective potential, most notably reflected in the structure of the aortic wall. Since hypertension in the SHR model progresses continuously with age, untreated SHR and normotensive WKY controls, assessed at the same time point, are still needed to determine the true extent of this benefit. These groups are currently being processed, and once completed will allow us to confirm whether these preliminary findings hold.

Heart failure with preserved ejection fraction: The new frontier

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Content:

Heart failure with preserved ejection fraction (HFpEF) is a common, lethal, disabling, and expensive condition. Its prevalence has reached epidemic proportions (~3 million in the US and ~32 million people worldwide). Annual mortality is ~15% and 5-year mortality 50-75%. Current therapies have limited efficacy. Thus, HFpEF constitutes a major (and growing) public health problem. HFpEF driven by the metabolic syndrome (MetS) accounts for 60-70% of all cases of HFpEF and is associated with obesity and hyperglycemia/insulin resistance. Amajor obstacle to progress in both the pathophysiology and therapy of MetS-induced HFpEF has been the lack of translationally relevant animal models, due to the difficulty in recapitulating the systemic, multiorgan dysfunction and comorbid-laden phenotype of patients with this syndrome. Most existing models of MetS-induced HFpEF use rodents, which may not be relevant to the human syndrome. We have developed a new large animal model of MetS-induced HFpEF that fully recapitulates the key elements of the clinical syndrome, including impaired exercise capacity, and can be used for preclinical studies of new therapies. This is the only porcine model of HFpEF published heretofore that exhibits all of the following components: a full MetS, a full metabolic characterization, liver fibrosis and dysfunction, and reduced exercise tolerance. This porcine model is unique in that it recapitulates the entire constellation of major comorbidities and multiorgan abnormalities and the hemodynamic, clinical, and metabolic features of MetS-driven human HFpEF: obesity, arterial hypertension, hyperlipidemia, glucose intolerance, insulin resistance, liver fibrosis, liver dysfunction, pulmonary hypertension, increased LV filling pressures, concentric LV hypertrophy, LV diastolic dysfunction, preserved LV systolic function, and impaired exercise capacity. Because of its high clinical relevance, this model is well-suited for exploring the pathophysiology of MetS-driven HFpEF and the efficacy of new therapies.

Age-Dependent Necroptosis and Pyroptosis in Renocardiac Syndrome

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Content:

Introduction: Heart and kidney function are physiologically interdependent, with cardiac output maintaining renal perfusion while the kidneys control volume homeostasis and the neurohormonal milieu. Disruption of this crosstalk refers to the renocardiac syndrome, where dysfunction in the kidney promotes heart damage. In this study, we have investigated if the proinflammatory necroptosis and pyroptosis, can contribute to the renocardiac syndrome due to acute ischemia-reperfusion injury (IRI) and if these events are age-dependent.

Methodology: Renal IRI was induced by midline abdominal incision surgery (bilateral renal pedicle clamping I= 40 minutes, R= 96 hours) in male Lewis rats of different age (3,6 and 18 months). Renal function was assessed by measuring creatinine, urea levels, and pro-inflammatory pro-death environment of kidney-heart axis.

Results: Plasma creatinine and urea were elevated in all IRI groups, indicating impaired glomerular filtration. In the kidney, acute IRI induced activation of both necroptotic and pyroptotic pathways irrespective of age. Renal IRI triggered cardiac necroptosis only in aged rats. Notably, upregulation of the NLRC4 inflammasome was observed only in aged rats and occurred in both the primary site of injury and the distant organ. In contrast, alterations in NLRP3 inflammasome expression were restricted to the kidney of aged animals, with no corresponding changes detected in the heart. Renal IL-1β levels increased following IRI across all age groups, whereas cardiac IL-1β elevation was observed solely in aged rats. Furthermore, only the renal CD163/CD68 ratio tended to decrease in IRI groups, suggesting reduced M2 macrophage predominance and an impaired anti-inflammatory capacity.

Conclusion: In renocardiac syndrome, both necroptosis and pyroptosis appear to contribute to IRI-induced renal injury across all age groups. In contrast, cardiac involvement as a remote consequence of renal IRI appears to be driven predominantly by necroptotic signalling and is particularly pronounced in aged individuals. These findings suggest that both anti-necroptotic and anti-pyroptotic strategies may represent effective therapeutic approaches for renal ischemic injury. However, in the setting of renocardiac syndrome, anti-necroptotic interventions may offer superior therapeutic benefits, especially in the aging population.

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Sex-Dependent Effects of Intermittent Fasting on Myocardial Ischemia-Reperfusion Injury and Oxidative Stress Response

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Content:

Intermittent fasting (IF) is a dietary pattern characterised by alternating periods of food intake and fasting. Growing evidence from both clinical and preclinical studies suggests that IF may exert cardioprotective effects. The metabolic switch induced by fasting promotes the production of ketone bodies, which serve not only as alternative energy substrates but also as signalling molecules, that activate cellular protective pathways. In the heart, these effects have been associated with improved metabolic homeostasis and reduced oxidative stress and inflammation, potentially involving antioxidant defence mechanisms.

Hypoxia-inducible factor-1α (HIF-1α) is a key regulator of cellular adaptation to hypoxia and contributes to cardioprotection by coordinating metabolic and redox responses. Furthermore, cardiovascular diseases are also associated with epitranscriptomic changes, particularly N6-methyladenosine (m6A), the most abundant internal modification of eukaryotic mRNA. The bidirectional interactions between m6A-dependent regulation and HIF-1α signalling may modulate myocardial tolerance to ischemia-reperfusion (I/R) injury.

To investigate mechanisms underlying IF-induced cardioprotection, adult wild-type (wt) and Hif1a heterozygous knockout (Hif1a+/-) mice of both sexes were fed either ad libitum or subjected to alternate-day fasting (24-h fasting every other day) for eight weeks. Hearts were subsequently isolated and exposed to I/R insult using the Langendorff technique. Expression of genes involved in oxidative stress responses and epitranscriptomic modifications was also assessed.

Our results showed that IF significantly reduced myocardial infarct size in male mice, whereas only a decreasing trend was observed in females. IF also increased the expression of antioxidant genes in both sexes, while Nox4 expression was elevated only in males. No significant changes in the gene expression of epitranscriptomic regulators were observed. These findings demonstrate a sex-dependent cardioprotective effect of IF, however, further characterization of the underlying molecular mechanisms is needed to elucidate the pathways involved in IF-induced cardioprotection.

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Sugar, salt and survival: the cardiovascular mandate of SGLT2 inhibitors

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Content:
Background: Sodium–glucose cotransporter 2 (SGLT2) inhibitors were introduced as glucose-lowering agents for type 2 diabetes (T2D), but results of the emerging cardiovascular outcome trials changed their clinical position. Their benefits, particularly in heart failure (HF) and chronic kidney disease (CKD), extend beyond glycaemic control and beyond diabetes itself, establishing SGLT2 inhibition as a major component of modern cardiorenal-metabolic therapy.
Cardiovascular and cardiorenal evidence: By inhibiting proximal tubular reabsorption of glucose and sodium, SGLT2 inhibitors induce glycosuria and natriuresis, restore tubuloglomerular feedback, and favourably modify renal and systemic haemodynamics. Across major outcome trials, these effects translate into consistent reductions in HF hospitalization and progression of CKD, with cardiovascular and renal benefits demonstrated across a broad spectrum of patients with T2D, HF and CKD. Importantly, efficacy in individuals without diabetes confirms that SGLT2 inhibitors should no longer be viewed primarily as antihyperglycaemic agents. Their mechanisms of action and benefit are multifactorial and may include optimization of volume and sodium homeostasis, reductions in blood pressure and intraglomerular pressure, improved myocardial energetics, and modulation of inflammatory and metabolic pathways.
Clinical implications: The therapeutic use of SGLT2 inhibitors can therefore be understood as a transition from sugar to salt to survival. Their incorporation into guidelines for diabetes, HF and CKD reflects a shift from glucose-centred treatment towards integrated multi-organ protection. Appropriate patient selection and awareness of adverse effects, including genital infections, volume depletion and rare euglycaemic ketoacidosis, remain essential.
Conclusion: SGLT2 inhibition exemplifies a major change in cardiovascular prevention: treatment initiated through a metabolic pathway can deliver clinically meaningful cardiorenal protection. The cardiovascular mandate is now to identify eligible patients early and translate this evidence into routine clinical practice.

Purkinje–Ventricular Junction as a Critical Site for Alternans-Induced Electrical Instability

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Content:

Background: Cardiac alternans, defined as beat-to-beat oscillations in action potential duration (APD) and intracellular Ca^{2+}-transients, is closely associated with electrical instability and the development of malignant ventricular arrhythmias. The Purkinje–ventricular junction (PVJ) represents a unique electrophysiological interface where two markedly different tissues interact, characterized by distinct action potential properties, repolarization dynamics, and pronounced source–sink mismatch. These features may predispose the PVJ to enhanced electrical heterogeneity and arrhythmogenic vulnerability. However, the behavior and mechanisms of alternans at this critical interface remain largely unexplored.

Methods: Action potentials from left ventricular Purkinje fibers and adjacent ventricular myocardium were recorded in canine preparations using a dual conventional microelectrode technique. Ca^{2+}-transients were measured in isolated Purkinje and ventricular cells. Alternans was induced by rapid pacing. Arrhythmogenic manifestations at the PVJ were characterized by assessing alternans magnitude, the occurrence of discordant alternans, APD dispersion, AP triangulation, spontaneous extrasystoles, and conduction block.

Results: Under control conditions, alternans magnitude and the incidence of discordant alternans and 2:1 conduction block increased with pacing rate, whereas APD dispersion and triangulation decreased. Impaired repolarization induced by 10 nM dofetilide markedly shifted alternans toward slower pacing rates and was accompanied by increased discordant alternans, enhanced APD dispersion, and the emergence of spontaneous extrasystoles. Ryanodine (5 μM) completely abolished alternans in both tissues. Consistently, Ca^{2+}-transient alternans in isolated Purkinje and ventricular cells displayed similar dynamics under rectangular voltage-clamp protocols.

Conclusion: These findings indicate that Purkinje and ventricular alternans share common, predominantly Ca^{2+}-dependent mechanisms. Although alternans under physiological conditions may not produce major electrical disturbances at the PVJ, impaired repolarization markedly enhances PVJ susceptibility, allowing alternans to generate pronounced electrical instability and increase arrhythmogenic vulnerability.

Effects of Chronic Testosterone Treatment on Cardiac Mitochondrial Bioenergetics and Calcium Tolerance in a Canine Model

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Content:

Chronic high-dose testosterone and anabolic-androgenic steroid (AAS) use is an increasing public health concern with cardiovascular effects. In our canine model, testosterone induces electrical remodeling characterized by shortened QT/QTc and APD90, with prolonged PQ and QRS intervals. These changes are consistent with an acquired short-QT phenotype and may increase arrhythmogenic susceptibility. Given the central role of mitochondria in energy production and calcium homeostasis, we investigated whether chronic testosterone exposure induces adaptive or maladaptive mitochondrial responses to calcium stress.

Male dogs received weekly testosterone undecanoate for 12 weeks (n=5/group). Left-ventricular mitochondria were isolated and assessed for swelling, respiration, membrane potential (ΔΨm), and calcium retention capacity (CRC) during progressive calcium loading. Cardiomyocyte expression of Nav1.5, Nav1.8, Kv4.3, Kv1.4, KChIP2, and Kv1.5 was assessed by immunocytochemistry.

Testosterone attenuated mitochondrial swelling during calcium overload. Respiratory function remained preserved. Testosterone-treated mitochondria showed increased CRC and better preservation of ΔΨm, indicating greater tolerance to calcium loading and a higher threshold for permeability transition. Nav1.5 expression was decreased, consistent with QRS prolongation, whereas KChIP2 was increased, consistent with shortened APD/QT.

Chronic high-dose testosterone induces electrical remodeling and mitochondrial adaptation. Enhanced calcium retention and preservation of ΔΨm suggest a transient adaptive increase in mitochondrial resistance to calcium stress, potentially delaying permeability transition while maintaining oxidative phosphorylation. Thus, the observed mitochondrial changes likely reflect a compensatory adaptation to altered cardiomyocyte calcium and energetic homeostasis, occurring alongside electrical remodeling that increases arrhythmogenic susceptibility.

MECHANISMS OF THE BENEFICIAL EFFECTS OF PROPIONYL L-CARNITINE IN DIABETIC CARDIOMYOPATHY

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Content:

Previously we have shown that treatment of diabetic rats with propionyl L-carnitine (PPLC), a metabolic intervention, improved cardiac function and attenuated sarcolemmal defects in Na+-K+ ATPase, Na+-Ca2+ exchange and Ca2+/Mg2+-ecto ATPase activities. Since cardiac function is mainly determined by sarcoplasmic reticulum (SR) Ca2+-pump and myofibrils (MF) Ca2+-ATPase activities, this study was undertaken to examine the efficacy of PPLC treatment on changes in SR and MF activities by employing a rat model of streptozotocin-induced diabetic cardiomyopathy. PPLC treatment was observed to attenuate both SR Ca2+-uptake and Ca2+-pump ATPase activities without affecting the depression in MF Ca2+-stimulated ATPase activity in diabetic hearts. Different biomarkers for oxidative stress in diabetic hearts were attenuated by PPLC therapy. PPLC treatment also depressed the elevated levels of plasma free fatty acids and cardiac long chain acylcarnitine. Furthermore, palmitoyl L-carnitine (PMLC) did not affect MF Ca2+-stimulated ATPase, unlike SR Ca2+-pump ATPase activities, in the absence or presence of PPLC. These data suggest that the beneficial effects of PPLC may be mediated through its antagonistic action on PMLC-induced alterations of cardiac membrane Ca2+-handling activities as well as anti-oxidative stress action. (The infrastructure support for this project was provided by the St. Boniface Hospital Albrechtsen Research Centre, Winnipeg).

Allogeneic stem cells and MXene quantum dots for cardiac repair and regeneration

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Content:

Stem cell therapy has shown promise for regenerating and repairing the injured heart. However, poor survival of transplanted stem cells in the ischemic heart has impaired the clinical translation of stem cells-based therapies. We reported that allogeneic stem cells after transplantation in the ischemic heart turned immunogenic and were rejected by host immune system. We are now developing nanomaterials-based strategies to prevent rejection of transplanted stem cells in the heart. We synthesized and characterized tantalum carbide MXene quantum dots (MQDs) and assessed their efficacy for immunomodulation and in preventing the rejection of transplanted stem cells. Our data demonstrate that the MQDs were able to get internalized into the immune cells through active endocytosis, and selectively reduce activation of CD4+IFN-γ+ T-lymphocytes and promote expansion of immunosuppressive CD4+CD25+FoxP3+ regulatory T-cells in an activated lymphocyte population. We also incorporated MQDs into a chitosan-based hydrogel to create a 3D platform for stem cell delivery to the heart. This composite immunomodulatory hydrogel-based platform improved survival of stem cells and prevented allo-immune responses. Therefore, tantalum carbide MQDs can mitigate host immune response and prevent rejection of implanted cells in the heart. These next generation immunomodulatory nanomaterials have the potential of bridge the gap in taking stem cell-based therapies to clinical application.

New paths to cardiovascular health and repair

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Content:

Aging profoundly reshapes cardiac tissue, driving structural remodeling, fibrosis, and functional decline. Across our recent studies, we identify cellular senescence and its impact on vascular integrity and intercellular communication as central mechanisms of cardiac aging. Senescent endothelial and mural cells compromise vascular, neurovascular, and lymphatic homeostasis, promote inflammatory microenvironments, and impair tissue repair. These alterations converge in the perivascular niche, a critical hotspot of "inflammaging" characterized by aberrant fibroblast–macrophage interactions and the persistence of immune-evasive senescent cells.

Importantly, our work demonstrates that these age-associated changes are not irreversible. Restoring lymphatic integrity and function improves cardiac homeostasis and limits pathological remodeling. In parallel, clearing senescent cells from the vascular and perivascular niche alleviates local inflammation and fibrosis and promotes a more reparative tissue environment. Together with strategies that restore vascular and neural integrity, including senolytic interventions and modulation of vascular growth factors such as VEGFB and VEGFC, these approaches improve autonomic balance, reduce fibrosis, and preserve cardiac function.

Collectively, our findings reveal the close interdependence of vascular, lymphatic, neural, and immune pathways in cardiac aging and position the vascular niche as a key therapeutic entry point. By either restoring dysfunctional vascular and lymphatic networks or clearing the senescent cells that corrupt their local environment, it may be possible to re-establish tissue homeostasis and enhance endogenous repair. Targeting senescence and its vascular crosstalk therefore opens new paths toward cardiovascular resilience, repair, and healthy aging.

Modulation of translocator protein (TSPO, peripheral benzodiazepine receptor) in isoprenaline-induced rat myocardial injury: Translational aspects in focus

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Content:

Background: The 18-kDa translocator protein (TSPO), formerly known as the peripheral benzodiazepine receptor, is an outer mitochondrial membrane protein involved in cholesterol transport, mitochondrial bioenergetics, oxidative stress regulation, apoptosis, and inflammation. Increasing evidence suggests that TSPO plays a significant role in cardiovascular pathophysiology, making it a promising therapeutic and diagnostic target. The present study aimed to evaluate the effects of pharmacological TSPO modulation in an experimental model of isoprenaline-induced myocardial injury and discuss its translational relevance.
Methods: Myocardial injury was induced in male Wistar rats by subcutaneous administration of isoprenaline. Animals received either a selective TSPO ligand or vehicle before isoprenaline challenge. Cardiac injury was assessed by biochemical markers, histopathological examination, oxidative stress parameters and inflammatory cytokines. Functional cardiac alterations were evaluated using electrocardiographic measurements. Results: TSPO modulation significantly attenuated isoprenaline-induced myocardial damage, as demonstrated by reduced myocardial necrosis, decreased serum cardiac injury biomarkers, and preservation of myocardial architecture. These effects were accompanied by reduced lipid peroxidation, restoration of endogenous antioxidant defenses, and suppression of pro-inflammatory cytokine production. Furthermore, it was proved that TSPO-targeted treatment favorably regulated apoptotic signaling by decreasing Bax/Bcl-2 ratio and caspase activation, resulting in improved cardiac functional parameters. Collectively, these findings indicate that TSPO modulation mitigates oxidative stress, mitochondrial dysfunction, inflammation, and programmed cell death, key mechanisms underlying catecholamine-induced myocardial injury.Conclusions: Pharmacological modulation of TSPO provides significant cardioprotection in experimental myocardial injury through preservation of mitochondrial function and attenuation of oxidative and inflammatory pathways. Considering the growing availability of TSPO-targeted imaging tracers and selective ligands, these findings support the translational potential of TSPO both as a biomarker of myocardial injury and as a novel therapeutic target for ischemic heart disease, stress-induced cardiomyopathy, and other cardiovascular disorders characterized by mitochondrial dysfunction. Further preclinical and clinical studies are warr

Comparative Antioxidant Potential of Eryngium amethystinum Flowers and Leaves: Perspectives for Cardiovascular Research

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Content:

Introduction

Eryngium amethystinum L. is distributed in the central Balkan Peninsula and Italy. Its aerial parts are traditionally used in Western Balkan countries and Italy as diuretic and antimalarial agents and are also consumed as food. This study evaluated and compared the antioxidant activity of ethanolic extracts from the flowers and leaves of E. amethystinum using complementary spectrophotometric assays.

Methodology

Aerial parts were collected in Gornje Ravno, Kupres Municipality, Bosnia and Herzegovina. Flowers and leaves were processed separately and extracted with 80% ethanol at a solid-to-solvent ratio of 1:10 (w/v) for 90 min at room temperature under constant agitation. Total polyphenolic content was determined, and antioxidant activity was assessed using ABTS radical-scavenging, phosphomolybdenum, and ferric reducing antioxidant power (FRAP) assays. All measurements were performed in triplicate.

Results

Flowers contained 40.46 ± 2.90 mg GAE/g dry mass, while leaves contained 19.60 ± 0.34 mg GAE/g. Polyphenol concentrations of 10, 20, 50, 100, and 500 µg GAE/mL were evaluated. ABTS demonstrated strong radical-scavenging activity in both extracts, with higher activity in the flower extract, as indicated by lower IC_{50} values (2.57 ± 0.07 vs. 5.68 ± 0.08 µg/mL). Polyphenolic content showed a strong negative correlation with ABTS values (Spearman's $r = -0.7714$), although it was not statistically significant ($p = 0.1028$). The phosphomolybdenum assay showed significantly higher activity of the flower extract at 100 µg/mL (3252.62 ± 162.95 vs. 1237.28 ± 123.91 mg vitamin C/mL, $p < 0.001$), whereas the leaf extract showed higher activity at 500 µg/mL (4740.28 ± 529.74 vs. 2403.66 ± 160.79, $p = 0.001$). Concentrated flower extract also showed significantly higher activity than the its leaf counterpart (6543.87 ± 444.60 vs. 3485.32 ± 205.39, $p = 0.001$). FRAP showed significantly higher reducing capacity of the flower extract at 500 µg GAE/mL (0.25 ± 0.02 vs. 0.15 ± 0.003 mmol Fe^{2+}/L, $p = 0.0005$), while no significant difference was observed at 100 µg GAE/mL ($p = 0.19$). Conclusion

Both extracts demonstrated pronounced antioxidant activity, with flowers generally showing stronger radical-scavenging and reducing capacities. These findings support further investigation of E. amethystinum, particularly its flowers, as a source of bioactive compounds relevant to cardiovascular research

NECROPTOSIS IN HEART FAILURE: INTRACELLULAR AND EXTRACELLULAR MECHANISMS AND PHARMACOTHERAPEUTIC STRATEGIES

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Content:

Necroptosis, a receptor-interacting protein kinase 3 (RIP3)-mediated cell death pathway, causes plasma membrane rupture and the subsequent release of intracellular damage-associated molecular patterns (DAMPs), which act as critical drivers of sterile inflammation and ongoing tissue injury.

Preclinical experiments utilizing a rat model of post-myocardial infarction (post-MI) heart failure have demonstrated active necroptosis, a receptor-interacting protein kinase 3 (RIP3)-mediated cell death pathway. This was accompanied by an increase in pro-inflammatory double-stranded high-mobility group box 1 (dsHMGB1) and a concomitant decrease in the tissue-repairing, fully reduced form of HMGB1 (frHMGB1). Other membrane-disrupting damage-associated molecular patterns (DAMPs), including C-X-C motif chemokine ligand 10 (CXCL10), fibronectin 1, and oxidized mitochondrial DNA (ox-mtDNA), were also elevated in post-MI failing hearts. Conversely, pharmacological RIP3 inhibition suppressed this pro-death signaling, normalized dysregulated microRNAs, and upregulated frHMGB1. Furthermore, RIP3 inhibition tended to reduce ox-mtDNAlevels, prevented local macrophage infiltration and tissue inflammation as well as decreased circulating HMGB1 levels. The translational arm of the project, analyzing serum from healthy controls and patients with heart failure, demonstrated significantly elevated levels of circulating HMGB1, which correlated positively with systemic C-reactive protein, alongside an upward trend in circulating RIP3 levels. Thus, myocardial damage in ischemic heart failure appeears to be fueled by necroptosis, and associated inflammation. The pro-necroptotic leakage of DAMPs and oxidation of mtDNAmight act as potent extracellular danger signals, establishing a vicious cycle of such heart injury. Targeted RIP3 inhibition represents an effective pharmacotherapeutic approach to retard necroptosis, prevent the propagation of heart-damaging DAMPs, and alleviate maladaptive tissue remodeling. Concurrently, elevated circulating necroptotic markers indicate the clinical relevance and diagnostic stratification potential of these pathways in human heart failure management.

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Cinnamaldehyde Attenuates Isoprenaline-Induced Myocardial Injury in Rats

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Content:

Introduction: Myocardial ischemia and the resulting myocardial injury represent major cardiovascular conditions associated with significant morbidity and mortality, emphasizing the need for effective preventive and therapeutic strategies. Cinnamaldehyde (CA), a naturally occurring aromatic aldehyde and one of the major bioactive compounds of cinnamon, has demonstrated antioxidant and anti-inflammatory properties, suggesting a potential protective role in cardiovascular disorders. Therefore, this study aimed to investigate the potential cardioprotective effects of CApre-treatment on isoprenaline-induced myocardial injury in rats.

Methods: Male Wistar albino rats were randomly divided into four groups (n = 6 per group): control, isoprenaline (I), cinnamaldehyde (CA), and CA+ I. CAwas administered orally by gavage at a dose of 90 mg/kg for 14 consecutive days, while propylene glycol was administered to the control and I groups. Myocardial injury was induced by subcutaneous administration of isoprenaline (85 mg/kg) on days 13 and 14 in the I and CA+ I groups, whereas the control and CA groups received physiological saline. Cardioprotective effects were assessed by electrocardiographic parameters, serum high-sensitivity troponin I (hsTnI), and markers of oxidative stress.

Results: CApre-treatment attenuated isoprenaline-induced myocardial injury. Asignificant reduction in serum hsTnI was observed in the CA+ I group compared with the I group, indicating reduced myocardial damage. Electrocardiographic findings demonstrated improved cardiac function in CA-pre-treated animals compared with the isoprenaline group.
Furthermore, CAalleviated isoprenaline-induced oxidative stress, as reflected by improvements in oxidative stress and antioxidant defense parameters.

Conclusion: Cinnamaldehyde pre-treatment mitigated isoprenaline-induced myocardial injury, as demonstrated by lower hsTnI levels, improved ECG findings, and reduced oxidative disturbances. These findings indicate that cinnamaldehyde may contribute to the preservation of myocardial function and warrants further investigation as a potential cardioprotective compound.

ABNORMAL ECG FINDINGS DURING PREPARTICIPATION SCREENING IN PEDIATRIC ATHLETES AGED 12-15 YEARS

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Content:

Introduction: Sudden cardiac death (SCD) is a rare and fatal event in athletes. Preparticipation cardiovascular screening aims to assess athletes before they engage in sports. The main goal is to detect asymptomatic cardiac abnormalities in order to prevent SCD. Screening protocols are not uniform and vary in different countries worldwide. An electrocardiogram (ECG) increases screening sensitivity for detecting silent, life-threatening heart conditions. ECG guidelines for athletes have evolved as additional evidence has emerged over the years. The 2026 clinical Consensus statement of the European Association of Preventive Cardiology (EAPC) of the ESC and the Association for European Pediatric and Congenital Cardiology (AEPC) is the first to provide specific ECG recommendations for pediatric athletes aged 12 to <16 years. ECG findings are classified as normal, borderline, or abnormal (requiring further evaluation).

The aim of this study is to present abnormal ECG findings from pediatric athlete screening at a single center over 3 years. Methodology: Athletes aged 12 to 15 who underwent regular preparticipation screening from January 2023 to August 2026 at the Serbian Institute of Sport and Sports Medicine were included. The exam included anthropometrics, sport type, training history, weekly training volume, physical exam, and a resting 12-lead ECG, interpreted according to the 2026 EAPC/AEPC Consensus.

Results: Atotal of 4,449 pediatric athletes (40.6% female), aged 13.05±1.08 years, were included. Basketball (n=945), football (n=859), and volleyball (n=697) were the most represented sports overall. Abnormal ECG findings (n=82) were: significant ST depression (n=1), significant T-wave inversion (n=7), short PR interval (n=41), ventricular pre-excitation (n=6), confirmed prolonged QT interval (n=1), suspected short QT interval (n=1), premature ventricular contractions (n=25). Appropriate diagnostic procedures were performed for these athletes. 5 athletes were lost to follow-up. 4 athletes underwent successful radiofrequency ablation for Wolff–Parkinson–White syndrome. After further workup, 77 were cleared to play, and no adverse events or SCD were observed during this period.

Conclusion: Abnormal ECG was observed in 1.8% of pediatric athletes. Regular screening with ECG and appropriate diagnostic workup increases the likelihood of diagnosing cardiac conditions associated with increased SCD risk while eliminating unnecessary sports restrictions.

Redefining neurocardiac interactions in the human heart

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Content:

Over the past decades significant progress has been made in understanding heart function, particularly in the context of excitation-contraction coupling and cardiac electrophysiology. These insights have provided a clear picture of the major pathophysiological mechanisms underlying cardiac diseases, including neurohormonal regulation of heart function.

Nevertheless, understanding neurogenic mechanisms and the influence of neuronal remodelling on cardiac diseases onset and progression has been representing a challenging experimental problem. It is clear that cardiac autonomic alterations are extremely important in the pathogenesis of many cardiovascular diseases. This highlight the relevance of single-cell and cell-cell interaction studies to comprehensively delineate both individual cardiomyocyte and cardiac neuron function, as the crosstalk between the two of them. However, there is a profound gap of knowledge regarding the characterization of the neurons in the heart, in our understanding of this crosstalk and in how or whether cardiovascular targeted therapies impact on the activity of the neurons. We explore neurocardiac interactions using for the first time human cardiac myocytes and neurons.

Prompt cardioprotective signaling by ischemic preconditioning is not only associated with a direct increase in mitochondrial respiration but also with activation of the mitochondrial fission mediator Drp1

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Content:

Introduction: The classical paradigm of cardioprotection is local ischemic preconditioning (IPC), which mitigates myocardial ischemia/reperfusion injury. Mitochondria are well-established effectors of cardioprotection; improved mitochondrial function maintains cardiomyocyte survival and thus reduce infarct size. The intracellular cardioprotective pathways, reperfusion injury salvage kinase (RISK) and survivor activating factor enhancement (SAFE), are upstream of the improved mitochondrial function. However, it is unclear whether the RISK and SAFE activation within minutes after IPC directly trigger mitochondrial function. This study aimed to characterize mitochondrial function after IPC alongside the activation of the SAFE and RISK pathways, as well as novel mediators regulating mitochondrial respiration and morphology (i.e., the dynamin-related protein-1 (DRP-1)).

Methodology: After stabilization, isolated perfused rat hearts were subjected to IPC (3x 5/5 min global ischemia/reperfusion) or respective time control (30 min). Cardiac tissue was snap frozen and lysed, the phosphorylation of prototypic cardioprotective proteins (extracellular-regulated kinase (Erk) and signal transducer and activator of transcription 3 (STAT3) as well as mitochondrial fission mediator DRP-1 in relation to total protein expression was quantified via Western blotting. In parallel, mitochondria were isolated and mitochondrial respiration was measured via high-resolution respirometry.

Results: In cardiac tissue lysates, we confirm an increased activation of the known cardioprotective mediators ERK and STAT3 and identified an increased phosphorylation of the mitochondrial fission mediator DRP-1 directly after IPC compared to time control. In isolated mitochondria, mitochondrial baseline and ADP-stimulated complex I respiration were increased directly after the IPC maneuver compared to time control, whereas complex II respiration was depressed.
Complex IV respiration did not differ between groups indicating an equal loading of the respiration chambers with viable mitochondria.

Conclusion: The novel insight into the direct effect of IPC on mitochondrial function, which may occur downstream of established cardioprotective and/or potentially novel signaling pathways, has the potential to facilitate the identification of new mitoprotective and thus cardioprotective signaling pathways that could be relevant for translation.

The Effect of Transcatheter Aortic Valve Replacement on Serum Lysophosphatidylcholine Concentrations in Patients With Severe Aortic Stenosis

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Content:

Introduction: Calcific aortic stenosis (AS) is an active fibrocalcific disease characterized by lipid infiltration, oxidative stress, inflammation, and osteogenic transformation of valvular cells. Lysophosphatidylcholine (LysoPC) is a bioactive lipid implicated in inflammatory and osteogenic processes involved in valve calcification. LysoPC 16:0 is an abundant circulating LysoPC species and has been identified within calcified regions of stenotic human aortic valves. Moreover, LysoPC serves as a substrate for autotaxin-mediated generation of lysophosphatidic acid, linking lipid metabolism with valvular mineralization. However, circulating LysoPC 16:0 concentrations in severe AS and their response to correction of valvular obstruction remain poorly characterized. The aim of this study is to investigate the effect of transcatheter aortic valve replacement (TAVR) on serum LysoPC 16:0 concentrations in patients with severe AS.

Methodology: This prospective observational study will include 60 patients with severe symptomatic AS undergoing TAVR and 20 control subjects without severe AS. Serum samples will be collected before TAVR and during follow-up. LysoPC 16:0 concentrations will be determined using enzyme-linked immunosorbent assay (ELISA). Pre- and post-TAVR concentrations will be compared, as well as concentrations between patients with severe AS and controls. Associations between LysoPC 16:0 and clinical, laboratory, and echocardiographic parameters will also be investigated.

Results: Patient recruitment and prospective serum sample collection are ongoing. LysoPC 16:0 analysis will be performed following completion of sample collection.

Conclusion: This study will characterize circulating LysoPC 16:0 in severe AS and its changes following TAVR, potentially providing further insight into lipid-mediated mechanisms of calcific aortic valve disease and the role of LysoPC 16:0 as a circulating biomarker.

Circadian Disruption Exacerbates Heart Failure with Preserved Ejection Fraction in a Sex Specific Manner

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Content:

characterized by obesity, insulin resistance, dyslipidemia, and hypertension. CMS is a leading contributor to heart failure with preserved ejection fraction (HFpEF), a condition that disproportionately affects women and for which effective therapies remain limited. Despite the established association between shift work and cardiometabolic disease, the molecular mechanisms by which circadian disruption accelerates CMS-driven HFpEF are poorly understood. This study aims to identify key circadian-regulated pathways linking shift work to CMS-induced HFpEF.

Methods: C57BL/6J mice were fed a high-fat diet and L-NAME for five weeks to induce a CMS-HFpEF phenotype, followed by five days of simulated night shift work through reversal of the light-dark cycle. Body weight, systolic and diastolic blood pressure, and cardiac function were assessed by echocardiography. Cardiac tissue was analyzed for circadian clock protein expression, while plasma was evaluated for lipid profiles and cardiac stress biomarkers.

Results: The CMS-HFpEF model was validated by preserved left ventricular ejection fraction, consistent with the HFpEF phenotype. Simulated night shift work disrupted the expression of core circadian clock proteins, confirming effective circadian misalignment. Importantly, circadian disruption significantly exacerbated both systolic and diastolic blood pressure in CMS mice compared with non-shift controls, indicating that shift work worsens the hypertensive component of HFpEF. Furthermore, circulating cardiometabolic and cardiac stress biomarkers were differentially altered in a sex-specific manner, suggesting distinct biological responses to circadian disruption in males and females.

Conclusion: By identifying the molecular pathways and regulatory genes altered by shift work, this research will provide new insight into the mechanisms linking circadian disruption, hypertension, and HFpEF. Ultimately, these findings may inform the development of targeted, sex-specific therapeutic strategies to prevent or treat HFpEF in populations exposed to chronic circadian disruption.

Diazepam in human pregnancy: experimental evidence for its effects on umbilical vascular function, oxidative stress, cell survival, and immune response

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Content:

Introduction: Diazepam, a benzodiazepine not routinely recommended during pregnancy, is nevertheless used off label in selected obstetric circumstances. Its effects at the maternal–fetal interface, including umbilical vascular function, oxidative homeostasis, and maternal cellular immune regulation, remain incompletely characterized. This study evaluated the ex vivo effects of diazepam on human umbilical arteries (HUAs) under physiological and hyperhomocysteinemic conditions, and its in vitro effects on $CD4^+$ and $CD8^+$ T-lymphocyte populations in healthy non-pregnant and healthy pregnant women. Methods: HUAs were exposed to diazepam (100 μM), homocysteine (1 mM), or their combination. Oxidative-stress parameters and vascular reactivity were measured in 6–10 samples, and histology and apoptosis in triplicate. Diazepam-induced relaxation (0.01–100 μM) and its underlying pathways were examined pharmacologically. Peripheral blood mononuclear cells from healthy non-pregnant women and healthy pregnant women (n = 4/group) were incubated with diazepam (2.5–10 μM) for 48 h, activated with anti-CD3/anti-CD28 beads, and analyzed by flow cytometry to assess the distribution and viability of $CD4^+$ and $CD8^+$ T-lymphocyte populations.

Results: Diazepam alone significantly reduced superoxide dismutase activity ($p < 0.05$). Under hyperhomocysteinemic conditions, it significantly decreased thiobarbituric acid-reactive substances and nitrite levels ($p < 0.05$), reduced endothelial disruption, smooth-muscle disorganization, and apoptosis compared with homocysteine alone. Diazepam induced concentration- and time-dependent, endothelium-independent HUArelaxation, reaching approximately 96% maximal relaxation at 100 μM. This effect involved sGC–cGMP signaling, potassium-channel activation, calcium-channel inhibition, and translocator protein signaling. In preeclamptic HUAs, diazepam-induced relaxation was approximately 50% lower than in healthy controls but remained more pronounced than the response to nicardipine. In PBMC cultures, diazepam did not induce apoptosis and promoted the survival of $CD4^+$ and $CD8^+$ T-lymphocyte populations in both tested group.

Conclusion: Diazepam exerts complex vasoactive, cytoprotective, and cellular immunomodulatory effects at the maternal–fetal interface. It partially counteracts hyperhomocysteinemia-associated vascular injury, strongly regulates umbilical vascular tone, and supports the survival of $CD4^+$ and $CD8^+$ T lymphocytes in vitro.

Potential of PARP inhibitors in Cardio-Oncology

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Content:

Cardiotoxicity is a serious adverse effect of cancer therapy that can substantially impair patients' quality of life and overall survival. Its most severe manifestation, heart failure, has a 5-year survival rate of approximately 50%, which is worse than that of many cancers. Both short- and long-term cardiovascular complications can arise from a wide range of anticancer treatments, including chemotherapy, immunotherapy, and hormonal therapy. However, pharmacological strategies aimed at mitigating treatment-related cardiotoxicity may potentially compromise the antineoplastic efficacy of cancer therapy. We propose the repurposing of inhibitors of the nuclear enzyme poly(ADP-ribose) polymerase (PARPi), currently used to treat cancers with defective homologous recombination DNArepair, as a strategy to reduce cancer therapy-induced cardiotoxicity. The cytoprotective, antioxidant, and anti-inflammatory properties of PARPi may be particularly valuable in treating cardiovascular conditions characterized by tissue injury and inflammation. Preclinical evidence suggests that PARPi can protect cardiomyocytes against ischemia–reperfusion injury and attenuate adverse cardiac remodeling following myocardial infarction. Their anti-inflammatory effects may also help mitigate the progression of atherosclerosis. We have reported that modulation of protein kinase B/Akt and mitogen-activated protein kinase signaling pathways contributes significantly to these cardioprotective effects of PARPi. Although prolonged administration of these drugs may raise concerns about malignant transformation associated with the accumulation of DNAdamage, the potential cardio-oncological benefits of these agents may ultimately outweigh these risks.

Modulation of NLRP3 Inflammasome and TGF-β1 Signaling Attenuates Cardiac Fibrosis

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Content:

Cardiac fibrosis is a maladaptive remodeling process characterized by excessive extracellular matrix deposition, progressive myocardial stiffening, and impaired cardiac function. TGF-β1 promotes fibroblast activation and differentiation into ECM-producing myofibroblasts, while NLRP3 inflammasome activation drives IL-1β- and IL-18-mediated inflammation, together synergistically promoting adverse cardiac remodeling. In the experimental model, uninephrectomy followed by DOCA-salt administration with 1% NaCl in drinking water induces volume expansion and hypertension in rats, accompanied by upregulation of TGF-β1 signaling and activation of the NLRP3 inflammasome, leading to enhanced collagen deposition and cardiac fibrosis. Beginning after uninephrectomy, rats received daily treatment for 28 days with glibenclamide (10 and 40 mg/kg), glimepiride (0.1 and 0.5 mg/kg), pirfenidone (100 mg/kg), lansoprazole (30 mg/kg), esomeprazole (30 mg/kg), pirfenidone + PPI (100 + 30 mg/kg), or Eclipta alba (200 and 400 mg/kg). Treatment improved anthropometric parameters, reduced blood pressure, and normalized ECG parameters. Furthermore, treatment improved left ventricular function, as evidenced by a significant reduction in LVEDP. Histopathological examination using Masson's trichrome staining revealed marked attenuation of cardiac histopathological alterations, accompanied by reduced collagen I and III content in heart homogenates. Moreover, treatment downregulated the expression of TGF-β1 and/or NLRP3 in cardiac tissue. Targeting these profibrotic and inflammatory pathways, sulfonylureas (glibenclamide and glimepiride) have demonstrated NLRP3 inflammasome-inhibitory activity, whereas proton pump inhibitors (PPI) (lansoprazole and esomeprazole), alone or in combination with the antifibrotic agent pirfenidone, and the coumarin-rich Eclipta alba extract exert antioxidant and antifibrotic effects, in part through suppression of TGF-β1 signaling. Collectively, these findings highlight their potential as therapeutic strategies for attenuating cardiac fibrosis

Pharmacokinetics and cardioprotective effects of intravenous miR-450a microRNA in a mouse model of acute myocardial infarction

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Content:

Introduction: MicroRNAs (miRNAs) are small, non-coding RNAsequences with the potential to modulate multiple therapeutic targets simultaneously. We previously identified miR-450a (rno-miR-450a-3p) as a potential cardioprotective microRNAin an isolated rat heart model. In the present study, we investigated the pharmacokinetics of intravenously administered miR-450a mimic and evaluated its effect on infarct size in an in vivo mouse model of acute myocardial infarction.

Methods: Myocardial ischemia was induced in C57Bl/6J male and female mice by coronary ligation for 45 minutes, followed by 24 hours of reperfusion. At the 40th minute of ischemia, 0.0625 mg/kg miRNA-450a mimic was administered intravenously to simulate a clinically relevant emergency treatment scenario. In addition to the therapeutic group, control groups treated with vehicle only and with Cel-miR-239b (a non-targeting control miRNAderived from C. elegans) were also included. At the end of reperfusion, the ischemic risk area and infarct size were assessed and compared between the groups.

Results: Following intravenous administration, the miR-450a mimic rapidly appeared in the plasma and showed transient accumulation in the myocardium from 30 minutes up to 4 hours. Treatment also had no significant effect on mortality or the incidence of arrhythmias. There was no difference in area at risk and infarct size data in male mice between the miR-450a and either control groups. However, infarct size was significantly reduced in female animals between miR-450a-treated and vehicle-treated animals.

Conclusions: Our results demonstrate that intravenously administered miR-450a mimic successfully reaches and transiently accumulates in the myocardium. Despite its previously demonstrated cardioprotective potential, miR-450a did not significantly reduce infarct size in male but only in female mice when administered intravenously at 0.0625 mg/kg 5 min before the onset of reperfusion. Further studies optimizing the timing and dose of administration, as well as delivery strategies and longer-term outcomes, are required to determine its therapeutic benefit in myocardial ischemia-reperfusion injury.

Space physiology: bed rest studies to evaluate cardiac deconditioning

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Content:

Introduction.

Head-down (-6°) tilt (HDT) bed rest (BR) is a validated ground-based model for investigating the changes induced by prolonged exposure to microgravity and immobilization, as well as to test developed countermeasure. For the cardiovascular system, HDT BR induces cardiac deconditioning, increases arrhythmogenicity, and alters cardiac autonomic regulation. However, while electrical markers have been widely studied, less is known about changes in cardiac mechanical function during HDT and following gravity restoration, and as well possible gender differences. Methods.

12 healthy volunteers (11 M, 9 F) underwent 21 days HDT without countermeasures, as part of the Italian Space Agency SCIENCE FOR BED-REST program. Continuous 24 h 1-lead electrocardiographic (ECG, 1024 Hz) and seismocardiographic (SCG, 256 Hz) recordings were performed (ECGMove4, Movisens GmbH) at baseline (BDC), on HDT days 5 and 19, and on the first recovery day after HDT (R+1). From the ECG, beat-to-beat RR intervals were extracted and heart rate variability (HRV) indices computed over 5-min segments. On SCG, by ECG-based template-matching approach and detection of isovolumetric contraction (IVC) and aortic valve opening (AO) points, temporal and morphological parameters were extracted. The effect of HDT was assessed (Friedman, $p<0.05$, Bonferroni-corrected post-hoc Wilcoxon signed-rank), and comparisons between genders performed (Mann-Whitney U, $p<0.05$).

Results.

Day-night differences in RR and SCG markers were preserved along HDT. The main alterations emerged at gravitational reinstatement: RR decreased in both daytime (-24% in M, -16% in F vs BDC; -20% in M, -25% in F vs BR19) and nighttime (-14% in M, -20% in F vs BDC; -17% in M, -19% in F vs BR19). Daytime LV Ejection Time increased at R+1 by +14% in M and +13% in F.

The IVC-AO amplitude decreased during bed rest both during the day (M up to -16% and F -22% at BR19), and night (up to -28% in M at BR19 and -39% in F at BR5), with an inverse trend observed at R+1 (up to +22% in M), except for the F group at night (-16%).

Conclusions.

These findings show that the largest cardiac electromechanical adjustments occur during return to normal gravity, with an early vagal predominance present in women. For Earth medicine, these results highlight how bedridden hospitalization may contribute to impaired cardiovascular compensation at dismission, with possible implications for post-hospitalization (i.e., increased risk of falling).

PEGylated ligands to explore cardiac β-adrenergic receptor signaling in the T-tubule vs. outer surface membrane

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Content:

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.

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).

No differences were seen in excitation-contraction coupling responses with identical ICa-L and Ca2+ responses to Iso and PEG-Iso stimulation. However, spatial cAMP and PKAdifferences 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 PKAwith a greater efficacy than free Iso but stimulates nuclear PKAwith a ≈50% lower efficacy reflected in a ≈50% reduction of PKAmediated 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.

Thus, only activation of OSM β-ARs is required to activate cytosolic PKAand the main mechanistic pathways of excitation-contraction coupling. However, activation of TTM β-ARs is needed for nuclear PKAstimulation or nuclear protein phosphorylation.

Coronary microvascular injury from myocardial ischemia/reperfusion

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Content:

The coronary circulation with its atherosclerotic plaques and their rupture or erosion is not only the culprit of myocardial ischemia, but it is also its victim. Multiple mechanisms contribute to coronary microvascular injury: 1. Interstitial edema and extravascular compression, 2. Impaired coronary vasodilation and enhanced vasoconstriction in response to norepinephrine, endothelin, serotonin and thromboxane, 3. Physical obstruction by microembolization of atherothrombotic debris from the epicardial lesion, 4. Leukocyte/platelet aggregates and erythrocyte stasis, 5.Leukocyte adherence, 6.
Pericyte contraction, 7. Endothelial destruction and capillary rupture with secondary intramyocardial hemorrhage. The clinical effects on coronary blood flow range from slow to no reflow at reperfusion on angiography, and edema, microvascular obstruction and intramyocardial hemorrhage on magnetic resonance imaging. Coronary microvascular obstruction and intramyocardial hemorrhage carry an adverse prognosis in patients with reperfused acute myocardial infarction. Some studies report attenuation of slow/no-reflow on reperfusion by calcium antagonists or alpha-blockade. In the experiment and in some clinical studies, all interventions which reduce infarct size, notably all forms of ischemic conditioning, also attenuate the signs of coronary microvascular injury. However, currently there is no specific protection from coronary microvascular injury in myocardial ischemia/reperfusion.

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Working Hard or Hardly Working?

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Content:

The COVID-19 pandemic presented a large number of challenges to populations all over the world. These challenges were not restricted to health concerns although the health implications of the pandemic were undoubtedly the most important and the one that attracted the most research, clinical and media attention. However, food availability, financial implications, climactic changes and the changes in social and work behavior due to the pandemic were also significant in every country infected. This talk will focus upon the unique opportunity that the pandemic allowed to investigate the effects the pandemic had on work habits in a hospital-based research institution in Winnipeg, Canada during the pandemic. The potential mechanisms responsible for these changes in work behavior will be a subject for discussion. This study represents the first documented examination of work behavior in a research environment. Supported by a Foundation grant from the Canadian Institutes for Health Research.

Endurance training induced pulmonary vein and atrial remodeling to promote atrial fibrillation

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Content:

Introduction: Long-term endurance exercise increases the risk of atrial fibrillation (AF). We investigated whether endurance training alters pulmonary vein (PV) electrophysiology and PV–left atrial (LA) conduction, increasing AF triggers and susceptibility.

Methodology: Adult Beagle dogs were randomised to sedentary (Sed, n=14) and trained (ExT, n=14) groups and underwent 16 weeks of treadmill training (5 days/week, 280 min/day). Epicardial stimulation, burst pacing, PV monophasic action potential (MAP) recordings and multielectrode array (MEA) mapping were performed after training. Ex vivo PV electrophysiology was assessed under β-adrenergic stimulation.

Results: Following acetylcholine (5 μg/kg), ExT dogs showed greater susceptibility to pacing-induced AF (incidence: Sed, 13.6 ± 4.3%; ExT, 42.8 ± 7.5%; duration: Sed, 2.2 ± 0.8 s; ExT, 8.3 ± 1.9 s; all $p<0.05$). LAMAP duration was shorter in ExT dogs (APD90: Sed, 150.8 ± 9.9 ms; ExT, 118.2 ± 9.5 ms; $p<0.05$), while PV–LAmapping demonstrated altered radial propagation (Sed, 96 ± 14°; ExT, 162 ± 24°; $p<0.05$). Spontaneous AP generation occurred in 83.3% of ExT PVs versus 0% of Sed PVs during 1 μM isoproterenol ($p<0.05$). Following 10 Hz pacing plus isoproterenol, self-sustaining evoked APs occurred in 83% of ExT versus 23% of Sed PVs ($p<0.05$), lasted 32.2 ± 11 versus 4.2 ± 2.9 s, and occurred at 83.3 ± 21.6 versus 20.3 ± 11.8 beats/min ($p<0.05$). ExT PVs showed enhanced β-adrenergically evoked firing, prolonged burst activity and a higher proportion of pacemaker-like APs. Training also caused moderate atrial fibrosis and extracellular matrix expansion. HCN4, CACNA1D and CACNA1G were upregulated, whereas SCN5Aand GJA1 (Cx43) were downregulated.

Conclusion: Endurance training induces marked electrophysiological remodelling of the PV–LAregion, characterised by enhanced β-adrenergic PV automaticity, increased ectopic firing and prolonged burst activity, together with altered atrial conduction. The increased prevalence of pacemaker-like APs and sustained PV activity provides an enhanced source of ectopic triggers, while altered PV–LAactivation may favour conduction heterogeneity and AF initiation. The accompanying structural and molecular changes provide a potential basis for these electrophysiological alterations. Together, the findings indicate that endurance training increases AF susceptibility through the combined effects of enhanced PV ectopic activity and a remodelled atrial electrophysiological substrate.

H9C2-Derived Mitochondrial Transfer: A Novel In Vitro Strategy for Investigating Cellular Senescence

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Content:

Introduction: Aging is characterized by mitochondrial dysfunction, increased oxidative stress, and impaired energy metabolism, all of which contribute to cellular senescence. Mitochondrial dynamics, regulated by the balance between fusion, fission, and mitophagy, are essential for maintaining mitochondrial quality. During aging, excessive mitochondrial fission promotes mitochondrial fragmentation, ATP depletion, and reactive oxygen species (ROS) production, accelerating cellular dysfunction. This study investigated whether pharmacological inhibition of mitochondrial fission followed by transfer of fusion-promoted mitochondria could improve mitochondrial function in an in vitro senescence model.

Materials and Methods: Cellular senescence was induced in H9C2 cardiomyoblasts by treatment with 50 mg/mL D-galactose for different incubation periods. Dose optimization of the mitochondrial fission inhibitor Mdivi-1 was performed using MTT and luminescence-based ATP assays. Mitochondrial fusion was morphologically confirmed by transmission electron microscopy (TEM). Mitochondria isolated from untreated or Mdivi-1-treated H9C2 cells were transferred into senescent H9C2 cells using a commercial mitochondrial isolation and transfer kit. Mitochondrial membrane potential (MMP), intracellular ROS, and intracellular pH were subsequently evaluated by fluorescence-based confocal microscopy.

Results: D-galactose treatment for 48 h successfully induced cellular senescence, evidenced by significant upregulation of p16 and p21 mRNAexpression. Based on TEM findings together with ATP and MTT analyses, treatment with 10 μM Mdivi-1 for 24 h was identified as the optimal condition for generating fusion-promoted donor mitochondria. Transfer of both normal and fusion-promoted mitochondria restored mitochondrial membrane polarization in senescent H9C2 cells. In contrast, intracellular ROS levels increased following mitochondrial transfer, whereas intracellular pH remained unchanged.

Conclusion: Mitochondrial transfer improved mitochondrial membrane polarization in senescent cardiomyoblasts, suggesting partial restoration of mitochondrial function. However, the accompanying increase in ROS indicates that mitochondrial transplantation may induce complex changes in cellular redox homeostasis. These findings support mitochondrial transfer as a promising in vitro tool for studying mitochondrial quality during cellular senescence.

Muscle mass, explosive strength and sedentary behaviour in healthy young adults: A cross-sectional study

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Content:
Introduction: Sedentary behaviour and physical inactivity are recognised factors that negatively affect musculoskeletal and cardiometabolic health, yet their association with muscle mass and lower-limb explosive strength remains understudied in healthy, young populations. This study examined the association between percentage of muscle mass, physical activity, and sedentary behaviour and gait biomechanical parameters, explosive strength, and speed in healthy young adults.

Methodology: Across-sectional study was conducted on 37 healthy young adults (27 women, 10 men; mean age 21.32 years). Physical activity and sedentary behaviour were assessed using the long form of the International Physical Activity Questionnaire (IPAQ), body composition using bioelectrical impedance analysis, and gait, explosive strength, and speed using a wearable inertial sensor system, including countermovement (CMJ) and plyometric jumps, a parkour test, and a quick feet test.

Results: Percentage of muscle mass was significantly positively associated with CMJ height (ρ=0.481; P=0.003), CMJ power (ρ=0.569; P<0.001), and plyometric jump height (ρ=0.503; P=0.002), but not with physical activity level or indicators of lateral asymmetry (ρ=0.059–0.171; P>0.05). Sedentary behaviour was not associated with any gait, strength, or speed parameter, although men reported significantly more time spent sitting than women (7.16 vs 5.36 hours/day; P=0.034). Temporal gait asymmetry differed across IPAQ activity categories, with the lowest-activity group showing the highest values, while spatial asymmetry did not differ significantly.

Conclusion: In healthy young adults, muscle mass is more strongly associated with explosive strength than with self-reported activity level or gait symmetry. At the same time, sedentary behaviour shows no measurable association with biomechanical or motor performance. These preliminary findings support combining questionnaire-based assessment, body composition analysis, and instrumented biomechanical assessment in future, larger-scale research addressing musculoskeletal and cardiovascular health in young populations.

Therapeutic potential of Tribulus terrestris L. on hypoxia induced pulmonary hypertension by targeting inflammasome in experimental animals

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Content:

Background: Pulmonary hypertension (PH) is a complex cardiopulmonary disorder characterised by a persistent increase in mean pulmonary arterial pressure, elevated pulmonary vascular resistance, right ventricular failure, and premature mortality and associated with poor prognosis along with low median survival rates. Inflammatory processes like dysregulated inflammasome signalling have been implicated in promoting vascular remodelling and disease progression. Tribulus terrestris L., a medicinal plant with well-documented antioxidant and anti-inflammatory properties, may modulate molecular pathways involved in hypoxia-mediated pulmonary vascular remodelling.

Objective: To evaluate the therapeutic effects of Tribulus terrestris on hypoxia induced PH in rodent model and mechanism by which these effects are exerted.

Materials and Methods: Thirty male Wistar rats were randomly divided into 5 groups with 6 animals in each group. Group I as normal control, Group-II as pulmonary hypertension exposed to intermittent hypoxia, Group-III exposed to intermittent hypoxia + Tadalafil drug, Group-IV exposed to intermittent hypoxia + Tribulus terrestris 250 mg/Kg and Group-V exposed to intermittent hypoxia + Tribulus terrestris 500 mg/Kg. Right ventricular systolic pressure (RVSP), serum levels of reactive oxygen and nitrogen species (ROS, RNS), and inflammatory markers- HIF-1α, TLR4, NF- κB, IL-1β, IL-18 in control and experimental groups were analysed.

Results: Treatment with T. terrestris significantly attenuated RVSP elevation and reduced serum levels of ROS, RNS and inflammatory mediators of inflammasome (HIF-1α, TLR4, NF- κB, IL-1β, IL-18) in hypoxic pulmonary hypertensive rats. T. terrestris exhibited therapeutic effects comparable to that of the standard drug tadalafil.

Conclusion: Tribulus terrestris exhibits anti- hypertensive, anti-oxidative and anti-inflammatory potential, likely mediated through modulation of oxidative stress and inflammatory signalling pathways. This provides a valuable lead that T. terrestris can prove to be a promising phytotherapeutic candidate in the management and treatment of pulmonary hypertension.

POSSIBLE ASSOCIATION BETWEEN APICAL PERIODONTITIS AND CARDIAC FUNCTION IN DIABETIC RATS

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Content:

Introduction:The study was aimedto investigatethe possible association between apical periodontitis (AP) and cardiac function in rats with type 2 diabetes mellitus (T2DM).

Methodology:Forty-eight Wistar albino, maleratswere randomly divided into four groups: control (CTRL), normoglycemic rats with AP (AP), rats with T2DM (T2DM), and rats with T2DM and AP (T2DM+AP). T2DM was induced by streptozotocin administration combined with a high-fat diet.AP has been induced on the first right molar lower jaw by exposing the pulp to the oral environment for 4 weeks. The animals were sacrificed by cervical dislocation, whilst hearts were isolated and perfused according to the Langendorff technique and analyzedpathohistologicaly.Biomarkers of oxidative stress were determined in cardiac tissue homogenate. The hemimandibles were analyzed radiographically.

Results:The values of systolic and diastolic left ventricular pressure in the T2DM+AP group were significantly increased at all CPPs compared to the CTRL, AP, and T2DM groups ($p<0.05$).The levels of index of lipid peroxidationin cardiac tissue homogenate were significantly increased, while the superoxide dismutase and catalase were significantly decreased in the T2DM+AP group compared to AP and CTRL groups($p<0.05$).The radiographic AP area was significantly largerin the T2DM+AP group compared to the AP group ($p<0.05$). Disrupted glycoregulation was observed in the T2DM+AP group compared to the T2DM, AP, and CTRL groups.

Conclusion:AP was associated with impaired cardiodynamics, disturbedcardiac oxidative stress and cardiac pathologic changes in diabetic conditions.Diabetes was associated with an increase in the AP radiographic area.

Medicinal Mushrooms and Type 2 Diabetes: Mechanistic Insights, Translational Evidence, and Clinical Caveats

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Content:

Introduction

Medicinal mushrooms have emerged as multi-target metabolic modulators with relevance for type 2 diabetes (T2D). Their polysaccharides, triterpenoids, phenolics, sterols, and peptide complexes influence insulin signaling, oxidative stress, inflammation, lipid metabolism, and gut microbiota. Although preclinical evidence is extensive, translational progress remains fragmented, and clinical validation is still limited.

Methodology

In vivo experiments were conducted using T. versicolor, P. cocos, H. erinaceus, and C. pulverulentus, focusing on glycemic control, insulin sensitivity, lipid metabolism, antioxidant defenses, inflammatory signaling, and nitric oxide–related pathways. Mechanistic endpoints included fasting glucose, glucose tolerance, lipid profile, and activities of SOD and CAT. Results

Our experimental data highlighted species-specific metabolic benefits. T. versicolor polysaccharide–phenolic complexes significantly reduced oxidative damage and improved insulin sensitivity, with marked activation of antioxidant enzymes and suppression of pro-inflammatory cytokines. H. erinaceus lowered fasting glucose and improved glucose tolerance, suggesting potent glycemic modulation beyond its neurotrophic profile. P. cocos enhanced redox balance and lipid metabolism, while C. pulverulentus demonstrated strong antioxidant activity with secondary improvements in glycemic indices.

Conclusion

Medicinal mushrooms exert robust, multi-target metabolic effects in T2D through convergent pathways integrating insulin signaling, oxidative stress, inflammation, and microbiota-driven mechanisms. Preclinical evidence is mechanistically coherent, and emerging clinical findings support translational potential. However, variability in species, extraction methods, dosing, and study design remains a major caveat. Standardization, biomarker-driven mechanistic trials, and controlled clinical studies are essential to advance medicinal mushrooms from promising metabolic modulators to validated therapeutic adjuncts in T2D management.

Non-linear dynamics and theory of chaos in cardiovascular medicine

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Content:

The cardiovascular system is a complex dynamic network characterized by continuous interactions among autonomic, hemodynamic, electrophysiological, and neurohumoral regulatory mechanisms. Normal cardiovascular function is neither strictly periodic nor random but exhibits complex fluctuations with fractal and nonlinear properties that can be described using concepts derived from nonlinear dynamics and chaos theory.

Heart rate variability (HRV) provides a unique non-invasive window into these complex regulatory mechanisms. Conventional time- and frequency-domain measures quantify the magnitude of variability but may not adequately characterize its organization and complexity. Nonlinear methods, including fractal dimension, detrended fluctuation analysis (DFA), approximate and sample entropy, and Poincaré plot analysis, provide complementary information on cardiovascular dynamics.

Our studies demonstrated significant alterations of nonlinear HRV characteristics in patients with coronary heart disease, arterial hypertension, heart failure, and stress-induced cardiomyopathy. Reduced short-term fractal scaling, decreased entropy, and altered fractal dimension indicate a loss of physiological complexity and adaptability associated with cardiovascular disease. Importantly, nonlinear abnormalities can also be detected in short-term ECG recordings and during dynamic conditions such as exercise testing.

These findings support the concept that cardiovascular disease is associated not only with changes in the magnitude of variability but also with disruption of the complex temporal organization of cardiovascular regulation. Integration of nonlinear biomarkers with conventional cardiovascular assessment and modern computational approaches may improve the detection of autonomic dysfunction and cardiovascular risk stratification. Nonlinear dynamics and chaos theory therefore provide a valuable framework for understanding cardiovascular regulation as a complex adaptive system and may contribute to more individualized cardiovascular medicine.

Two bioassays to comprehensibly characterize vascular ischemia/reperfusion damage

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Content:

Introduction: So far, infarct size resulting from cardiomyocyte injury was considered the main factor affecting patient prognosis after acute myocardial infarction. However, attention has turned to coronary circulation, as microvascular damage also determines patients' prognoses, independent of infarct size. The coronary (micro)vascular damage in response to ischemia/reperfusion (I/R) is manifold – endothelial dysfunction is one of the underlying mechanisms. Our aim was to establish reproducible bioassays reflecting vascular I/R injury to later characterize and address this damage. Since I/R injury occurs throughout all vascular beds, we utilized mesenteric vessels as they are comparable to coronary arterioles in receptor composition and vasomotor function.

Methodology: In two different bioassays, vascular I/R injury was induced by 60min of (simulated) ischemia followed by 10min (simulated) reperfusion or vessels were subjected to a respective time control (TC). In isolated rat mesenteric arterioles, isometric force development was recorded in the wire myograph. After simulated I/R, endothelial functionality was assessed using serotonin (3x10-6mol/L) preconstriction and carbachol-induced endothelium-dependent vasodilation (1x10-9mol/L–1x10-4mol/L). Mesentery flow and reactive hyperemia as measure of microvascular function and endothelial reactivity was quantified in an isolated perfused rat mesentery before and after ischemia.

Results: (Simulated) I/R reduced endothelium-dependent vasodilation in both bioassays: in the isolated rat mesenteric arterioles the dose-response to carbachol was shifted right. In the isolated perfused rat mesentery, reactive hyperemia was reduced.

Conclusion: We simulate the vascular I/R injury in two different bioassays, in both endothelial-dependent vasodilation is reduced. The wire myograph is a high-throughput system that allows characterization of the underlying mechanisms of endothelial dysfunction and the establishment of treatment strategies to counteract it. The isolated, perfused rat mesentery, however, more accurately reflects in vivo conditions and allows for follow-up functional analyses, i.e. intracellular signaling pathways and mitochondrial function. In this setting, blood perfusion may also enable the investigation of potential humoral vasculoprotective signaling pathways. In sum: we here build the basis to characterize the mechanisms of vascular damage and protection from it.

Activation of adrenergic and nicotinic/muscarinic receptors induces the release of cardioprotective humoral factors from the spleen

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Content:

Introduction: The spleen's protective role in acute myocardial infarction was recently characterized. Vagal activation via remote conditioning releases spleen-derived circulating cardioprotective factors in pigs and humans, which reduce infarct size (IS) when transferred to isolated perfused rat hearts after global ischemia/reperfusion injury (GI/R). Different intra-splenic pathways activated by neuronal signaling have been described, however, it is unclear which, if any, of these are involved in cardioprotection. The acetylcholine analogon carbachol (CA) triggers the release of cardioprotective factors in the in vitro setting of isolated perfused rat spleens. However, such CAadministration does not fully reflect the broad spectrum of known neuronal-activated splenic signaling pathways: noradrenergic nerve activation and consecutive norepinephrine (NE) release activate splenic T-cells via β2-adrenergic receptors, inducing acetylcholine release; acetylcholine then activates α7-nicotinic acetylcholine receptors on macrophages which ultimately reduces pro-inflammatory cytokine release. We now aimed to identify if this splenic cholinergic anti-inflammatory pathway is also involved in the release of cardioprotective factors.
Methodology: Isolated rat spleens and hearts were buffer-perfused at constant pressure. Spleens were either infused with saline, NE (50nmol/l) or CA(500pmol/l) with or without β-receptor antagonist propranolol (4nmol/l; PP), nicotinic receptor antagonist α-bungarotoxin (100pmol; BTX) or muscarinic receptor antagonist atropine (100pmol/l; AT). Collected splenic effluate (SEff) was infused into isolated hearts before being subjected to 30min global ischemia and 120min reperfusion. IS was demarcated by triphenyl tetrazolium chloride and calculated as percent of ventricular mass.
Results: With SEff(NE) and SEff(CA), IS was reduced to 21±5% and 20±5% compared to SEff(saline) (29±5%). Both AT and BTX abrogated these protective effects (SEff(NE+AT): 33±3%, SEff(NE+BTX): 35±3%, SEff(CA+AT): 40±3%, SEff(CA+BTX): 41±2%) while PP only abolished the effect of NE but not of CA(SEff(NE+PP): 33±3%, SEff(CA+PP): 25±3%). Conclusion: We translate the cholinergic anti-inflammatory pathway to the cardioprotective context: β2-adrenergic and acetylcholine receptors are involved in the splenic release of humoral cardioprotective factors. Therefore, future research must aim to identify the involved cell subtypes as well as the mediators that are being released.

Mechanism for stem cells to rejuvenate aged tissue – Marrow Cross-Talk with Organs

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Content:

Aging is associated with progressive deterioration of tissue function and a decline in endogenous repair and regenerative capacity. Although stem cell therapy has traditionally focused on replacing damaged cells within individual organs, increasing evidence suggests that stem cells may regulate tissue repair through systemic cross-talk between the bone marrow and peripheral organs. We propose that the bone marrow functions not only as a source of hematopoietic and progenitor cells, but also as a central regulator of tissue homeostasis, repair, and rejuvenation.

Our studies demonstrate that aging significantly impairs bone marrow stem cell number and function, reducing their capacity for tissue repair. Transplantation of young bone marrow stem cells into aged recipients can reconstruct the aged bone marrow niche, establish sustained young-cell populations, and enhance the recruitment of bone marrow-derived cells to injured or aged tissues. Importantly, the beneficial effects extend beyond the bone marrow to multiple organs, including the heart and brain, supporting the existence of a functional marrow–organ axis.

Mechanistically, young bone marrow-derived cells may rejuvenate aged tissues through multiple complementary pathways, including cell homing and tissue repopulation, modulation of inflammation and immune responses, restoration of vascular and stromal microenvironments, and paracrine regulation of resident cells. These mechanisms can improve the regenerative competence of aged tissues without requiring complete replacement of aged parenchymal cells. Our ongoing studies further investigate the identity and fate of marrow-derived cells within target organs and define the molecular signals governing bidirectional communication between bone marrow and aged tissues.

Together, these findings support a new paradigm in regenerative medicine: rejuvenating the bone marrow may promote systemic organ rejuvenation through marrow–organ cross-talk, providing a potential strategy to enhance tissue repair, preserve organ function, and improve resilience to injury during aging.

Remodeling of ipsilateral ulnar artery after radial artery harvesting for coronary artery bypass graft

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Content:
There are controversies in the literature on the blood supply to the forearm after surgical removal of the radial artery in coronary artery bypass grafting (CABG). The objective was to investigate the arterial remodeling of the ulnar artery after the removal of the radial artery in myocardial revascularization by means of ultrasound examination with color Doppler in the preand post-operative periods. This paper describes an observational prospective study of the remodeling of the left brachial and ulnar arteries (donor arm) in 103 right-handed non-consecutive adult patients undergoing CABG with removal of the ipsilateral radial artery using the color Doppler ultrasound examination. In the ulnar artery, a significant increase ($P < 0.05$) was seen in the following measurements: lumen diameter by 13%, lumen area by 26%, peak systolic flow by 40%, and average flow by 46%. Intima-media thickness measured in the ulnar artery did not show a statistically significant difference ($P = 0.22$), except in diabetic patients ($P = 0.007$). We conclude that the ulnar artery undergoes positive physiological remodeling, adapting to the new requirements of chronic increase in flow after the ipsilateral removal of the radial artery to serve as a graft in CABG. There was no evidence of increased intima-media thickness, except in diabetic patients.

Sodium-Glucose Cotransporter 2 Inhibitors Reduce MAO Expression and Oxidative Stress in Human Adipose Tissue

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Content:

Background:
The global prevalence of the obesity/overweight has been constantly raising over the past decades. Adipose tissue expansion impairs redox signaling and promotes oxidative stress but the sources of reactive oxygen species (ROS) are far from being elucidated. Monoamine oxidase (MAO) with 2 isoforms, MAO-Aand MAO-B, is a mitochondrial enzyme whose expression increases with ageing and comorbidities that has emerged as a relevant source of ROS in the cardiovascular system. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) provide cardiovascular protection in the setting of obesity via pleiotropic, partially elucidated beneficial effects, among which the antioxidant one is largely investigated.
Methods: Samples of visceral and subcutaneous adipose tissue (VAT, SAT) harvested from a pilot group of obese patients with indication of elective abdominal surgery were incubated (12 h) with angiotensin II (Ang II, 100 nM) in the presence vs. absence of empagliflozin (EMPA) or dapagliflozin (DAPA) in a concentration relevant for the clinical setting (1 μM). MAO expression (assessed by qPCR and immune-fluorescence) and ROS production hydrogen peroxide (assessed by FOX assay and superoxide assessed by DHE staining) and were evaluated ex vivo.
Results: VAT samples showed higher ROS level and MAO expression at baseline as compared to SAT ones. Ang II elicited increased MAO expression and ROS production in both types of adipose tissue, but the pro-oxidant effect was more important in VAT. Acute incubation with either EMPAor DAPAsignificantly decreased MAO expression and oxidative stress in all samples of human adipose tissue.
Conclusions: In human adipose tissue, especially visceral fat, Ang II stimulates MAO upregulation and oxidative stress. Acute, ex vivo incubation with a relevant concentration of SGLT2 inhibitors prevented MAO increase and mitigated ROS production in presence or absence of Ang II, demonstrating a putative protective role against adipose tissue oxidative dysfunction in obese patients.

Monoamine Oxidases As Emerging Targets for Vascular Protection

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Content:

Oxidative stress is a central pathomechanism underlying vascular dysfunction and remodeling in chronic cardiovascular and metabolic pathologies. Monoamine oxidases (MAO) are mitochondrial flavoenzymes with two isoforms, MAO-Aand MAO-B, traditionally recognized for their role in the catabolism of catecholamines and serotonin. In the past decades, MAOs have emerged as important sources of reactive oxygen species (ROS), particularly hydrogen peroxide, significantly contributing to the vascular oxidative stress. Their involvement appears to extend across both arterial and venous vascular beds, suggesting a broader role in vascular pathophysiology than previously appreciated. Several studies in isolated murine arteries have demonstrated upregulation of MAO-Aand MAO-B in the vascular walls associated with enhanced ROS generation and impaired endothelium-dependent vasorelaxation. Pharmacological inhibition of MAOs reduced hydrogen peroxide production in aortic rings and improved endothelial function, supporting a causal contribution of MAO-derived oxidative stress to vascular dysfunction. In human vascular tissues, increased MAO expression has also been observed in association with obesity and inflammatory activation. In particular, mesenteric arteries from obese individuals exhibited enhanced MAO expression, increased ROS generation, and impaired vascular reactivity, while ex vivo inhibition of MAOs attenuated oxidative stress and improved endothelial responses. Furthermore, stimulation with interleukin-6 increased MAO expression in human arterial bed, linking MAO-dependent oxidative pathways to inflammatory signaling.

Evidence from venous vessels further supports the concept that MAOs may contribute to oxidative stress beyond the arterial circulation. Because veins are exposed to inflammatory and hemodynamic alterations in pathological settings, e.g. in chronic venous disease, increased MAO activity may promote local ROS accumulation and endothelial dysfunction.

Collectively, these findings identify MAOs as inducible enzymatic sources of oxidative stress in both arteries and veins in diseases characterized by chronic inflammation and highlight MAO inhibition as a potential adjunctive therapeutic strategy for addressing vascular complications associated with cardiometabolic diseases.

Can pyridostigmine prevent heart failure after isoprenaline-induced acute myocardial injury in rats?

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Content:

Background/Aim: Heart failure (HF) affects more than 60 million people worldwide and imposes a substantial clinical and economic burden. Less than 60% of patients diagnosed with HF survive beyond 5 years. The role of cholinergic potentiation in the treatment of HF remains unclear. This study aimed to determine whether early treatment with pyridostigmine could prevent the development of HF following acute myocardial injury in rats.

Methods HF was induced in albino Wistar rats by subcutaneous administration of isoprenaline (5 mg/kg) for 7 consecutive days. Control groups received saline (1 mL/kg subcutaneously) for 7 days. Pyridostigmine was administered either immediately after isoprenaline treatment (22 mg/kg orally in tap water for 6 weeks) or after HF had developed (starting at week 4 and continuing for 2 weeks). The corresponding control groups received tap water only. Cardiac ultrasound and electrocardiography were performed at weeks 0, 1, 5, and 7. Histopathological and biochemical analyses were conducted after sacrifice at week 7.

Results: Early pyridostigmine treatment significantly prevented the development of HF, as demonstrated by reduced left ventricular dilatation (LVIDs, LVIDd, EDV, and ESV), preserved systolic function (ejection fraction; $p < 0.001$ vs the isoprenaline group), and preservation of myocardial structure, with a significant reduction in fibrosis ($p < 0.05$). In rats with established HF, pyridostigmine prevented further disease progression observed in untreated animals. It also improved cardiac function, as evidenced by an increased ejection fraction ($p < 0.001$ vs the isoprenaline group), and attenuated the development of myocardial fibrosis.

Conclusion: Pyridostigmine treatment significantly improved cardiac function following isoprenaline-induced myocardial injury, both when initiated early and after HF had developed. Early treatment was more effective.

Diabetes-Induced Intestinal Inflammation: A Potential Link to Cardiovascular Risk

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Content:

Background and Aim: Cardiovascular disease is a major cause of morbidity and mortality in type 2 diabetes (T2D). Emerging evidence suggests that intestinal inflammation and barrier disruption may contribute to cardiovascular risk by promoting systemic inflammation. This study investigated structural and inflammatory changes in the small and large intestines in experimental T2D, focusing on macrophage activation and pro-inflammatory mediators relevant to the gut–cardiovascular axis.

Materials and Methods: Twenty-two Sprague–Dawley rats were divided into four groups: female control (n=5), male control (n=5), female diabetic (n=6), and male diabetic (n=6). T2D was induced by a high-fat diet with repeated low-dose streptozotocin injections and confirmed by blood glucose >250 mg/dL. Two weeks after diabetes confirmation, intestinal tissues were collected. Histopathology was assessed by hematoxylin and eosin staining. Gene expression of CD68, inducible nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) was quantified by RT-qPCR, while protein expression was evaluated by immunohistochemistry. Group differences were analyzed by one-way ANOVA with Tukey's post hoc test ($p<0.05$).

Results: Diabetic rats showed marked alterations in intestinal regions, including epithelial desquamation, villous shortening and atrophy, reduced goblet cell numbers, inflammatory infiltration, and submucosal edema. Diabetes was associated with increased gene and protein expression of CD68, iNOS, TNF-α, and IL-6, although the magnitude and significance varied by sex, intestinal region, and marker. Female diabetic rats generally exhibited a more pronounced inflammatory response than males. These findings indicate macrophage accumulation, pro-inflammatory activation, and cytokine-associated mucosal injury in experimental T2D.

Conclusions: Experimental T2D induces substantial structural and inflammatory intestinal changes characterized by macrophage activation and increased expression of pro-inflammatory mediators. The stronger response in female rats suggests sex-related differences in susceptibility to diabetes-associated intestinal inflammation. Although the gut–cardiovascular axis was not directly assessed, the observed mucosal injury and inflammatory activation support the hypothesis that intestinal inflammation may contribute to systemic inflammation and cardiovascular risk in diabetes.
Further studies are needed to clarify this mechanistic link.

Calcium Recirculation Fraction – A revisitation with potential translational applicability

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Content:

SERCA2a stimulators are a promising tool for heart failure treatment; their large-scale development might profit from the availability of tests for the screening of new molecules. The Ca2+ recirculation fraction (RF) is the fraction of the Ca2+ transient recycled within the myocyte at each heartbeat, largely reflecting competition between SERCA2a-dependent reuptake and NCX-dependent extrusion. We have devised a protocol, based on optical cytosolic Ca2+ measurements in mouse myocytes, yielding several parameters reflecting RF. We have tested the effect of selective modulation of SERCA2a, Na/Ca exchanger and Na/K pump on each parameter, thus defining the respective roles of the main effectors in determining RF. Moreover, we have applied ROC analysis to the results to assess the sensitivity/specificity ratio of the measured parameters in detecting modulation of each effector and to assess optimal cutoff values. This has identified patterns suitable for first-line detection of SERCA2a modulation and its discrimination from that of the other effectors. Since it can be applied to simultaneous recordings from many cells, the method is suitable for high-throughput screening of molecules.

RIP3 INHIBITION ATTENUATES MITOCHONDRIAL DNA OXIDATIVE DAMAGE AND PRESERVES MITOCHONDRIAL HOMEOSTASIS IN EXPERIMENTAL POST-ISCHEMIC HEART FAILURE

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Content:

Introduction: Necroptosis, a form of necrosis-like cell death, has been shown to underlie the pathomechanisms of heart failure (HF) following myocardial infarction (MI). However, the link between necroptosis and mitochondria remains poorly understood.
Objective: To evaluate how pharmacological inhibition of receptor-interacting protein kinase 3 (RIP3), a key necroptotic signalling molecule, affects mitochondrial homeostasis and integrity in the context of necroptosis in experimental post-ischemic HF.
Methods: Male Wistar rats underwent 1-hour coronary artery occlusion followed by 1-week reperfusion. Left ventricular tissue was harvested from sham, infarcted (HFi), and non-infarcted (HFni) regions. RIP3 was inhibited using GSK'872. Protein and gene expressions were analyzed via immunoblotting and qRT-PCR; mitochondrial DNAcopy number (mtDNAcn) and oxidized mtDNA(ox-mtDNA) were determined by qPCR.
Results: Total and phosphorylated RIP3 and mixed lineage kinase domain-like pseudokinase (MLKL), key necroptotic mediators, were increased in failing hearts, together with reduced mtDNAcn, indicating impaired mitochondrial function. Phosphorylated MLKL negatively correlated with mtDNAcn, suggesting a link between necroptotic activation and mitochondrial deterioration. RIP3 inhibition mitigated ox-mtDNAin HFni. Monomeric voltage-dependent anion channel proteins (VDAC1,2,3) decreased in HFi, whereas dimeric VDAC1,2,3, associated with mitochondrial pore formation and dysfunction, tended to decrease following RIP3 inhibition. HF altered the gene expression of mitochondrial calcium uniporter (MCU) complex, permeability transition pore (mPTP), ATP synthase, and calcium-handling. In HFi, RIP3 inhibition modulated mPTP-related genes by attenuating Slc25a3 and enhancing Ppif expression. Mitogenic and mitophagic genes were upregulated in HF groups, whereas RIP3 inhibition selectively reduced Tfam, a regulator of mitochondrial DNA replication and transcription, in HFi.
Conclusion: Antinecroptotic RIP3 inhibition attenuates mtDNAoxidative damage and modulates mitochondrial-channel gene expression in post-MI HF. Decreased VDAC1,2,3 dimers and ox-mtDNAsuggest that suppressing RIP3-dependent signaling preserves mitochondrial integrity by limiting membrane destabilization and oxidative injury, highlighting necroptosis as a promising therapeutic target in HF management.

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Distinct Autonomic Characteristics of Syncope Patients with Orthostatic Hypertension

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Content:

Background/Introduction

Syncope is a common clinical condition most frequently related to reflex mechanisms characterised by transient hypotension and/or bradycardia. In contrast, orthostatic hypertension (OHT) is an underrecognized condition associated with increased cardiovascular and cerebrovascular risk. Excessive pressor responses during orthostasis may represent a distinct haemodynamic phenotype contributing to orthostatic intolerance.

Purpose

To assess autonomic nervous system function in patients with syncope according to the presence of OHT during head-up tilt testing (HUTT) and to identify autonomic and haemodynamic predictors of this response.

Methods

Atotal of 723 patients with ≥1 syncope episode during the previous 12 months were included; 90 (12.4%) developed OHT during HUTT. OHT was defined as a sustained blood pressure increase to ≥140/90 mmHg lasting ≥1 minute during HUTT. All patients underwent Valsalva manoeuvre, handgrip test (HGT), heart rate response to deep breathing (HRB), 5-minute heart rate variability analysis, and resting blood pressure variability assessment. Binary logistic regression identified independent predictors of OHT, including a model adjusted for pre-existing hypertension.

Results

Patients with OHT were older (48.7±15.4 vs. 45.1±15.5 years, p=.038), more frequently male, and more often had pre-existing hypertension. They also more frequently exhibited normal/borderline HGT responses, abnormal HRB, and extreme or low resting blood pressure variability. Resting HRV indices (pNN50, total power, very low- and high-frequency power) were lower in the OHT group. In multivariable analysis, abnormal HRB (OR 2.517, p=.005), extreme resting blood pressure variability (OR 20.839, p=.009), and low resting blood pressure variability (OR 3.629, p=.005) were independently associated with OHT, whereas abnormal HGT (OR .134, p=.016) and female sex (OR .518, p=.012) were inversely associated. These findings remained significant after adjustment for pre-existing hypertension, which was not an independent predictor (OR 1.643, p=.075).

Conclusion

Asubset of patients with syncope develops OHT during orthostatic challenge. This phenotype is more common in men and patients with pre-existing hypertension and is characterised by abnormal resting blood pressure regulation, preserved sympathetic reactivity, and impaired cardiovagal modulation, independently of pre-existing hypertension.

Significance of Immunohistochemical Detection of Hydroxyproline as a Potential Marker of Myocardial Fibrosis in an Experimental Wistar Rat Model

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Content:

Introduction

Myocardial fibrosis is a complex process characterized by excessive extracellular matrix deposition and collagen accumulation, leading to structural remodeling of the myocardium. Hydroxyproline, a major component of collagen, is widely used as a marker of connective tissue metabolism and fibrosis. However, biochemical determination of total hydroxyproline may yield falsely elevated values, as hydroxyproline-rich collagen fragments can accumulate intracellularly following phagocytosis. This study aimed to evaluate immunohistochemical (IHC) detection of hydroxyproline as a potential marker of fibrotic changes in experimentally injured myocardium.

Methodology

Paraffin-embedded heart tissue samples from 24 male Wistar albino rats were analyzed, including a control group (n=9) and an isoprenaline-treated group (n=15). Myocardial injury was induced by subcutaneous administration of isoprenaline (ISO). Hematoxylin and eosin staining was used for general morphological assessment and Masson's trichrome staining for collagen deposition visualization. IHC staining was performed for hydroxyproline and α-smooth muscle actin (α-SMA), a marker of activated myofibroblasts, using HRP/DAB detection. Integrated Optical Density (IOD) for hydroxyproline was evaluated between control and ISO-treated group.

Results

R version 4.2.3 was used for statistical analysis. The normality of the numerical data distribution was assessed using skewness and kurtosis values and the Shapiro–Wilk test. Differences between the two independent groups were analyzed using the independent-samples t-test (Student's t-test) when the data were normally distributed. Hydroxyproline IOD was significantly higher in the ISO-treated group than in the control group (31,699.73 ± 7,491.23 vs. 11,102.05 ± 4,924.67, respectively; $p < 0.001$). Increased hydroxyproline expression was particularly observed in areas exhibiting morphological changes and increased collagen deposition.

Conclusion

The findings suggest that IHC detection of hydroxyproline may be a useful approach for the assessment of myocardial fibrosis. Its localization within areas of collagen deposition and its association with α-SMAexpression may provide complementary information and support its potential as a marker of fibrosis in experimentally injured myocardium.

CORRELATION BETWEEN PERIAPICAL LESION AND HEART FUNCTION IN DIABETIC RATS WITH TYPE 2 DIABETES MELLITUS

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Content:

Introduction: This study aimed to investigate the possible correlation among periapical lesions (PA), cardiac function, and oxidative stress (OS) in rats with type 2 diabetes mellitus (T2DM).

Methodology: Forty-eight (Wistar albino, male, 6 weeks old) rats were randomized into four equal groups: control healthy (CTRL), normoglycemic with PA(PA), T2DM, and T2DM with PA(T2DM+PA). T2DM was induced by streptozotocin and a high-fat diet. AP was induced by pulp exposure to the oral environment for 4 weeks and analyzed using pathophysiological and histomorphometric methods. In the blood samples, insulin and glucose were established. Ex vivo cardiac function was assessed by the Langendorff technique. OS was determined spectrophotometrically in the coronary venous effluent. Results: Impaired glycoregulation was observed in the T2DM+PAgroup compared to the T2DM, AP, and CTRL groups.

Pathohistological analyses demonstrated that the size of the apical lesion and the extent of inflammatory infiltrate were significantly greater in the T2DM+PAgroup than in the PAgroup ($p<0.05$). The values of the maximum rate of left ventricular pressure development were significantly higher in the T2DM+PAgroup compared with the CTRL, PA, and T2DM groups ($p<0.05$). The values of the minimum rate of left ventricular pressure change were significantly decreased in the T2DM+AP group than in the CTRL, PA, and T2DM groups ($p<0.05$). The levels of superoxide anion radical in coronary venous effluent were statistically higher in the T2DM+PA, T2DM, and PAgroups compared to the CTRL group ($p<0.05$).

Conclusion: PAwas associated with increased glucose levels, impaired cardiac function, and disturbed cardiac OS in diabetic rats. Diabetes was related to an increased PAinflammatory infiltrate extension compared with nondiabetic conditions.

Neurocardiology and Biosignal Processing: A New Approach to Understanding Disease Pathogenesis

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Content:

Background: The autonomic nervous system (ANS) plays a key role in cardiovascular homeostasis and represents an important link between neural regulation and cardiovascular function. Advanced biosignal analysis may provide new insights into autonomic alterations involved in the development and progression of different diseases.

Objective: To describe an integrative approach combining neurocardiology and multimodal biosignal processing for improved understanding of disease pathogenesis.

Methods: Comprehensive autonomic assessment combines cardiovascular autonomic reflex tests, short- and long-term heart rate variability, continuous beat-to-beat blood pressure and hemodynamic monitoring, ambulatory blood pressure monitoring, and head-up tilt testing. Advanced computational methods enable integration of multiple physiological signals and recognition of complex patterns that may not be detected using conventional analyses.

Conceptual framework: Autonomic dysfunction may represent not only a consequence of disease but also an important component of its pathophysiology. Integration of cardiovascular and autonomic biosignals may reveal specific autonomic signatures and novel digital biomarkers reflecting alterations within the brain–heart–vascular axis.

Conclusion: The combination of neurocardiology and advanced biosignal processing offers a promising framework for investigating disease mechanisms and may contribute to improved phenotyping, risk stratification, and personalized diagnostic approaches.

Arrhythmogenic mutations of cardiac ryanodine receptor and their EC-coupling consequences

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Content:

Cardiac rhythm is initiated by electrical impulses generated in the sinoatrial node and propagated throughout the heart through a network of electrically coupled cardiomyocytes connected by connexin-containing gap junctions. Although inherited or acquired abnormalities in ion channels and conduction pathways are well-established causes of arrhythmia, defects in mechanisms regulating intracellular Ca^{2+} signaling have only recently been recognized as important contributors to cardiac rhythm disturbances.

Aberrant sarcoplasmic reticulum (SR) Ca^{2+} release can generate arrhythmogenic depolarizing currents through the Na^+/Ca^{2+} exchanger (NCX), which extrudes one Ca^{2+} ion in exchange for three Na^+ ions. This electrogenic activity can produce delayed afterdepolarizations (DADs) and, under some conditions, contribute to abnormal electrical activity. RyR2 mutations have traditionally been classified according to whether they increase or decrease channel activity or Ca^{2+} sensitivity. More than 200-point mutations in the ryanodine receptor (RyR2), the principal SR Ca^{2+} release channel in cardiomyocytes, have been identified to associate with cardiac arrhythmias. Using patient-derived cardiomyocytes and CRISPR/Cas9-engineered human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), we investigated how point mutations in specific domains of RyR2 alter Ca^{2+} signaling and electrophysiological function. Contrary to our expectation, mutations within the N- and C-terminal and central domains did not produce mutation-specific arrhythmogenic phenotype or pharmacological specificity. In sharp contrast, however, mutations affecting RyR2 Ca^{2+}-, caffeine-, and FKBP-binding sites produced distinct electrophysiological profiles and established causative nature of the mutations. Particularly surprising were the RyR2 Ca^{2+} binding mutations that despite completely suppressed Ca^{2+}-induced Ca^{2+} release (CICR) maintained their spontaneous beating by developing alternate remodeled Ca^{2+} signaling pathways. The most striking remodeling occurred following substitution of a single glutamate residue with glutamine (E→Q) within the RyR2 Ca^{2+}-binding site. Importantly, this compensatory response was heterogeneous among individual cells, where different cardiomyocytes engaged different remodeling pathways that included increased: IP_3 receptor expression, L-type Ca^{2+} current, or mitochondrial and nuclear Ca^{2+} signaling.

These findings reveal unexpected plasticity and redundancy in cardiac Ca^{2+} signaling. Beyond canonical RyR2-mediated CICR, cardiomyocytes appear to possess alternative Ca^{2+}-signaling mechanisms that can be recruited when RyR2 function is compromised. This adaptive remodeling may help preserve cardiac activity during disease but may also contribute to heterogeneous arrhythmogenic phenotypes and therapeutic responses.

Cardiovascular health in the age of obesity

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Content:

Obesity is a chronic, multifactorial disease which is increasingly recognised as an important contributor to cardiovascular disease, yet it remains suboptimally addressed compared with other modifiable cardiovascular risk factors. This presentation reviews the relationship between obesity and cardiovascular disease, highlighting its impact on major cardiovascular risk factors and manifestations.

Obesity is strongly associated with a range of diseases and conditions, including type 2 diabetes mellitus (T2DM), cardiovascular diseases such as hypertension and dyslipidaemia, as well as chronic obstructive pulmonary disease, cancer and mental health problems. 85% of individuals with T2DM have overweight or obesity, and obesity is associated with a threefold higher risk of developing T2DM. Excess body weight is associated with a higher incidence of hypertension, with data from Framingham Heart Study showing that the risk of hypertension is 78% higher in men and 65% higher in women with overweight or obesity. Obesity is also associated with at least double the risk of dyslipidaemia.

Obesity increases the risk of coronary heart disease by 81%, with a significant association persisting after adjustment for blood pressure and cholesterol levels. Obesity also increases the risk of atrial fibrillation, sudden cardiac death, venous thromboembolism and aortic valve stenosis, and is associated with a twofold higher risk of heart failure.

Collectively, epidemiological data demonstrate that obesity is associated with multiple cardiovascular risk factors and disease manifestations, underscoring the importance of recognising obesity as a major determinant of cardiovascular health. Given its high prevalence globally, obesity requires much stronger prevention and management efforts.

Early Cardiometabolic and Myocardial Alterations in a Rat Model of Prediabetes

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Content:

Introduction: Prediabetes is generally regarded as a benign metabolic stage, yet cardiovascular changes may begin well before overt diabetes. How the myocardium responds to mild hyperglycaemia, and through which mechanisms, remains unclear.
Aim: To examine whether hyperglycaemia within the prediabetic range is sufficient to trigger early cardiometabolic disturbances and cardiac remodelling in rats.
Methodology: Prediabetes was induced in male Wistar rats with low-dose streptozotocin (8 mg/kg/day i.p. for 5 days); controls received saline. Body mass and glycaemia were followed for 28 days. At sacrifice, we measured serum lipids, homocysteine, insulin, HOMA-IR, hepatic and renal markers, and cardiomyocyte injury markers (LDH, high-sensitivity troponin T). In cardiac tissue we assessed oxidative stress (MDA, CAT, SOD), LDH and malate dehydrogenase (MDH) isoform activities, matrix metalloproteinase-2 and -9 (MMP-2, MMP-9) activities, histomorphometry and proliferating cell nuclear antigen (PCNA) immunohistochemistry.
Results: Treated rats showed stable borderline hyperglycaemia (5.6-6.9 mmol/L), hyperinsulinaemia and insulin resistance, together with dyslipidaemia, raised homocysteine and mild liver and kidney impairment, while circulating cardiomyocyte injury markers were unchanged. Cardiac MDAwas significantly higher, whereas CAT and SOD activities were unaltered. Total LDH and MDH activities were similar between groups, but isoform distribution shifted: LDH1 decreased and LDH3/LDH4 increased, and peroxisomal MDH rose as cytosolic MDH fell, suggesting an early move toward anaerobic metabolism despite preserved overall enzymatic capacity. MMP-2 activity increased more than sevenfold and MMP-9 also rose significantly. Cardiomyocytes were hypertrophic, although wall thickness was maintained and no overt histological damage was seen. PCNApositivity was significantly lower in the left ventricle, right ventricle and septum, pointing to reduced proliferative and reparative capacity.
Conclusion: Prediabetes triggers coordinated early cardiac reprogramming, comprising extracellular matrix activation, metabolic isoenzyme shifts and weakened regenerative signalling, without overt myocardial injury. Subclinical cardiac remodelling thus emerges as an early and potentially targetable event in prediabetes.

DIFFERENTIAL EFFECTS OF ENALAPRIL AND LISINOPRIL ON ENDOTHELIAL FUNCTION DESPITE SIMILAR ANTIHYPERTENSIVE EFFICACY

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Content:

Introduction: Angiotensin-converting enzyme (ACE) inhibitors represent a cornerstone first-line therapeutic approach in the management of essential hypertension. Although current clinical management guidelines do not distinguish among individual agents within the ACE inhibitor drug class, substantial pharmacological variations exist, most prominently regarding tissue affinity and lipophilicity. Here, we evaluated whether drug lipophilicity influences cardiovascular efficacy and vascular parameters when utilized as an initial monotherapy in newly diagnosed hypertensive individuals in a
prospective comparative study.

Methodology: Cardiovascular and endothelial efficacy was prospectively evaluated in newly diagnosed hypertensive patients (n = 59) treated with hydrophilic lisinopril (8.3 ± 3.0 mg/day) or lipophilic enalapril (5.5 ± 2.3 mg/day). Brachial flow-mediated dilation (FMD) and carotid intima-media thickness were assessed by high-resolution sonography. Peripheral blood pressure was recorded by 24-hour ambulatory monitoring, and central hemodynamics (aortic blood pressure,
augmentation index, pulse wave velocity) were determined via arteriography before and after therapy.

Results: Both enalapril and lisinopril achieved equivalent efficacy in reducing systemic blood pressure across the patient cohort. In contrast to its antihypertensive effect, lisinopril failed to induce a significant improvement in arterial endothelial function as assessed by FMD. Conversely, the lipophilic agent enalapril elicited a pronounced improvement in endothelial function, which positively correlated with its blood-pressure-lowering capacity. No correlation between the reduction in
systolic blood pressure and changes in FMD was observed following lisinopril administration.

Conclusion: The blood-pressure-lowering capabilities of ACE inhibitors are largely independent of their chemical lipophilicity. In sharp contrast, vascular protective actions, particularly the restoration of arterial endothelial function, are intimately associated with lipophilicity, favoring lipophilic enalapril over hydrophilic lisinopril. The absence of correlation between pressure reduction and FMD improvement under lisinopril points toward divergent regulatory pathways governing vasodilation and endothelial restoration.

Disease-associated autoantibodies in abdominal aortic aneurysm: towards novel biomarkers

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Content:

Introduction: Abdominal aortic aneurysm (AAA), long regarded as degenerative and atherosclerosis-related, is increasingly recognised as an immune-mediated, possibly autoimmune, aortic-wall disorder. Rupture is often fatal, yet risk stratification relies almost solely on diameter, and no circulating biomarker reliably predicts growth or rupture. Routine systemic (non-tissue-specific) autoantibodies lack disease specificity and established prognostic value, whereas those targeting aortic-wall proteins may be more relevant but remain poorly characterised.

Objective: To determine the prevalence, tissue and isotype pattern, and clinical correlates of aortic tissue-reactive autoantibodies in AAA.

Methods: Sera of 60 AAA-repair patients (30 positive, 30 negative for systemic autoantibodies) and 36 non-aneurysmal controls with severe aortic stenosis (AS) were screened by Western blot (1:1,000) against pooled lysates of control aorta, aneurysmal wall from systemic-autoantibody-positive (NSA+) and -negative (NSA-) donors and, in 20 cases, myocardium. IgG- and IgM-reactive bands were identified by densitometry and ROUT outlier analysis and sized by molecular weight (MW). Findings were related to autoantibody status and perioperative laboratory data.

Results: Reflecting the abundance of tissue autoreactivity, 75% of AAAsera reacted with at least one aortic tissue. AAAsera recognised control aorta more often than AS sera (65% vs 22%, $p<0.001$; age/sex-adjusted OR 8.1, 95% CI 2.6-25.2).
Reactivity with aneurysmal tissue was lower (NSA+ 30%, NSA- 18%; both $p<0.001$ vs control aorta). Among the paired sera, myocardium was recognised less often than control aorta (40% vs 75%, $p=0.039$). IgG predominated and targeted higher-MW antigens (~70-80 kDa), whereas NSA- tissue was recognised mainly by IgM (~40-55 kDa); recurrent ~40, ~55 and ~80 kDa bands suggested shared targets. Tissue autoreactivity was largely independent of systemic autoantibody status and unrelated to CRP, IL-6, complement or laboratory values.

Discussion: AAApatients harbour a frequent, disease-associated humoral response to aortic-wall antigens, undetected by routine serology and unrelated to systemic inflammation. Lower aneurysmal reactivity may reflect immune-mediated antigen depletion, leaving open a causal role for this autoimmunity. This signature is a candidate biomarker; linking it to aneurysm growth and rupture and identifying its antigens are the next steps.

RIPC-mediated Cardioprotection in Indian ACS patients in a Randomized Sham Control Trial: Impact of Vitamin D

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Content:
Background: Remote ischemic preconditioning (RIPC) attenuates cardiac injury in NSTEMI patients undergoing PCI. Vitamin D (VD) deficiency is also associated with worse outcomes in acute coronary syndrome (ACS). This study for the first time, we evaluated the effect of RIPC in ACS patients receiving primary PCI and the beneficial effect of VD in the Indian cohort.

Methods: In this prospective study, 180 ACS patients were randomized to allocate either RIPC (Before PCI, upper limb underwent 4-cycles of 5-minute ischemia-reperfusion) or a Sham Control group (no RIPC). Myocardial injury and inflammatory markers were assessed at baseline and 24 hours post-PCI. Cardiac parameters were evaluated by echocardiography along with major adverse cardiovascular events (MACE) 30 days after PCI.

Results: Baseline characteristics and VD status were comparable between groups, with a high prevalence of VD deficiency. Post 24 hours, RIPC significantly reduced myocardial injury markers (i.e. Troponin-I, CK-MB, LDH, and MLC-1; all $p < 0.05$) and inflammatory markers (IL-8 and IL-33) and anti-inflammatory IL-10 increased ($p < 0.05$). In subgroup analysis, we observed that this beneficial effect of RIPC was depend on serum level of VD. Patients with sufficient VD (>30 ng/mL) had lower cardiac injury (CK-MB, LDH, WBCHO) and inflammatory markers (IL-33, IL-8, CRP) than those having serum level of VD <30 ng/mL subjected to RIPC. Moreover, the basal levels of cardiac injury and inflammatory markers were significantly higher in VD deficient patients. However, the echocardiographic assessment showed non-significant improvements in cardiac parameters, such as LVEF, ESV, EDV, and WMSI, along with MACE in the RIPC arm compared to the control arm.

Conclusion: RIPC attenuates myocardial injury and favorably modulates inflammatory responses in ACS patients undergoing PCI. The cardioprotective and anti-inflammatory effect of RIPC in ACS patients undergoing PCI is influenced by serum level of VD, suggesting its role as an important modifying factor.

TESTING THE ANTIOXIDANT ACTIVITY OF CURCUMIN IN AN ANIMAL MODEL OF CARDIOTOXICITY IN WISTAR ALBINO RATS

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Content:

Introduction: The use of curcumin may have a protective effect due to the manifestation of anti-inflammatory activity and antioxidant protection in the initial stages of cardiotoxicity, and the use of curcumin before the induction of cardiotoxicity significantly delays the development of more severe forms of heart dysfunction and the onset of an inflammatory response through antioxidant activity. The general aim of the study would be to test the antioxidant activity of curcumin in an animal model of doxorubicin-induced cardiotoxicity. In addition, to examine the potential relationship between oxidative stress, cardiac function and the use of curcumin in rats treated with doxorubicin as a widely used agent.

Methods: The study will include 48 male Wistar Albino rats, average age 8 weeks and body weight 250±20 grams. Experimental animals will be divided into 4 groups (Control group, Curcumin group, Doxorubicin group and Curcumin+Doxorubicin group) depending on the agent used. During the four-week treatment with curcumin, the effects of this supplement on systemic oxidative stress in the presence and absence of chemotherapy will be examined.

Results: Given the widespread use of doxorubicin not only as an anticancer drug but also as an immunosuppressant, for the first time a study should provide answers on the topic of curcumin's efficacy in terms of heart protection and delaying early cardiotoxicity due to therapeutic doses of antineoplastics in a previously healthy heart.

Conclusion: The positive results of this study will contribute to the development of new therapeutic modalities and the application of appropriate adjuvant antioxidant therapy with the aim of modulating oxidative stress and cardiac function in patients undergoing antineoplastic and immunosuppressive therapy.

Exercise Training in Cardiovascular Patients: Current Perspectives and Clinical Importance

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Content:

Exercise training has become an integral component of contemporary cardiovascular prevention and rehabilitation. Current evidence supports its use, with appropriate individualization, in virtually all major groups of patients with cardiovascular disease. Among these populations, the most extensive evidence is available for patients with coronary artery disease and heart failure, in whom structured exercise training improves functional capacity, quality of life, cardiovascular risk profiles, and clinical outcomes. Consequently, exercise-based cardiac rehabilitation is strongly recommended as part of comprehensive secondary prevention and long-term disease management.

Aerobic exercise remains the cornerstone of exercise prescription in cardiovascular patients, with moderate-intensity continuous training considered the gold standard. Higher-intensity and interval-based protocols may provide additional improvements in cardiorespiratory fitness in appropriately selected and clinically stable patients. Nevertheless, contemporary recommendations increasingly emphasize the importance of resistance training. Once considered primarily an adjunct to aerobic exercise, resistance training is now recognized as an important component of comprehensive cardiac rehabilitation because of its beneficial effects on muscular strength, functional independence, body composition, metabolic health, and overall physical performance. Combined aerobic and resistance training may therefore provide broader benefits than either modality alone, particularly in older, frail, or obese patients with cardiovascular disease.

Exercise prescription should be individualized according to the underlying cardiovascular condition, clinical stability, functional capacity, comorbidities, symptoms, and individual risk. Appropriate assessment and progression of training are essential to maximize benefits while maintaining safety. Future research should further define optimal training modalities, intensity, and exercise volume for specific cardiovascular populations and support the implementation of individualized exercise programs in routine clinical practice.

EMPAGLIFLOZIN ATTENUATES GLUCOLIPOTOXICITY INDUCED ENDOTHELIAL DYSFUNCTION THROUGH MODULATION OF OXIDATIVE STRESS AND MITOCHONDRIAL FUNCTION

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Introduction: Cardiovascular complications are a major cause of morbidity and mortality in type 2 diabetes mellitus (T2DM). In T2DM, chronic hyperglycemia and elevated circulating fatty acids create a glucolipotoxic environment that contributes to endothelial dysfunction through oxidative stress and mitochondrial impairment. Although empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, provides cardiovascular benefits beyond glycemic control, its direct effects on endothelial cells under glucolipotoxic conditions remain incompletely understood. This study investigated the effects of empagliflozin on cell viability, mitochondrial membrane potential, and redox homeostasis in human umbilical vein endothelial cells (HUVECs) exposed to combined high-glucose and high-palmitate stress.

Methodology: HUVECs were pretreated with empagliflozin (0.1, 1, 10, 50, and 100 μM) for 2 h, followed by exposure to high glucose and high palmitic acid for 16 h. Cell viability was assessed by MTT assay. Mitochondrial membrane potential was evaluated by JC-1 staining and flow cytometry. Intracellular ROS-associated fluorescence was assessed using H2DCFDA by confocal microscopy, and mitochondrial superoxide production was evaluated using MitoSOX by flow cytometry.

Results: Glucolipotoxic exposure markedly reduced HUVEC viability, whereas empagliflozin partially restored cell viability, with the greatest protection observed at lower concentrations. Glucolipotoxicity increased the JC-1 red/green fluorescence ratio, consistent with mitochondrial hyperpolarization. Empagliflozin attenuated this alteration and shifted the ratio toward control levels. Glucolipotoxic exposure also disturbed cellular ROS-related fluorescence, while empagliflozin partially normalized the altered redox response.

Conclusion: Empagliflozin protects endothelial cells against glucolipotoxic injury. Its cytoprotective effect is accompanied by attenuation of mitochondrial hyperpolarization and improvement of the disturbed cellular redox response. These findings suggest that modulation of mitochondrial function and redox homeostasis may contribute to the direct endothelial protective effects of empagliflozin and support a potential role in limiting diabetes-associated endothelial dysfunction.

GLP-1 agonist mediated mitochondrial zinc redistribution in insulin resistant senescence model

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Content:

Aging and insulin resistance are intertwined factors in the development of metabolic diseases such as type 2 diabetes and cardiovascular disorders. Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has shown promising cardioprotective effects in preclinical and clinical studies of metabolic disease; however, its role in insulin-resistant aged-like cellular systems remains incompletely understood. This study aimed to investigate the effects of liraglutide on intracellular zinc homeostasis, as well as its modulation of oxidative stress, mitochondrial function, and endoplasmic reticulum (ER) stress in a novel insulin-resistant senescent model.

Insulin resistance and cellular senescence were confirmed by reduced glucose uptake, increased β-galactosidase staining, and elevated phosphorylated H2A.X (Ser139) levels following 24 h co-incubation with bovine serum albumin (BSA)-conjugated palmitic acid (PA; 50 µM) and 278 mM D-galactose in human AC16 cells. Notably, liraglutide improved glucose uptake in the senescent model, indicating enhanced metabolic function. In parallel, intracellular zinc dynamics were temporally synchronized with liraglutide-induced metabolic responses, suggesting coordinated regulation of zinc homeostasis during treatment. In chronic treatments, liraglutide significantly increased cytosolic zinc levels. Consistently, analyses using ER- and mitochondria-targeted zinc sensors demonstrated a decrease in mitochondrial zinc content following liraglutide administration but not in ER, supporting a redistribution of zinc from mitochondrial compartments toward the cytosol may likely to regulate glucose metabolism. Overall, these results suggest that liraglutide improves glucose uptake while concurrently reshaping intracellular zinc distribution, particularly by increasing cytosolic zinc and reducing mitochondrial zinc, which may contribute to its metabolic effects in senescent cells.

QT Interval Prolongation as a Convergent Phenotype of Drug-Induced Electrical Cardiotoxicity

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Introduction: The hERG (human ether-à-go-go-related gene) potassium channel carries the rapid delayed rectifier current (IKr) and plays a central role in cardiac repolarization. Its inhibition is the primary mechanism of drug-induced QT prolongation: the blocked channel delays the ventricle from resetting, favoring early afterdepolarizations and increasing the risk of life-threatening arrhythmia, namely Torsades de Pointes (TdP) and sudden cardiac death. Drugs from unrelated classes converge on this phenotype, which is underreported and increasingly relevant in cardio-oncology, where patients receive multiple QT-prolonging and cardiotoxic therapies.

Methodology: Narrative review of repolarization physiology, QTc correction formulas, risk factors and clinical evidence on drugs affecting the QT interval or QT dispersion (QTd), with management strategies.

Results: QTc >500 ms or a rise >60 ms from baseline indicates high TdP risk. QTd, the difference between the longest and shortest QT intervals across ECG leads, reflects regional heterogeneity of repolarization. Risk factors include age, sex, genetic predisposition, electrolyte disturbances, diuretics, CYP450 inhibitors and polypharmacy; in hospitalized patients, four or more concurrent QT-prolonging drugs markedly increased risk up to OR 5.28. Clarithromycin inhibits CYP3A-mediated pimozide metabolism, enhancing QTc prolongation. Epirubicin increased QTd in lymphoma, whereas dexrazoxane kept QTd stable. In a phase III doxorubicin trial in sarcoma (n=326), cardiotoxicity was reported as heart failure (5-9%) and LVEF reduction (10-15%). Immune checkpoint inhibitors may cause QT changes and myocarditis, where ECG supports risk stratification. Bedaquiline raised QTc by up to 15.7 ms over 24 weeks. Not all agents prolong QT: trametinib did not at supratherapeutic doses, yet when combined with agents as Drabafenib, it may add risk to QT prolongation. Management centers on withdrawing the culprit drug, correcting electrolytes and giving IV magnesium for TdP.

Conclusion: Despite diverse mechanisms, many drugs converge on delayed ventricular repolarization. Safe use requires weighing benefit against arrhythmic risk, serial ECG and review of interactions, supported by multidisciplinary collaboration among cardiologists, oncologists and pharmacologists.

ECMO in Cardiogenic Shock

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Content:

Cardiogenic shock is a life-threatening circulatory condition characterized by severely impaired cardiac function that is unable to maintain adequate cardiac output, leading to tissue hypoperfusion and subsequent end-organ dysfunction. Despite substantial advances in intensive cardiac care, mortality in patients with cardiogenic shock remains unacceptably high. In recent years, mechanical circulatory support, particularly extracorporeal membrane oxygenation (ECMO), has become an established therapeutic option for supporting patients during the most critical phases of cardiogenic shock.
Nevertheless, the current evidence supporting the use of ECMO and other mechanical circulatory support devices in this setting remains limited.

Although randomized clinical trials have shown no overall improvement in clinical outcomes with ECMO in cardiogenic shock, these studies have important limitations, particularly with respect to patient selection and inclusion criteria. Recent analyses indicate that comprehensive hemodynamic assessment may help identify patients who are most likely to benefit from mechanical circulatory support. Available data suggest that patients with severe hypotension, low cardiac output, and evidence of tissue hypoperfusion defined, in accordance with recent guidelines, by low venous oxygen saturation (SvO2) or an increased veno-arterial carbon dioxide partial pressure difference (pCO2 gap), rather than by elevated lactate levels alone, may benefit most from early initiation of ECMO support.

Specific clinical scenarios in which ECMO may be considered include severe aortic stenosis, right ventricular failure, and selected patients with mechanical complications of acute myocardial infarction. Moreover, recently introduced synchronized pulsatile extracorporeal flow may potentially reduce some of the unfavorable effects of ECMO on left ventricular function. Despite continuing advances in this field, several important clinical questions remain unanswered, highlighting the need for further research in this rapidly evolving area.

From hypercontractility to reserve: the paradox of myosin inhibitors beyond HCM

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Content:

Cardiac myosin inhibitors (mavacamten, aficamten) treat hypertrophic obstructive cardiomyopathy (oHCM) by facilitating the DRX→SRX myosin transition, reducing myofilament Ca^{2+}-sensitivity (pCa_{50}), maximal active force (Fmax), and myosin ATPase activity — directly opposing sarcomeric hypercontractility while accelerating cross-bridge detachment and improving diastolic relaxation.

Acentral clinical question concerns the obligatory LVEF reduction during myosin inhibitor therapy. To address whether this reflects true hemodynamic compromise, we characterized aficamten's effects across multiple levels of cardiac organization. In permeabilized cardiomyocytes from rat, dog, healthy human donor, and HCM myocardium, aficamten reduced Fmax and pCa_{50} consistently, yet length-dependent activation (LDA) — the sarcomere-level basis of the Frank-Starling mechanism — was largely preserved. In intact canine cardiomyocytes, aficamten shortened contraction duration and accelerated relaxation without altering Ca^{2+} transients, confirming a purely myofilament-level lusitropic mechanism. In sedated rats, echocardiography revealed increased end-diastolic volume alongside LVEF reduction, while cardiac output remained unchanged — demonstrating that Frank-Starling recruitment maintains forward flow despite reduced cross-bridge cycling.

In obstructive HCM, LVOT obstruction relief provides an additional afterload-reducing mechanism augmenting stroke volume independently of Frank-Starling recruitment. The negative ODYSSEY-HCM trial confirms that this hemodynamic component is critical for functional benefit. Genotypic heterogeneity — spanning thick- and thin-filament mutations with distinct mechanistic signatures — introduces further variability in myosin inhibitor response.

These findings reframe LVEF reduction during myosin inhibitor therapy as a physiologically compensated state, supporting integration of cardiac output alongside LVEF into monitoring algorithms. Sarcomere length is more — even when myosin is less.

This work was supported by a grant from the National Research, Development, and Innovation Office (K147173 to ZP). Project no. K147173 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the K_23 „OTKA" funding scheme.

SGLT2 Inhibitors Enhance Cardiac Conduction and Contractility Through Increased Membrane Nav1.5 and L-Type Calcium Current

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Content:

Introduction: SGLT2 inhibitors (empagliflozin [EMPA], dapagliflozin [DAPA]) reduce cardiovascular mortality and heart-failure hospitalization, and recent studies suggest protection against some arrhythmias. We investigated whether they have (direct) ion-channel-modulating properties, particularly effects on peak sodium current (INa), responsible for depolarization and L-type calcium current (ICaL), regulating contraction.

Methods: Action potentials (APs) were recorded during acute application of 1–3 µM EMPA or 1–10 µM DAPAin healthy canine and explanted human heart-failure samples using conventional microelectrodes. Effects of 8–12 h incubation with 1 µM EMPAor DAPAon APs, calcium transients (CaT), ICaL, and late sodium current (INaL) were assessed using patch clamp in canine preparations. Nav1.5 expression was examined by immunocytochemistry after 24 h SGLT2-inhibitor incubation. Findings were further tested using cellular and multidimensional (2D reentry and biventricular) simulations based on human and canine AP models.

Results: 1 and 3 µM EMPAsignificantly increased AP amplitude (+3.3% and +5.0%; n/N = 9/9) and reduced conduction time (−5.1% and −9.8%; n/N = 7/7) versus control. 3 µM EMPA increased maximum upstroke velocity (+24.7%; n/N = 9/9), while AP duration was unchanged. DAPAcaused no significant changes in canine samples (n/N = 7/7). In failing human preparations, both agents tended to reduce conduction time. In incubated canine slices, both similarly increased Vmax (+33–34%) and amplitude (+4.5–6.5%), while APDx remained unchanged (n/N = 14/7). Nav1.5 expression increased significantly: EMPA+47%, DAPA+38.4% (n/N = 35/7). In incubated canine cardiomyocytes, CaT increased by45% with EMPAand 21% with DAPA(n/N = 12/4), while ICaL increased by42% and 36%,
respectively (n/N = 6/3). I NaL magnitude was unchanged (n/N = 7/5). Computer simulations correctly predicted the depolarization change based on immunocytochemical findings. In 2D tissue simulations, increased peak sodium current accelerated conduction and caused reentry drift.

Conclusion: SGLT2 inhibitors may enhance conduction velocity by increasing peak sodium current and improve contractile strength by increasing calcium current. This dual mechanism may be critically important in heart failure, where impaired electrical conduction and contractility coexist.

The Overlap Syndrome (OSA and COPD): Implications for Cardiovascular Risk and Clinical Management

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Content:

Introduction: Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) are common respiratory disorders that frequently coexist. Their combination, referred to as COPD–OSAoverlap syndrome (OVS), is increasingly recognized as a distinct clinical phenotype. Both conditions independently contribute to cardiovascular morbidity, while their coexistence may further amplify cardiovascular risk through interacting mechanisms involving nocturnal hypoxaemia, systemic inflammation, oxidative stress, endothelial dysfunction and autonomic imbalance.

Methodology: The available evidence on OVS was reviewed, with emphasis on its pathophysiological mechanisms, cardiovascular consequences, diagnostic challenges and therapeutic approaches. Observational studies, systematic reviews and recent data addressing cardiovascular outcomes and positive airway pressure therapy were considered. Results: OVS is characterized by more pronounced nocturnal oxygen desaturation and sleep-related gas-exchange abnormalities than either COPD or OSAalone. The coexistence of COPD and OSAhas been associated with a greater burden of systemic and pulmonary hypertension, cardiac arrhythmias, heart failure, cerebrovascular and atherosclerotic disease, as well as increased exacerbations, hospitalizations and mortality. From a clinical perspective, disproportionate nocturnal hypoxaemia, cardiovascular comorbidities, resistant hypertension, pulmonary hypertension or unexplained nocturnal symptoms should raise suspicion of concomitant OSAin patients with COPD. Management requires an integrated approach, including optimal COPD treatment, smoking cessation, physical activity, appropriate weight management, cardiovascular risk assessment and positive airway pressure therapy when clinically indicated.

Conclusion: COPD–OSAoverlap syndrome represents an underrecognized high-risk phenotype at the interface between respiratory and cardiovascular medicine. Early identification and comprehensive management may reduce nocturnal hypoxaemia, cardiovascular complications and exacerbations. Amultidisciplinary approach and prospective studies are needed to define optimal strategies for cardiovascular risk reduction and personalized management of patients with OVS.

HYPERBARIC OXYGEN THERAPY AS A NOVEL POTENTIAL CARDIOPROTECTIVE STRATEGY IN EXPERIMENTAL AUTOIMMUNE MYOCARDITIS: MODULATION OF MYOCARDIAL OXIDATIVE STRESS

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Content:

Introduction: Myocarditis is a significant global health concern characterized by myocardial injury that is mediated by oxidative imbalance, the immune system and has variable clinical outcomes. Oxidative stress plays an important role in the progression of myocardial damage, highlighting the need for therapeutic strategies that can influence both oxidative and inflammatory processes. Hyperbaric oxygen therapy (HBOT) is a promising non-pharmacological intervention, with potential antioxidant, anti-inflammatory, and cardioprotective effects. Given the limited efficacy of currently available pharmacological treatments, the present study aimed to evaluate the effects of HBOT on oxidative status and antioxidant capacity in the cardiac tissue of rats with experimental autoimmune myocarditis (EAM).

Methodology: Thirty-six male Dark Agouti rats were randomly assigned to six experimental groups (n=6 per group). The 21-day experimental groups consisted of healthy control rats (CTRL21d), rats with experimental autoimmune myocarditis (MIO21d), and rats with EAM treated with hyperbaric oxygen therapy (HBOT) from day 0 to day 21 (MIO+HBOT21d). The 42-day experimental groups included healthy control rats (CTRL42d), rats with EAM (MIO42d), and rats with EAM treated with HBOT from day 21 to day 42 (MIO+HBOT42d). Experimental autoimmune myocarditis was induced by immunization with cardiac myosin. Hyperbaric oxygen therapy was administered at 2.6 ATA during either the acute (days 0–21) or subacute (days 21–42) phase of the disease. Myocardial tissue oxidative stress were evaluated spectrophotometrically in cardiac tissue homogenates by measuring the levels of lipid peroxidation, expressed as thiobarbituric acid reactive substances (TBARS), catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH).

Results: Compared with untreated EAM rats, HBOT-treated animals exhibited lower levels of pro-oxidant biomarkers and improved antioxidant enzyme activities. These findings suggest that HBOT attenuated oxidative damage and restored myocardial redox balance.

Conclusion: HBOT influenced myocardial oxidative status by modulating pro-oxidant biomarkers and antioxidant defense, highlighting its cardioprotective potential in experimental autoimmune myocarditis.

In vitro effects of diazepam on IFN-γ production by peripheral blood mononuclear cells in healthy pregnancy and gestational diabetes mellitus

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Content:
Introduction: Gestational diabetes mellitus (GDM) is a common metabolic pregnancy disorder biochemically rooted in disrupted immune homeostasis. It is associated with an increased risk of developing type 2 diabetes mellitus and cardiovascular complications after pregnancy. Although diazepam is used in pharmacotherapy of pregnant women, its potential immunomodulatory effects on T-lymphocyte subsets and cytokine production, under these specific conditions remain poorly understood.
Methodology: Peripheral blood mononuclear cells (PBMC) were isolated from peripheral venous blood of healthy non-pregnant women, healthy pregnant women and pregnant women with diagnosed GDM. The immunomodulatory effects of diazepam were investigated by pre-treating PBMCs with different concentrations of diazepam (2.5, 5, and 10 μM) for 48 h at 37 °C in a humidified atmosphere containing 5% CO_2. Following the pre-treatment period, PBMCs were stimulated with anti-CD3/CD28 beads for 16 h. IFN-γ production was assessed by flow cytometry following surface and intracellular staining with fluorochrome-conjugated antibodies.
Results: Basal IFN-γ production by T-lymphocytes was suppressed in GDM pregnancies. Diazepam dose-dependently and significantly increased IFN-γ production by both CD4+ and CD8+ T lymphocytes and in all three groups. The most pronounced increase in IFN-γ production was observed in pregnant women diagnosed with gestational diabetes mellitus. Conclusion: These results demonstrate that diazepam induces statistically significant, dose-dependent stimulation of IFN-γ production in CD4+ and CD8+ T-lymphocytes, confirming its in vitro immunomodulatory effect on PBMC cultures of healthy non-pregnant, healthy pregnant and pregnant women with GDM. Further research is needed to elucidate the potential beneficial or adverse effects associated with its clinical use.

ECHOCARDIOGRAPHIC EVALUATION OF HYPERBARIC OXYGEN THERAPY IN EXPERIMENTAL AUTOIMMUNE MYOCARDITIS: EFFECTS ON VENTRICULAR FUNCTION AND REMODELING

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Content:

Introduction: Inflammatory myocardial injury is a hallmark of experimental autoimmune myocarditis (EAM). Although hyperbaric oxygen therapy (HBOT) reduces inflammation and protects tissues, evidence of its effects on heart function during different stages of autoimmune diseases, including EAM, remains limited. We evaluated the impact of HBOT on left ventricular function using standard echocardiographic parameters in acute and subacute EAM.

Methodology: We randomly assigned 36 male Dark Agouti rats into six different groups (n=6 per group). The 21-day experimental groups included healthy control rats (CTRL21d), rats with EAM (MIO21d) and rats with EAM treated with HBOT from day 0 to day 21 (MIO+HBOT21d). The 42-day experimental groups included healthy control rats (CTRL42d), rats with EAM (MIO42d) and rats with EAM treated with HBOT from day 21 to day 42 (MIO+HBOT42d). EAM was induced via cardiac myosin immunization. HBOT was applied at 2.6 ATA either during the acute (days 0-21) or subacute phase (days 21-42) of the disease. Transthoracic echocardiography was performed before treatment and at the end of each experimental period. Left ventricular function was assessed using the following parameters: ejection fraction (EF), fractional shortening (FS), left ventricular internal diameters (LVIDd, LVIDs), interventricular septal thickness (IVSd, IVSs), and posterior wall thickness (LVPWd, LVPWs).

Results: Untreated EAM rats (MIO21d and MIO42d) developed systolic dysfunction at both time points, shown by reduced EF and FS and increased LVIDs. HBOT significantly improved EF and FS while reducing LVIDs to control values. LVIDd remained unchanged during the acute phase but increased by day 42 in untreated rats, indicating progressive ventricular remodeling; HBOT attenuated this change. IVSd increased in untreated rats at both time points, whereas HBOT restored septal thickness to control values, suggesting protection against myocardial remodeling. No differences were observed in the remaining echocardiographic parameters.

Conclusion: In EAM, HBOT preserved left ventricular systolic function and limited remodeling. Improved EF, FS, LVIDs, and IVSd indicate preserved cardiac function and reduced adverse ventricular remodeling, supporting HBOT as a potential adjunctive therapy for inflammatory heart disease.

Alterations in serum biomarker levels and their correlation with cardiac function and morpholgy can predict prognosis in patients with established acute coronary syndrome

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Content:

Introduction: Acute coronary syndromes (ACS), as unstable angina (UA) and acute myocardial infarction (MI) may progress into more severe complications such as a cardiac death, re-occlusion or repeated infarction. Currently, there are no reliable diagnostic modality, which could accurately predict the chance for occurrence of major adverse cardiovascular events (MACE). Therefore, we aimed to compare laboratory parameters, novel biomarker candidates, and imaging findings between UAand post MI patients, and to investigate their correlations for the improvement of acute care and patient follow-up to facilitate the secondary prevention of MACE.
Methods: Thirty UA(60.8±8.4 years; 88% female) and 27 post MI patients (64.2±8.6 years; 80% female) were enrolled. Venous blood sampling and echocardiography were performed on first day of hospitalization. Cardiac magnetic resonance (CMR) imaging was conducted 3–5 days in UAand 30 days in post MI patients after hospitalization, infarct size (IS), risk area (AAR), myocardial edema (ME), and microvascular obstruction (MVO) were assessed. Echocardiography was performed to measure cardiac morphology and function. Serum metabolites were determined by the central laboratory, nitrotyrosine (NYTR) was quantified by ELISA, and matrix-metalloproteinase (MMP) activity by gelatin zymography.
Results: The IS, AAR, MVO and glucose levels were significantly higher in post-MI patients as compared to UApatients. In the post MI group, MMP 9 with E and A, while in the UAgroup, MMP 2 with E and E/Acorrelated negatively. In the post-MI group, NYTR correlated positively with MMP 2 and negatively with MVO and glucose, whereas creatinine correlated negatively with E, Aand total cholesterol; while positively with infarct size. Further positive correlations were found between SG and AAR, between BUN and ME, and between EDV and TG. In UApatients AAR correlated negatively with MMP 9 and positively LVEF, MMP-2 correlated negatively with E and E/A, while a positive correlation has been found between TC and SG, and between TG and ESV.
Conclusion: MMP 2 in UApatients, as well as MMP-9 in post-MI patients correlated significantly with parameters of diastolic dysfunction. NYTR may represent a promising marker in post MI. In summary, MMPs and routine biochemical parameters may support the prediction of disease progression and may provide potential markers to identify risk and prevent MACE in patients with established ACS.

Analysis of the molecular mechanisms and sex-dependence of necroptosis in pressure-overload heart failure

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Introduction: The cardiac response to pressure overload differs between sexes; however, the underlying molecular mechanisms of cell death remain unclear. This study aimed to investigate the role of necroptosis and its potential sex dependence in pressure overload-induced heart failure (HF).
Methodology: Pressure overload was induced in Wistar rats by abdominal aortic constriction (AAC) at 2 days of age. After 90 days, biometric, echocardiographic, and molecular analyses were performed.
Results: Cardiac hypertrophy developed in both sexes after AAC, as evidenced by increased relative left- and right-ventricular weights. Both sexes exhibited necroptosis, indicated by increased levels of phosphorylated receptor-interacting protein kinase 3 (RIP3) and mixed lineage kinase domain-like pseudokinase (MLKL). However, necroptosis appeared to be activated through distinct pathways: canonically via tumour necrosis factor receptor 1 (TNFR1) in females and non-canonically via toll-like receptor 4 in males. In addition, females subjected to AAC showed evidence of a pro-inflammatory response, characterized by increased expression of TNF, interleukin-6 (IL-6), and cyclooxygenase-2 (COX2). In contrast,
males exhibited a predominantly pro-oxidative environment, reflected by increased expression of NADPH oxidases and inducible nitric oxide synthase (iNOS).
Conclusion: These findings demonstrate the involvement of necroptosis in pressure overload-induced HF and suggest that it is activated through and accompanied by divergent sex-specific mechanisms. These results support the potential need for sex-specific pharmacological strategies in the treatment of pressure overload-induced HF.

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NON-INVASIVE "CONDITIONING" STRATEGIES AIMED TO TRIGGER CELLULAR CARDIOPROTECTIVE MECHANISMS IN HEALTHY AND PATHOLOGICALLY ALTERED HEART

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Content:

Background: Remote ischemic preconditioning (RPC) is a form of innate cardioprotection when brief episodes of stress in any organ protect distant organs/tissues against prolonged ischemia/reperfusion (I/R), similar to the ischemic PC. Despite promising experimental results, large clinical trials failed to show benefits of RPC, which is to a major extent related to the presence of comorbidities, such as hypertension. RPC has been shown to be mediated through the activation of Reperfusion Injury Salvage Kinase (RISK) and SAFE (Survival Activating Factor Enhancement) pathways.

However, less is known about these effects in the hearts of hypertensive animals. We aimed to clarify whether: hypertension modifies the effect of RPC on I/R injury, and affects RISK signaling in the preconditioned hearts of adult male Wistar and SHR rats.

Methods: RPC was induced by 3 cycles of 5-min occlusion/5-min reperfusion of a. femoralis by inflation/deflation of the pressure cuff on the hind limb of anesthetized rats. Hearts were then excised, Langendorff-perfused and exposed to 30 min global ischemia/2hrs reperfusion, focused on the post-I/R recovery of function, arrhythmias and infarct size (IS). In parallel groups, heart tissue samples were processed (WB) to investigate the levels/activity of proteins involved in RISK cascade (PI3K/Akt, eNOS, GSK-3β, PKCε) and apoptosis.

Results: At baseline, SHR rats had higher blood pressure, heart weight and left ventricular hypertrophy, compared with normotensive rats, and increased IS, incidence of ventricular arrhythmias and reduced functional recovery after I/R. In normotensive rats, RPC significantly decreased IS, contractile dysfunction and incidence of arrhythmias, while in SHR rats, these effects were significantly lower. Beneficial effects of RPC were associated with increased activity of RISK proteins and decreased apoptotic signaling in the hearts of normotensive rats, whereas in the hearts of SHR rats, these effects were not observed.

Conclusions: The results confirm the effectiveness of RPC in protection against I/R in the healthy heart and a key role of of RISK cascade. Hypertension not only increases susceptibility of the heart to I/R, but attenuates a response to RPC. Downregulated mechanisms of RPC in the hearts of hypertensive rats fail to augment an ischemic tolerance to the same level as in the normotensive animals. Increasing the intensity or mode of conditioning stimuli may facilitate its stronger effect.

Biased and β3-independent: uncovering the effects on cGMP of NO donors and nebivolol in human atrial myocytes

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Content:

Background: Nebivolol, a third generation beta1-blocker, has gained popularity as a treatment for heart failure due to its high cardio-selectivity and ability to reduce afterload by peripheral vasodilation, which occurs via endothelial NO pathway activation by β3-adrenoceptor (AR) agonism. Because rodent cardiomyocytes lack functional NO pathway machinery, it was assumed the same applied to humans; thus, nebivolol was only tested as a beta-blocker in human cardiomyocytes. This study investigates nebivolol's modulation of the NO pathway in human atrial myocytes.

Methods: Transcripts of β-ARs (β1, β2, β3), NO synthases (NOS1, NOS2, NOS3) and soluble guanylyl cyclase (sGC) subunits (sGCα1, sGCα2, sGCβ) were measured by RT-qPCR in 14 atrial samples. 119 isolated myocytes from 46 human atrial tissue samples were used to study cyclic nucleotides levels by Fluorescence Resonance Energy Transfer (FRET) live-cell imaging. Cells were transduced with adenoviral vectors encoding cGMP- (red cGES-DE5) or cAMP-sensitive (Epac1-camps) FRET biosensors. Effects of S-Nitroso-N-acetylpenicillamine (SNAP, 300 nM), Nebivolol (1 µM), 3-Isobutyl-1-methylxanthine (IBMX, 100 µM), L-NAME (200 nM), CGP-20712A(CGP, 50 nM) and ICI-118551 (ICI, 100 nM)
were tested.

Results: We detected measurable levels of β1- and β2-ARs, NOS3, and all sGC subunits in human atria. Conversely, β3-AR, NOS1 and NOS2 transcripts were not detected. While L-NAME did not affect basal cGMP in human atrial myocytes, SNAP increased it. Nebivolol successfully reduced cAMP levels in isolated cardiomyocytes, but surprisingly increased cGMP levels. Interestingly, NOS inhibition with L-NAME completely abolished the cGMP rise. Similarly, β1- and β2-AR blockade with ICI and CGP prevented the effect of nebivolol on cGMP.

Discussion: Our results support the presence of functional machinery for independent activation of the NO-cGMP pathway in human atrial myocytes. We also show nebivolol activates this pathway in a β3-AR-independent manner, suggesting a potential biased agonism mediated by β1- and/or β2-ARs. While biased agonism towards β-arrestin was shown for nebivolol, its connection with the NO pathway had never been demonstrated.

Conclusion: We demonstrate for the first time that unlike in mouse models, NO donors increase cGMP levels in human atrial myocytes. Furthermore, we show an unknown effect of nebivolol, a β3-independent pathway by which nebivolol activates NO and cGMP productionin human atrial myocytes.

Evidence that Phospholipid N-Methylation Governs the Lipid Architecture of Cardiac Vulnerability

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Content:

Cardiac function is critically dependent on the structural and functional integrity of cellular membranes, yet the contribution of dynamic phospholipid remodeling to cardiac vulnerability remains incompletely understood. Phospholipid N-methylation represents an important biochemical pathway through which phosphatidylethanolamine is sequentially methylated to phosphatidylcholine, potentially modifying membrane lipid composition and the activity of membrane-associated proteins. Experimental studies have demonstrated phospholipid N-methylation activity in cardiac SL, SR and mitochondria, supporting a role for this pathway across functionally distinct membrane compartments. Importantly, phospholipid N-methylation has been linked to regulation of cardiac Ca^{2+} handling. Alterations in methylation influence Ca^{2+}-stimulated ATPase activity, Ca^{2+} transport and SL Na^{+}/Ca^{2+} exchange, suggesting that remodeling of the membrane lipid environment can modify processes fundamental to excitation-contraction coupling. The pathway is also responsive to physiological and pathological stimuli. β-adrenergic stimulation rapidly activates cardiac phospholipid N-methylation, whereas oxidative stress inhibits methylation reactions. Furthermore, experimental diabetes produces compartment-specific alterations in cardiac membrane phospholipid N-methylation that are reversible with insulin treatment, linking metabolic status to membrane lipid regulation. Collectively, these observations support the concept that phospholipid N-methylation represents more than a phospholipid biosynthetic pathway; it may function as a dynamic regulator of the lipid-protein interface within cardiac membranes. Re-examination of this pathway using contemporary lipidomics, proteomics and mechanistic approaches may reveal how altered membrane lipid architecture contributes to impaired Ca^{2+} homeostasis, metabolic stress and cardiac vulnerability, while identifying previously underappreciated targets for cardiovascular investigation.

Receptor Dependent Mitochondrial Protection by GLP-1(7-36) in H9c2 Cardiomyoblasts Exposed to Glucolipotoxic Stress

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Content:

Introduction: Glucolipotoxicity is a key driver of cardiomyocyte injury in diabetes, with mitochondrial dysfunction and oxidative stress playing central roles. Previous studies have demonstrated cardiomyocyte protection by GLP-1 or GLP-1 receptor agonists under lipotoxic, hyperglycemic, or ischemic stress. However, the mitochondrial actions of native GLP-1(7-36) under combined lipotoxic and glucotoxic stress, and the receptor dependency of these effects, remain insufficiently characterized. We therefore investigated whether GLP-1(7-36) preserves mitochondrial function in H9c2 cardiomyoblasts exposed to combined palmitate/high-glucose stress and whether avexitide modifies this response.

Methodology: H9c2 cells were pretreated with GLP-1(7-36) (50 or 250 nM) for 2 h and subsequently exposed to high palmitate/high glucose for 5 h. Avexitide was used to assess receptor involvement. Cell viability was evaluated by MTT assay. Mitochondrial membrane polarization and mitochondrial superoxide production were assessed by flow cytometry using JC-1 and MitoSOX, respectively.

Results: Combined palmitate/high-glucose exposure reduced cell viability and produced a mitochondrial injury phenotype characterized by loss of membrane polarization and increased mitochondrial superoxide production. GLP-1(7-36) partially restored mitochondrial polarization and reduced mitochondrial superoxide generation, accompanied by a modest improvement in cell viability. Notably, avexitide largely attenuated the beneficial effects of GLP-1(7-36) on both JC-1 and MitoSOX responses, whereas its influence on cell viability was less pronounced.

Conclusion: Native GLP-1(7-36) attenuates mitochondrial dysfunction during acute glucolipotoxic stress in H9c2 cells. The parallel improvement in mitochondrial polarization and superoxide burden, together with their attenuation by avexitide, supports the involvement of receptor-dependent signaling in mitochondrial protection. These findings extend previous cardioprotective observations with GLP-1-based therapies by highlighting receptor-sensitive mitochondrial preservation under combined lipid and glucose stress.

Quilombola ancestral knowledge as a source for cardiovascular drug discovery

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Content:

Background: The quilombola communities preserve knowledge about medicinal plants that may help identify compounds relevant to cardiovascular drug discovery. This study examined agreement between cardiovascular uses reported by elders in the Mumbuca and Prata communities in Tocantins, Brazil, and published pharmacological evidence.

Methods: In October 2025, the authors interviewed 10 elders recognized by their communities as holders of medicinal-plant knowledge. The authors collected and botanically identified cited plants and searched Google Scholar, PubMed, and SciELO for pharmacological and phytochemical studies of species associated with cardiovascular conditions.

Results: The field study cataloged 81 medicinal-plant taxa. Elders associated 11 (13.6%) taxa with cardiovascular treatment or protection. The literature review identified at least 21 potentially cardioactive substances among these species. Evidence was most consistent for antihypertensive, antioxidant, anti-inflammatory, anticoagulant, and cardioprotective effects.

Conclusions: Traditional recommendations and published evidence converged for several species, supporting careful, community-engaged investigation of quilombola knowledge as a source of hypotheses for cardiovascular drug discovery. Evidence gaps identify priorities for pharmacological, toxicological, and clinical research conducted with ethical safe-guards and equitable recognition of knowledge holders.

PHARMACONUTRITION AND LIFESTYLE MODIFICATIONS ARE THE BEST STRATEGIES TO REDUCE THE GLOBAL BURDEN OF CARDIOMETABOLIC DISEASES

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Content:

The global rise in cardiometabolic diseases (CMDs), obesity, and diabetes is driving up healthcare costs. Therefore, we urgently need cost-effective strategies to prevent CMDs. Acomprehensive approach that includes eating healthy foods rich in flavonoids, polyphenols, and carotenoids, such as fresh fruits and vegetables, along with probiotics and prebiotics; reducing sugar-sweetened beverages and saturated fats; quitting smoking; limiting alcohol intake; and engaging in moderate exercise for 30 minutes daily is known to be effective in preventing myocardial infarction and stroke. This comprehensive approach is likely the most cost-efficient way to improve health and prevent CMDs, diabetes, obesity, neurodegenerative diseases, and cancer. Substantial evidence indicates that a Mediterranean-type diet, featuring whole grains, omega-3 fatty acids, poultry, fish, nuts, seeds, olive oil, dairy products, limited red meat, and moderate red wine, is associated with lower mortality and morbidity from CMDs. Additionally, recent studies suggest that nutraceuticals containing antioxidant/anti-inflammatory compounds can influence gene and protein expression, modify metabolic pathways, and maintain bodily homeostasis, thereby reducing the risk of complex chronic disorders. Gut microbiomes play a crucial role in human health and disease and influence numerous CMDs. Trimethylamine N-oxide (TMAO), produced by the gut microbiota from dietary phosphatidylcholine and L-carnitine, is associated with atherosclerosis, hypertension, and kidney dysfunction. Dysbiosis caused by ultra-processed foods increases gut permeability, leading to leaky gut syndrome. Gut dysbiosis has also been implicated in the pathogenesis of a wide array of ailments, including cardiovascular, neurological, and psychiatric disorders. Probiotics, prebiotics, and synbiotics counteract dysbiosis by promoting a healthy gut microbiota, enhancing gut barrier integrity, and strengthening immune function, thereby preventing obesity, diabetes, and CMDs.

Holistic Approaches to Health Education and Health Promotion for the Prevention and Management of Cardiovascular Diseases

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Content:

The global rise in cardiovascular diseases (CVDs), obesity, and diabetes is driving up healthcare costs. Therefore, we urgently need cost-effective strategies to prevent CVDs. Acomprehensive approach that includes eating healthy foods rich in flavonoids, polyphenols, and carotenoids, such as fresh fruits and vegetables, along with probiotics and prebiotics; reducing sugar-sweetened beverages and saturated fats; quitting smoking; limiting alcohol intake; and engaging in moderate exercise for 30 minutes daily is known to be effective in preventing myocardial infarction and stroke. This comprehensive approach is likely the most cost-efficient way to improve health and prevent CVDs, diabetes, obesity, neurodegenerative diseases, and cancer. Substantial evidence indicates that a Mediterranean-type diet, featuring whole grains, omega-3 fatty acids, poultry, fish, nuts, seeds, olive oil, dairy products, limited red meat, and moderate red wine, is associated with lower CVD mortality and morbidity. Additionally, recent studies suggest that nutraceuticals containing antioxidant/anti-inflammatory compounds can influence gene and protein expression, modify metabolic pathways, and maintain bodily homeostasis, thereby reducing the risk of complex chronic disorders. Gut microbiomes play a crucial role in human health and disease and influence numerous cardiometabolic disorders. Trimethylamine N-oxide (TMAO), produced by the gut microbiota from dietary phosphatidylcholine and L-carnitine, is associated with atherosclerosis, hypertension, and kidney dysfunction. Dysbiosis caused by ultra-processed foods increases gut permeability, leading to leaky gut syndrome. Gut dysbiosis has also been implicated in the pathogenesis of a wide array of ailments, including cardiovascular, neurological, and psychiatric disorders. Probiotics, prebiotics, and synbiotics counteract dysbiosis by promoting a healthy gut microbiota, enhancing gut barrier integrity, and strengthening immune function, thereby preventing obesity, diabetes, and insulin resistance. Overall, holistic approaches are needed to reduce the incidence of CVDs and the risk of other chronic diseases, including obesity, diabetes, cardiometabolic disorders, dementia, arthritis, gut dysfunction, depression, and cancer. Public education and awareness are important for promoting consumption of fresh fruits and vegetables, wholesome foods, and probiotics; reducing consumption of ultra-processed foods high in salt, sugar, seed oils

Molecular Hydrogen as a Multitarget Adjunct in Cardiovascular Disease Management

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Content:

Introduction: Cardiovascular diseases (CVD) remain the leading cause of death worldwide. Their progression is driven by oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, and maladaptive cardiac and vascular remodeling processes only partially addressed by current guideline-directed therapies. Molecular hydrogen (H_2) is an emerging adjunctive strategy that simultaneously modulates these pathways. H_2 is the smallest molecule, highly diffusible, and selectively reacts with cytotoxic reactive species ($\cdot OH$, $ONOO^-$) while preserving physiological redox signaling. It rapidly penetrates tissues, cells, and subcellular compartments, including mitochondria. Beyond direct radical scavenging, H_2 activates endogenous cytoprotective pathways (Nrf2/ARE, SIRT1), stabilizes mitochondrial function and dynamics, enhances mitophagy, and suppresses pro-inflammatory and apoptotic signaling (NF-κB, PI3K/Akt). These actions promote a stress-resistant phenotype in cardiomyocytes and vascular cells.

Results: Preclinical models demonstrate consistent benefits across major CVD phenotypes. In myocardial ischemia-reperfusion injury, inhaled H_2 or hydrogen-rich solutions reduce infarct size by 30-50%, improve hemodynamics, and lower injury biomarkers. In pressure- or neurohormonal overload induced heart failure, H_2 attenuates hypertrophy and fibrosis, preserves systolic and diastolic function, and restores mitochondrial bioenergetics. In experimental atherosclerosis, H_2 reduces plaque burden, improves endothelial function, decreases oxidized lipoprotein formation, and attenuates arterial stiffening. Early clinical studies, though small, support feasibility and safety in acute and chronic cardiovascular settings. In post-cardiac arrest syndrome, low dose inhaled H_2 shows signals of improved 90-day survival and neurological outcome, accompanied by reduced oxidative and inflammatory biomarkers. Inhalation, hydrogen-rich water, hydrogen-rich saline, and organ preservation solutions have all demonstrated excellent tolerability without major safety signals.

Conclusion: Mechanistic, preclinical, and early clinical evidence supports molecular hydrogen as a biologically plausible, safe, and versatile adjunct for CVD management, uniquely positioned to target oxidative, inflammatory, and mitochondrial pathways simultaneously.

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Persistent LVOT Obstruction After Aortic Valve Replacement: Look Beyond the Valve

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Content:

INTRODUCTION:The differential diagnosis of marked left ventricular hypertrophy (LVH) in patients with aortic stenosis (AS) represents a diagnostic challenge, particularly when the degree of hypertrophy appears disproportionate to the severity of valvular obstruction. In such patients, it is essential to distinguish adaptive hypertrophy resulting from chronic pressure overload from concomitant hypertrophic cardiomyopathy (HCM) and other potential causes of left ventricular outflow tract (LVOT) obstruction (Figure 1). We present a 64-year-old woman with a history of arterial hypertension, dyslipidemia, and osteoarthritis who was followed by a cardiologist for aortic stenosis.
METHODS:Transthoracic echocardiography demonstrated marked LVH (IVSd 16 mm, LVPWd 15 mm) and severe AS. Coronary angiography revealed a subtotal proximal RCAstenosis. The patient underwent surgical aortic valve replacement with a 25-mm Edwards INSPIRIS RESILIAbioprosthesis, Y-incision aortic annular enlargement with a pericardial patch, and single-vessel coronary artery bypass grafting (SVG–PDA).
RESULTS: Although the valvular component of the obstruction was successfully treated surgically, postoperative echocardiography demonstrated normal bioprosthetic valve function with unexpectedly high trans-LVOT/aortic Doppler velocities and gradients (peak gradient 103 mmHg, Vmax 5.1 m/s), accompanied by systolic anterior motion (SAM) of the mitral valve, raising suspicion of an additional dynamic LVOT obstruction. Further diagnostic work-up supported the diagnosis of concomitant HCM with dynamic LVOT obstruction. Genetic testing was performed, and treatment with mavacamten was initiated. During follow-up, a marked reduction in LVOT obstruction was observed, with a peak gradient of 36 mmHg and Vmax of 3.0 m/s.
CONCLUSION:In patients with severe aortic stenosis and marked left ventricular hypertrophy, particularly when the degree of hypertrophy appears disproportionate to the valvular disease, concomitant causes of LVOT obstruction should be carefully considered. These include subaortic and supravalvular obstruction as well as hypertrophic cardiomyopathy.
Multimodality imaging and a multidisciplinary Heart Team approach are essential for accurate diagnosis, appropriate follow-up, and optimal therapeutic planning, particularly given the possibility of coexisting aortic and left ventricular abnormalities that may significantly influence surgical and subsequent medical management.

CV rehabilitation - State of the art and future

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Content:

Cardiac rehabilitation (CR) reduces readmissions by up to 30% and significantly decreases mortality following major cardiac events. However, traditional center-based programs face severe underutilization due to geographical, financial, and scheduling barriers. This abstract outlines the shifting paradigm of CR toward personalized, decentralized, and tech-enabled care models designed to overcome these historical limitations.

Asynthesis of contemporary clinical trends reveals a transition from rigid, in-clinic group sessions to dynamic, patient-centric interventions. These advancements leverage digital health infrastructure, remote patient monitoring (RPM), and artificial intelligence (AI) to optimize delivery and clinical outcomes.

The future of CR is defined by three interconnected pillars. First, decentralized telerehabilitation and hybrid models enable home-based, guideline-structured exercise. Safety is maintained via real-time vitals tracking using smartwatches, continuous blood pressure monitors, and electrocardiogram patches. This model also expands CR access to underserved populations, including stroke, transient ischemic attack (TIA), and heart failure patients. Second, AI and precision medicine are driving highly individualized programming. Adaptive algorithms dynamically adjust exercise parameters based on real-time biometric feedback, while Synchronized Cardiorespiratory Rehabilitation (SCR) optimizes exercise efficiency by pairing controlled movements with specific breathing patterns. Third, modern CR adopts a holistic approach by incorporating behavioral economics, structured psychosocial support to combat post-event depression, and comprehensive care pathways that simultaneously manage multimorbidities like diabetes and hypertension.

Conclusion: The integration of virtual platforms, wearable technology, and AI into cardiac rehabilitation represents a critical evolution in cardiovascular care. By replacing a one-size-fits-all approach with adaptable, remote, and holistic interventions, next-generation CR significantly improves patient uptake, adherence, and long-term survival rates.

Anthracycline-Related Ventricular Arrhythmia in Childhood Acute Lymphoblastic Leukaemia

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Content:

Anthracycline cardiotoxicity in childhood acute lymphoblastic leukemia (ALL) is defined predominantly by the occurrence of left-ventricular dysfunction, whereas arrhythmia remains a less-reported complication.

We report here two cases of pediatric patients diagnosed with ALL who developed ventricular extrasystoles at cumulative doses of anthracyclines and required different clinical management.

Both underwent serial 24-hour Holter monitoring, and echocardiography during the follow-up.

Cumulative anthracycline exposure was calculated from the treatment protocols as doxorubicin-equivalent.

An 18-month-old girl diagnosed with B-cell precursor ALL, intermediate risk (European Standard Clinical Practice Recommendations for ALL, 2022), received 240 mg/m² doxorubicin-equivalent. During reinduction she developed monomorphic, monotopic ventricular extrasystoles arising from the His bundle/right branch. Ejection fraction remained normal (61–82%), and although the Holter burden reached 7.5%, the arrhythmia was assessed as benign. Magnesium and propafenone achieved control; dexrazoxane was not required.

A4-year-old boy diagnosed with T-cell ALL, high risk (same protocol), received 390 mg/m² doxorubicin-equivalent. Polymorphic ventricular and supraventricular extrasystoles emerged after the first high-risk block. Dexrazoxane, a cardioprotective iron-chelating agent that reduces free-radical myocardial injury, was introduced to allow the anthracyclines to be continued and the protocol completed. Furthermore magnesium, propafenone and metoprolol were also administered. Persistent severe neutropenia followed, initially suspected to represent relapse. Marrow relapse was excluded and withdrawal of propafenone resolved the neutropenia, confirming an extremely rare propafenone-induced agranulocytosis.

In these two cases the same drug class elicited ventricular arrhythmia of different severity, each requiring an individual therapeutic approach. Therefore, cardiac evaluation pre- and post-anthracycline therapy should include also assessment of the heart rhythm, not only of the ejection fraction.

HYPERHOMOCYSTEINEMIA-ASSOCIATED CHANGES IN GINGIVAL BLOOD FLOW AND PERIODONTAL TISSUES

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Content:

Background: Hyperhomocysteinemia (HHcy) is associated with inflammation and bone resorption and is an established cardiovascular risk factor. Its effects on gingival blood flow and periodontal tissues remain insufficiently understood. This study examined these effects in mice with cystathionine β-synthase (CBS) deficiency and evaluated the potential protective effects of Lactobacillus rhamnosus (LGG).

Methods: Twenty-four mice were divided into four groups: wild-type mice (WT), CBS-deficient mice (CBS+/−), WT mice treated with LGG, and CBS+/− mice treated with LGG. LGG was administered orally at a reported dose of 2.5×10^5 CFU/day. Gingival blood flow was measured using laser Doppler flowmetry. Periodontal tissues were assessed by histomorphometry of hematoxylin and eosin (H&E) stained sections. MMP-9 activity was assessed by zymography, and the expressions of TNF-α, IL-1β, IL-6, OPG, and RANKL were assessed by quantitative real-time polymerase chain reaction. Results: HHcy was associated with reduced gingival blood flow, an increased distance between the cementoenamel junction and the alveolar bone crest, greater epithelial downgrowth, and fewer fibroblasts. LGG treatment was associated with lower inflammatory cytokine levels and improved periodontal tissue findings in CBS+/− mice.

Conclusion: HHcy was associated with impaired gingival blood flow and periodontal tissue damage in this mouse model. LGG showed potential protective effects on periodontal tissues, although its effect on gingival blood flow should be stated explicitly only if your measured results confirm it.

CAN HYPERBARIC OXYGENATION RESTORE REDOX BALANCE? INSIGHTS FROM EXPERIMENTAL AUTOIMMUNE MYOCARDITIS IN RATS

Aleksandra Stojanovic [1,2], Bozidar Pindovic [1,2], Maja Muric [2,3], Nevena Lazarevic [1,2,4], Ivan Srejovic [3,4], Djurdjina Petrovic [2], Aleksandar Kocovic [1,2], Vladimir Jakovljevic [2,3,5]

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Content:

Introduction: Myocarditis is still a major global health issue that frequently manifests due to oxidative stress, immune-mediated myocardial damage and unpredictable clinical progression. Given the pivotal role of oxidative stress in the pathogenesis of autoimmune myocarditis and the limited therapeutic options currently available, there is growing interest in non-pharmacological interventions that target redox imbalance and associated inflammatory processes. Hyperbaric oxygen therapy (HBOT) has been shown to modulate oxidative stress by restoring redox homeostasis while also exerting anti-inflammatory and cardioprotective effects. The aim of the study was to investigate the effects of HBOT on oxidative status and antioxidant capacity in rats with experimental autoimmune myocarditis (EAM).

Methodology: We randomly assigned 36 male Dark Agouti rats into six different groups (n=6 per group). The 21-day experimental groups included healthy control rats (CTRL21d), rats with EAM (MIO21d) and rats with EAM treated with HBOT from day 0 to day 21 (MIO+HBOT21d). The 42-day experimental groups included healthy control rats (CTRL42d), rats with EAM (MIO42d) and rats with EAM treated with HBOT from day 21 to day 42 (MIO+HBOT42d). EAM was induced via cardiac myosin immunization. HBOT was applied at 2.6 ATA either during the acute (days 0-21) or subacute phase (days 21-42) of the disease. Systemic redox status was determined spectrophotometrically in plasma and erythrocyte lysates by measuring the following pro-oxidant and antioxidant biomarkers: lipid peroxidation, expressed as TBARS, nitrites ($NO2^-$), superoxide anion radical ($O2^-$), hydrogen peroxide (H2O2), catalase (CAT), superoxide dismutase (SOD) and reduced glutathione (GSH).

Results: HBOT significantly increased the activity of the antioxidant enzymes CAT and GSH levels in the MIO+HBOT21d and MIO+HBOT42d groups compared with the untreated MIO21d and MIO42d groups, while SOD activity was increased in MIO+HBOT21d group. Compared with the untreated MIO groups, HBOT significantly reduced TBARS and H2O2 levels at both 21 and 42 days. HBOT also modulated $NO2^-$ and $O2^-$ levels.

Conclusion: HBOT improved redox homeostasis by reducing oxidative stress and enhancing endogenous antioxidant defenses. Specifically, HBOT decreased pro-oxidant biomarkers while increasing antioxidative capacity, supporting its potential as a cardioprotective therapy in EAM.

Effects of Four Weeks of Treadmill Training on Cardiovascular and Digestive System Alterations in Hyperhomocysteinemic Rats: Oxidative Stress, Biochemical Biomarkers, and Histomorphometric Changes

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Content:

Introduction: The aim of this study was to evaluate the effects of a four-week aerobic treadmill training program on oxidative stress and histomorphometric changes in the heart and colon of hyperhomocysteinemic rats.

Methodology: Male Wistar albino rats were divided into four groups (n = 10/group): control (C), receiving 0.9% NaCl subcutaneously twice daily; hyperhomocysteinemia (H), receiving homocysteine (0.45 μmol/g body weight/day, s.c., twice daily); control plus physical activity (CPA), receiving saline and treadmill training; and hyperhomocysteinemia plus physical activity (HPA), receiving homocysteine and treadmill training.

Results: In cardiac tissue, active hyperhomocysteinemic rats exhibited increased lipid peroxidation and higher relative Mn-superoxide dismutase activity compared with sedentary animals. Aortic atherosclerotic plaques were detected in the HPA group, together with increased left ventricular wall thickness, interventricular septal thickness, and cardiomyocyte transverse diameter relative to sedentary groups. In the colon, HPArats showed significantly higher malondialdehyde levels than CPArats, while catalase activity was significantly higher than in C, H, and CPAgroups. Total superoxide dismutase activity was also significantly increased in HPAanimals compared with all other groups. These findings indicate that aerobic treadmill training under hyperhomocysteinemic conditions may exacerbate oxidative stress and structural alterations in the cardiovascular system, while simultaneously inducing an antioxidant response in the colon through increased superoxide dismutase and catalase activities.

Conclusion: Overall, subchronic aerobic exercise in hyperhomocysteinemic rats appears to produce tissue-specific effects, potentially increasing cardiac and vascular injury while enhancing antioxidant defense mechanisms in the colon. These results highlight the importance of considering homocysteine status when evaluating systemic effects of exercise.

Augmented parasympathetic input in the treatment of heart failure

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Content:

Background. Autonomic imbalance, characterised by increased sympathetic activity and diminished parasympathetic influence on the heart, plays an important role in the development and progression of heart failure. Enhancement of cardiac cholinergic transmission through acetylcholinesterase inhibition has therefore been proposed as a potential cardioprotective strategy. The present study investigated the effects of pyridostigmine, a reversible, peripherally acting acetylcholinesterase inhibitor, in two experimental models of isoprenaline-induced cardiac dysfunction in rats.

Methods. Cardiac injury was induced using two different isoprenaline regimens: (1) two subcutaneous injections of 85 mg/kg administered on consecutive days, followed by a three-week treatment-free period, or (2) daily subcutaneous injections of 5 mg/kg for seven days, followed by four weeks without treatment. Subsequently, rats received pyridostigmine (20 mg/kg/day) in drinking water for two weeks. Cardiac function was evaluated by echocardiography and electrocardiography before and after pyridostigmine treatment. At the end of the experiments, tissue and blood samples were collected for histopathological examination and assessment of oxidative stress parameters.

Results. The two isoprenaline regimens produced different degrees of cardiac dysfunction. Acute administration of high doses caused only a modest reduction in left ventricular ejection fraction, whereas repeated administration of lower doses resulted in more pronounced systolic impairment, with ejection fraction values below 50%. Pyridostigmine improved echocardiographic parameters and attenuated histopathological alterations in both experimental models. Disturbances in oxidative stress parameters were observed primarily following repeated low-dose isoprenaline administration, and these changes were alleviated by pyridostigmine treatment.

Conclusion. Enhancement of peripheral cholinergic transmission by pyridostigmine improved cardiac functional and morphological parameters in rats with isoprenaline-induced cardiac dysfunction. These findings suggest that pharmacological augmentation of parasympathetic influence on the heart may represent a promising complementary approach to heart failure treatment, warranting further investigation.

Pomegranate seed oil promotes wound repair and modulates redox homeostasis in rats: Potential relevance to microvascular function

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Content:

Introduction: Oxidative stress and microvascular dysfunction are closely linked processes that may impair tissue repair. Pomegranate seed oil (PSO), rich in bioactive fatty acids, particularly punicic acid, has antioxidant and anti-inflammatory potential. This study investigated the effects of a topical PSO-containing gel formulation on wound contraction and selected markers of redox status in a rat excisional wound model, with consideration of mechanisms relevant to microvascular tissue repair.

Methodology: Standardized cutaneous wounds were established in rats assigned to control and PSO gel treated groups. Wound healing was evaluated on days 3, 7, and 14. Wound area was quantified from dermoscopic images using ImageJ, and wound contraction was calculated. Redox status was assessed by measuring thiobarbituric acid-reactive substances (TBARS), nitrite (NO_2^-), superoxide dismutase (SOD), reduced glutathione (GSH), and catalase (CAT) in skin tissue homogenates.

Results: Wound contraction in the PSO treated group reached 27.46%, 60.30%, and 100% on days 3, 7, and 14, respectively, compared with 5.05%, 26.02%, and 83.60% in control group. TBARS levels were lower in the treated group at all time points (4.35, 4.04, and 1.99) than in controls (5.22, 5.06, and 2.27), while NO_2^- concentrations were also reduced. SOD activity increased over time and reached 24.12 on day 14 in the treated group versus 21.71 in controls. CAT activity was consistently higher following PSO treatment, whereas GSH remained relatively stable.

Conclusion: Topical PSO-containing gel accelerated wound contraction and was associated with decrease of oxidative stress and enhancement of enzymatic antioxidant defense. These findings support a role for PSO in mechanisms regulated by redox signaling involved in tissue repair and suggest potential relevance to microvascular repair mechanisms. Further studies directly assessing angiogenesis, perfusion, and endothelial function are warranted.

Targeting MAO-Associated Oxidative Stress in Peritumoral Adipose Tissue with Metformin and SGLT2 Inhibitors

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Content:

Background: Peritumoral visceral adipose tissue represents an active component of the tumor microenvironment and may promote cancer progression through multiple pathomechanisms, with oxidative stress being one of the most extensively investigated one. Monoamine oxidases (MAO-Aand MAO-B), mitochondrial enzymes that generate hydrogen peroxide during amine catabolism, may represent previously underrecognized sources of reactive oxygen species (ROS) in the tumor-associated adipose tissue. This study investigated MAO expression and oxidative stress in human peritumoral and non-tumoral visceral adipose tissue (VAT) and evaluated the effects of metformin and SGLT2 inhibitors.

Methods: Paired peritumoral and non-tumoral VAT samples were collected from patients undergoing elective abdominal surgery for digestive malignancies. Tissue fragments were incubated ex vivo with metformin (10 µM), empagliflozin (1 µM), or dapagliflozin (1 µM). ROS production was assessed using the ferrous oxidation-xylenol orange (FOX) assay and dihydroethidium(DHE) staining. MAO-Aand MAO-B expression was evaluated by quantitative real-time PCR and immunofluorescence.

Results: Peritumoral VAT displayed significantly increased ROS production compared with the paired non-tumoral tissue, indicating a pronounced pro-oxidative phenotype. Both MAO-Aand MAO-B expression (mRNAand protein levels) was significantly elevated in peritumoral VA. Ex vivo incubation (12 h) with metformin, empagliflozin, or dapagliflozin significantly mitigated oxidative stress in both types of tissue sapmples. These treatments were also associated with a significant decrease in MAO-Aand MAO-B mRNAexpression.

Conclusions: Human peritumoral visceral adipose tissue exhibited enhanced oxidative stress and increased expression of both MAO isoforms. Metformin and SGLT2 inhibitors at relevant clinical doses attenuated this pro-oxidative phenotype and reduced MAO expression under ex vivo conditions, suggesting a potential pharmacological strategy for modulating redox imbalance within the tumor microenvironment.

Computational Approaches to Cardiovascular Drug Discovery

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Content:

Computational methods are increasingly shaping modern drug discovery by enabling the exploration of complex chemical spaces, prediction of molecular interactions, and prioritization of promising candidates before experimental evaluation. In cardiovascular research, where multiple molecular pathways and therapeutic targets are involved, in silico approaches provide valuable tools for connecting molecular structure with potential biological activity.

This lecture will provide an overview of computational strategies in cardiovascular drug discovery, with particular emphasis on molecular docking and molecular dynamics (MD) simulations. While molecular docking enables the prediction of plausible binding modes and key protein–ligand interactions, MD simulations extend this static picture by exploring the stability and dynamics of molecular complexes over time. Particular attention will be given to the interpretation and limitations of computational results and to their integration with experimental approaches.

Natural products offer an especially interesting field for such integrative strategies. As an illustrative case study, Geranium robertianum L., a medicinal plant with a history of traditional use, including applications related to elevated blood pressure, will be considered as a source of structurally diverse bioactive compounds. Its phytochemical profile includes ellagitannins, flavonoids and phenolic acids, providing a chemically rich starting point for investigating interactions with cardiovascular targets. Using angiotensin-converting enzyme (ACE1) as a representative antihypertensive target, the case study will illustrate how phytochemical information can be translated into a computational workflow involving ligand selection, molecular docking, analysis of protein–ligand interactions and MD simulations.

By linking traditional knowledge and phytochemical diversity with molecular-level investigation, computational approaches can help generate mechanistically informed and experimentally testable hypotheses. Rather than replacing experimental pharmacology, they provide a rational framework for prioritizing compounds, targets and experiments, thereby supporting more efficient exploration of natural products in cardiovascular drug discovery.

Levosimendan Pretreatment Attenuates Mesenteric Artery Ischemia/Reperfusion Injury and Cardiac Damage in Rats

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Content:

Background and Aim: Remote myocardial injury represents an important manifestation of multiple-organ dysfunction following mesenteric ischemia–reperfusion (I/R). Systemic oxidative stress and inflammatory responses triggered by intestinal I/R may contribute to myocardial damage, highlighting the need for effective cardioprotective strategies.
Levosimendan, a calcium-sensitizing inodilator with reported antioxidant, anti-inflammatory, and anti-apoptotic properties, may attenuate these effects. This study aimed to investigate the cardioprotective effects of levosimendan, focusing on oxidative stress, inflammation, apoptosis, and the potential involvement of nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) and sirtuin 1 (SIRT1) signaling pathways.

Materials and Methods: Twenty-four male Wistar albino rats were randomized into four groups: control (sham), I/R, levosimendan (LS), and LS + I/R. Mesenteric ischemia was induced by superior mesenteric artery occlusion for 30 minutes, followed by 90 minutes of reperfusion. Levosimendan (1 mg/kg, intraperitoneally) was administered 30 minutes before ischemia. Myocardial injury was assessed by histopathology, biochemical analysis of oxidative stress markers (TBARS, NO_2^-, SOD, CAT, GSH), gene expression analysis (CAT, SOD, Nrf2, NF-κB, HO-1, SIRT1), and immunohistochemistry (CC3, phosphorylated NF-κB, SIRT1, Nrf2, HO-1).

Results: Levosimendan pretreatment significantly reduced myocardial damage, preserving cardiomyocyte integrity and reducing inflammatory infiltration. Biochemical analysis demonstrated reduced cardiac TBARS and nitrite levels and increased CAT and GSH activity. These improvements were accompanied by increased myocardial mRNAexpression of CAT, SOD, SIRT1, Nrf2 and HO-1. Immunohistochemical analysis revealed enhanced SIRT1, Nrf2, HO-1 expression, along with reduced phosphorylated NF-κB and cleaved caspase-3 staining, suggesting attenuation of inflammatory and apoptotic responses.

Conclusions: Levosimendan pretreatment attenuated remote myocardial injury following mesenteric I/R. Its cardioprotective effects were associated with reduced oxidative stress and modulation of inflammatory and apoptotic responses, potentially involving the SIRT1, Nrf2/HO-1 and signaling pathways.

CHOOSING A REPLICABLE ECHOCARDIOGRAPHIC ENDPOINT: A WITHIN-LABORATORY REPRODUCIBILITY ANALYSIS OF FIVE ISOPRENALINE STUDIES IN RATS

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Content:

Introduction

The isoprenaline (ISO) rat model is among the most widely used methods in experimental cardiology, yet its reproducibility is usually assumed rather than measured, and has been examined between laboratories far more often than between successive experiments within one. We audited five consecutive ISO studies from a single laboratory to ask which echocardiographic endpoints actually replicate.

Methods

We retrospectively analysed all echocardiographic records from five consecutive ISO studies performed in our laboratory between August 2024 and March 2025: 90 records (34 control, 56 ISO) forming nine ISO-versus-control contrasts from 24 h to 35 days after exposure. Three studies used a high-dose bolus (85 mg/kg on two consecutive days), and two used repeated dosing (1 or 5 mg/kg/day for 7 days). Fifteen structural and functional parameters were compared within studies by repeated-measures or one-way ANOVA with Holm correction, and between studies by random-effects pooling of standardised effect sizes (pooled Hedges' g), with I^2, and 95 % prediction intervals.

Results

ISO indicated depressed systolic function in all nine contrasts, with the magnitude of the fall in ejection fraction (EF) ranging from 30.6% to 51.6% ($p < 0.001$). Control cohorts were themselves not interchangeable (baseline body mass 204-373 g, baseline EF 70.8-82.8 %; both $p \leq 0.017$), and cohort predicted baseline geometry independently of body mass. Reproducibility proved to be an attribute of the endpoint rather than of the model: end-systolic volume was the most stable (g 2.30, I^2 13 %, prediction interval 1.25 to 3.34), then fractional shortening (g 3.61, I^2 28 %) and end-systolic diameter (g 2.67, I^2 38 %), whereas EF had the largest pooled effect (g 3.92) but the greatest heterogeneity (I^2 59 %).

Dose-dependence was preserved within one experiment (5 vs 1 mg/kg at 28 days: -11.7 % of EF, $p = 0.028$).

Conclusions

In single laboratory using one nominal protocol, the direction of the isoprenaline effect was perfectly reproducible, but its magnitude varied enough that a future replication could not be confidently predicted, and reproducibility depended strongly on the endpoint chosen. End-systolic measures should serve as the primary echocardiographic endpoint in this model.

Each study needs its own concurrent controls and sample size calculations based on the lower bound of the prediction interval, rather than on the last effect observed.

Assessment of the arrhythmogenic effect of action potential – and Ca2+ transient alternans in a canine athlete's heart model

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Content:

Introduction: Regular physical training is widely recognized for its beneficial effects on the cardiovascular system and overall quality of life. However, increasing number of evidence indicates a higher prevalence of cardiac arrhythmias and an increased incidence of sudden cardiac death (SCD) among elite athletes. The underlying mechanisms of these exercise-induced adverse outcomes remain incompletely understood. Here we report on a large animal model of athlete's heart and demonstrate that intensive exercise-induced electrical remodelling facilitates the development of cardiac alternans, which may serve as a substrate for arrhythmogenesis.
Methods: Atotal of 24 Beagle dogs of both sexes were randomly assigned to sedentary control or trained groups. The trained group was subjected to a 16-week vigorous treadmill running protocol. Following the training period, comprehensive electrophysiological and molecular assessments were performed, including in vivo arrhythmia provocation, action potential measurements in left ventricular cardiomyocytes and tissue slices, patch-clamp recordings from isolated left ventricular cells, and Western blot analyses.
Results: Trained animals exhibited increased susceptibility to arrhythmias in vivo compared to sedentary controls. At the cellular level, cardiomyocytes from trained animals exhibited prolonged action potential duration, and enhanced action potential- and Ca2+ transient alternans. Additionally, sarcoplasmic reticulum Ca2+ content was reduced, while Ca2+ buffering capacity was increased, indicating remodelling of calcium dynamics. Western blot analysis revealed downregulation of CACNA1C (L-type Ca2+ channel) expression.
Conclusion: These findings suggest that chronic intensive physical training induces electrical and calcium handling remodelling in the canine heart, promoting the development of cardiac alternans. This proarrhythmic substrate may underlie the increased susceptibility to ventricular arrhythmias observed in elite athletes. Overall, our results provide novel insights into the mechanisms underlying malignant cardiac arrhythmias and sudden cardiac death in competitive athletes.

CADASIL and small vessel disease – defining new therapeutic targets for vascular dementia

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Content:

Small vessel disease (SVD) is a pathological condition that involves vessels <250 μm in diameter. It is characterized by abnormal vascular smooth muscle (VSMC) function leading to altered vasoreactivity, arterial remodeling and fibrosis and ultimately results in tissue damage and progressive organ failure. SVD has a wide array of clinical presentations, including hypertension, microvascular angina, kidney failure, blindness, stroke and dementia and is a major cause of morbidity and mortality. Aunifying concept is that SVD of specific organs is indicative of systemic disease that worsens with age and vascular risk factors. Hence the notion that SVD is a multisystem disorder. SVD of the brain (cerebral SVD, cSVD) causes dementia, a growing health burden worldwide. Dementia is defined by deterioration of cognitive function that surpasses the expected age-related cognitive decline. The impact of dementia to the individual, their families and communities is enormous. There are no specific treatments and exact mechanisms remain unclear. Genetic studies revealed an important pathophysiological role for NOTCH3 receptor in cSVD since NOTCH3 mutations cause Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), a monogenic form of cSVD. CADASIL is the most common inherited cause of stroke and is a debilitating progressive disease leading to vascular dementia in young adults. Studying SVD in one clinical context may uncover shared pathologic mechanisms that could inform novel treatments. Here we address gaps in knowledge by focusing on CADASIL. Studies from my lab have identified an important role for oxidative stress, ER stress and activation of RhoA/Rho kinase in vascular dysfunction in CADASIL. These are druggable targets. We focus on RhoA/Rho kinase inhibition as a potential therapeutic strategy, especially since the Rho kinase inhibitor fasudil is an FDA-approved drug for rare diseases.

Mechanistic Approaches to Sudden Cardiac Arrest: Insights from Experimental Animal Model Studies on the Roles of Nutraceuticals

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Content:

Sudden cardiac arrest (SCA) remains a major global health challenge, characterized by the abrupt cessation of effective cardiac activity and an exceptionally high mortality rate. Although ventricular arrhythmias, electrical instability, structural cardiac remodeling, and disturbances in intracellular ion homeostasis are recognized as major contributors to SCA, the complex molecular and cellular mechanisms underlying its initiation and progression remain incompletely understood. Increasing evidence from experimental animal models indicates that increased oxidative stress at the systemic and organ levels, together with impaired energy metabolism, may converge to create a highly arrhythmogenic cardiac substrate. In this context, we aimed to evaluate the effects of pine bark extract (PBE), a nutrient-derived supplement with antioxidant properties, in an isoproterenol (ISO)-induced cardiac injury model to determine whether PBE exerts preventive, therapeutic, or both types of cardioprotective effects.

PBE supplementation administered either before or after ISO treatment significantly attenuated oxidative stress at both the systemic and organ levels, not only in the heart but also in the liver. Furthermore, the increased heart rate and prolonged QRS duration and QT interval observed in in situ ECG recordings of the ISO group were significantly normalized following PBE administration, accompanied by improvements in cardiac tissue structure. Importantly, the prolonged Tpeak–Tend (Tp-e) interval, a marker of ventricular repolarization heterogeneity and arrhythmogenic risk, was also significantly restored by both pre- and post-ISO PBE administration. To further investigate whether PBE exerts cardioprotective effects through restoration of mitochondrial redox homeostasis, complementary in vitro studies were performed using AC16 human cardiomyocytes subjected to aging combined with metabolic stress or direct β-adrenergic stress, with or without PBE treatment.

Overall, our findings demonstrate that PBE protects mitochondrial function through the regulation of oxidative stress, significantly improves mitochondrial membrane potential, normalizes markers of mitochondrial fission, reduces excessive ROS accumulation, restores intracellular ATP levels, and attenuates inflammatory and apoptotic responses, accompanied by improved cellular morphology. Collectively, these in vivo and in vitro findings suggest that PBE exerts multifaceted cardioprotective effects in pathological c

ICE guided pulse field electroporation for AF ablation

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Content:

Background: Pulsed field ablation (PFA) has emerged as a revolutionary, non-thermal energy modality for the catheter-based treatment of atrial fibrillation (AF). By leveraging ultra-rapid electrical pulses to induce irreversible electroporation, PFAselectively destabilizes myocardial cell membranes while sparing vital adjacent structures, such as the esophagus and phrenic nerve. However, standard PFAworkflows remain heavily reliant on fluoroscopy for positioning and assessing tissue contact, introducing cumulative radiation risks to both patients and operators. Intracardiac echocardiography (ICE) offers a compelling solution to achieve a near-zero or completely fluoroless workflow by providing real-time, high-resolution visualization of left atrial anatomy and catheter apposition.

Methods: We analyzed a cohort of consecutive patients with symptomatic paroxysmal AF who underwent PVI using a multi-electrode PFAcatheter system. Procedures were performed utilizing an integrated workflow where all critical stages—including transseptal puncture, left atrial navigation, catheter deployment, and circumferential tissue contact verification—were guided continuously under ICE visualization. Procedural metrics, including total procedure duration, total fluoroscopy exposure time, acute isolation success, and peri-procedural safety outcomes, were systematically evaluated.

Results: Active ICE-guided PFAachieved 100% acute pulmonary vein isolation across all targeted segments. Direct ultrasound visualization facilitated optimized catheter-tissue contact. No major adverse events, including cardiac tamponade, stroke, or persistent phrenic nerve injury, were observed. The integration of ICE led to a reduction in median fluoroscopy time compared to standard historic control workflows, successfully establishing a near-zero radiation environment without significantly extending overall procedural duration or compromising lesion deployment efficiency.

Conclusions: Integrating ICE into pulsed field electroporation procedures is highly feasible, safe, and efficient. Real-time ultrasound imaging enables direct tissue contact evaluation to maximize lesion durability. Most importantly, an ICE-guided approach drastically reduces or eliminates ionizing radiation exposure for the clinical team and the patient, representing a significant milestone in modern fluoroscopy sparing arrhythmia management workflows.

Multi-Scale Membrane Biophysics in Atherosclerosis: From Disease Signatures to Endothelial Mechanisms

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Content:

Introduction:Atherosclerosis is characterized by profound alterations in lipid metabolism,although these changes converge into a common membrane biophysical phenotype across different biological scales remains unknown.Because membrane organization governs receptor signalling, cellular metabolism and homeostasis, understanding its functional significance could provide new mechanistic insight into vascular disease.We therefore investigated membrane biophysical remodeling across complementary biological systems and examined its mechanistic relevance in endothelial dysfunction, the earliest pathological event in atherosclerosis. Methodology:Acomplementary multi-scale workflow was established.Spectral biophysical cytometry was used to profile membrane order and mitochondrial polarization across immune cell subsets from patients with atherosclerosis.Single-particle profiling was subsequently used to characterize membrane biophysical properties of circulating extracellular vesicles across disease stages.To investigate the functional significance of membrane remodeling, mechanistic endothelial studies employed cholesterol depletion (MβCD), followed by pharmacological modulation with isoproterenol or tirzepatide.
Results:SBC identified cell type-specific membrane biophysical remodeling in circulating immune cells, characterized by coordinated alterations in membrane order and mitochondrial polarization, most pronounced in $CD4^+$ and $CD8^+$ T-cells.Lipidomic and transcriptomic analyses linked these signatures to ether lipid depletion,lysophospholipid enrichment and metabolic adaptation.Independent SPP analyses demonstrated stage-dependent remodeling of extracellular vesicle membrane biophysical properties, indicating that membrane remodeling is detectable at both cellular and nanoscale levels. Mechanistic endothelial studies showed that cholesterol depletion reorganized caveolae-associated signalling networks, resulting in oxidative stress, mitochondrial dysfunction and endothelial impairment, whereas pharmacological modulation with isoproterenol or tirzepatide restored membrane organization and downstream endothelial homeostasis. Conclusion:Together, these findings establish membrane biophysical remodeling as a shared feature of atherosclerosis across multiple biological scales and demonstrate that membrane organization is a functional determinant of endothelial homeostasis.

Diagnostic Utility of a Chromogenic Factor X Assay: From Dose Optimization to Emergency Thrombolysis

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Content:

Introduction:
Coagulation factor X (FX) has become a primary target for anticoagulant therapies due to its central role in the coagulation cascade. However, conventional coagulation assays are unreliable to monitor the efficacy of direct FX inhibitors.
Nonetheless, identification of individuals under Factor Xa inhibitory medication is critical during thrombotic emergencies, where thrombolysis is contraindicated until the absence of a clinically significant anticoagulant effect is confirmed to mitigate the risk of fatal bleeding. Here we made an effort to develop a quantitative assay suitable for measuring the effects of direct FX inhibitors and to determine the diagnostic value in indentify patients taking such drugs.
Methodology:
Measurements were performed across ascending 4- to 1024-fold serial dilutions using a COBAS Integra 400 clinical chemistry analyzer. FX was activated using Russell's viper venom (RVV). Following a 3- to 12-minute incubation, a chromogenic substrate (Z-D-Arg-Gly-Arg-pNA) was applied to assess enzymatic activity. The clinical study included 137 cardiology patients divided into a retrospective cohort (n=60) and a prospective cohort (n=76; 54 untreated controls, 22 treated with FX inhibitors based on self-reporting).
Results:
Receiver operating characteristic (ROC) analysis of the retrospective cohort yielded an area under the curve (AUC) of 0.85. In this cohort, we distinguished patients before and after taking FX inhibitors with 72.73% sensitivity and 81.48% specificity, and identified 14 patients whose FX inhibitor therapy could be optimized to reduce bleeding risk. For the prospective cohort, ROC analysis yielded an AUC of 0.977, enabling the differentiation of treated and untreated patients with 100% sensitivity and 90.74% specificity.
Conclusion:
The established chromogenic FX activity measurement can reliably distinguish between FX inhibitor-treated and untreated patients while quantifying individual pharmacodynamic differences. This assay may support critical clinical decision-making during thrombotic emergencies and improve the therapeutic monitoring and adherence of patients receiving FX inhibitor therapy. In particular, the assay can be used to optimize Factor Xa inhibitory drug treatment tailored to the individual patient's needs.

Coronary CT Angiography as a Primary-Care Gatekeeper: A 230-Patient Analysis of Diagnostic Yield, Safety, and Radiation Dose

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Content:

Introduction: Coronary CT angiography (CCTA) is increasingly positioned by contemporary (2024 ESC) guidelines as a first-line, non-invasive gatekeeper for suspected chronic coronary syndrome, potentially reducing unnecessary invasive angiography. Real-world data on CCTAperformance, safety and radiation exposure when ordered directly from primary care, rather than hospital cardiology, remain limited. We report a single-center descriptive experience from this pathway.

Methodology: We retrospectively analyzed 230 consecutive CCTAexaminations (mean age 64.6 years, 67% female) referred directly from primary care. For each patient we recorded coronary artery calcium score (CACS), CAD-RADS-oriented findings, high-risk plaque (HRP) morphology extracted from report text, documented adverse events, need for direct escalation to hospital-based invasive care, and radiation exposure (dose-length product converted to estimated effective dose).

Results: CACS was 0 in 37% of patients and severe (>400) in 20%. High-risk plaque morphology, predominantly heterogeneous plaque, was described in 9.1% (21/230); no CACS=0 patient showed HRP features in this sample. Only 1.3% (3/230) required direct escalation to hospital care for severity, suggesting CCTAeffectively filtered most referrals before invasive work-up. Adverse events were uncommon (1.7%): two contrast anaphylactic reactions, one urticaria, and one post-procedural chest pain/presyncope episode, all without lasting sequelae. Mean estimated effective dose was approximately 9.0 mSv (range 0.5–30.9), broadly consistent with reported CCTAdose ranges; the most recently scanned patients showed a modest reduction versus the earlier cohort (8.2 vs 9.1 mSv), suggesting possible incremental protocol optimization over time.

Conclusion: In this primary-care-initiated cohort, CCTAappeared to serve as a reasonably effective and safe triage tool, reassuring most patients while appropriately escalating only a small minority to invasive care. Radiation exposure remained within reported ranges, with a suggestion of improvement over time, though further dose-optimization consistent with ALARAprinciples may be warranted. Given the retrospective, single-center, descriptive design and modest sample size, these observations are preliminary and hypothesis-generating, warranting confirmation in larger, prospective, multicenter cohorts before informing broader recommendations on primary-care CCTApathways.

HELICHRYSUM ITALICUM ESSENTIAL OIL - BASED OINTMENT ALLEVIATES CARRAGEENAN-INDUCED ACUTE INFLAMMATION THROUGH REDOX MODULATION

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Content:

Introduction: Helichrysum italicum (immortelle) essential oil is recognized for its antioxidant and anti-inflammatory properties, making it a promising candidate for the development of topical formulations intended for inflammatory skin disorders. However, its efficacy in acute inflammation models has not been sufficiently investigated. Therefore, this study aimed to evaluate the anti-inflammatory and antioxidant effects of an ointment containing immortelle essential oil in a carrageenan-induced paw edema model in rats.

Methodology: Acute inflammation was induced by subplantar injection of 0.5 mL of 1% carrageenan into the left hind paw of Wistar albino rats. Atotal of 24 animals were divided into four experimental groups: untreated control (CTRL), 1% hydrocortisone ointment, ointment base, and 0.5% immortelle essential oil ointment. Topical formulations were applied 60 min before carrageenan administration. Paw thickness was measured before carrageenan injection and at 1, 2, 3, and 4 h thereafter to evaluate edema formation. At the end of the experiment, paw tissues were collected to determine lipid peroxidation (TBARS) and antioxidant defense parameters, including catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH).

Results: The immortelle essential oil ointment significantly attenuated carrageenan-induced paw edema, with the most pronounced effect observed during the late inflammatory phase. Edema inhibition reached 42.55% and 59.00% at the third and fourth hour, respectively, and was consistently greater than that achieved with the ointment base. Biochemical analysis of paw tissue demonstrated a marked reduction in TBARS levels in the immortelle-treated group, indicating decreased lipid peroxidation. In addition, CAT and SOD activities were significantly increased compared with the control groups, suggesting enhanced endogenous antioxidant defense. No significant differences in GSH levels were observed among the experimental groups.

Conclusion: Topical treatment with an Helichrysum italicum essential oil-based ointment effectively reduced acute inflammatory edema and improved the oxidative status of inflamed tissue. These findings indicate that immortelle essential oil ointment may represent a promising natural topical approach for the management of acute inflammatory conditions through the combined modulation of inflammatory responses and oxidative stress.

Evaluation of a Galium verum-Based Formulation for the Treatment of Recurrent Aphthous Stomatitis: Effects on Oral Ulcer Healing and Oxidative Stress in Rats

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Content:

Introduction: Recurrent aphthous stomatitis (RAS) is the most prevalent chronic ulcerative disorder affecting the oral mucosa. Based on the clinical presentation and morphological characteristics of the lesions, RAS is classified into three clinical forms. Increasing evidence suggests that oxidative stress contributes to the pathogenesis of RAS, as patients with the disease exhibit an imbalance between pro-oxidant production and antioxidant defense mechanisms. Current treatment is primarily aimed at relieving symptoms and reducing inflammation, with antiseptic agents commonly included in therapeutic protocols. In recent years, medicinal plants have attracted growing interest as complementary therapeutic agents. Owing to its diverse pharmacological properties, particularly its wound-healing potential, Galium verum L. represents a promising natural candidate for the treatment of aphthous lesions.This study aimed to evaluate the therapeutic efficacy of a Galium verum L. extract-based formulation in an experimental rat model of aphthous stomatitis.

Materials and Methods: The study was conducted on 36 Wistar albino rats with experimentally induced aphthous stomatitis. The animals were randomly assigned to three experimental groups. Clinical progression and healing of the oral ulcers were monitored daily throughout the study. Animals were euthanized on days 0, 3, 6, and 10, and buccal tissue samples were collected for further analyses. In addition to clinical assessment, oxidative stress parameters in the buccal tissue were determined using spectrophotometric methods to evaluate the effects of the applied formulation.

Results: Treatment with the Galium verum extract-based formulation significantly accelerated ulcer healing, resulting in a marked reduction in lesion size and inflammatory changes compared with the control group. Furthermore, administration of the formulation significantly improved the redox balance in the affected buccal tissue, indicating its antioxidant activity. Conclusion: The findings of this study demonstrate that a Galium verum L. extract-based formulation promotes healing of aphthous lesions and favorably modulates oxidative stress in an experimental model of recurrent aphthous stomatitis.

These results suggest that this herbal formulation may represent a promising adjunctive therapeutic approach for the management of oral ulcerative lesions.

HIF-1α Protects the Chronically Hypoxic Heart Through Mitophagy and mPTP Regulation

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Content:

Adaptation to chronic hypoxia (CH) is a cardioprotective phenomenon that enhances ischemic tolerance, providing long-lasting protection exceeding any forms of preconditioning. Adaptation to CH is characterized by stabilization of transcription factor hypoxia-inducible factor-1α (HIF-1α). However, the precise molecular mechanisms underlying the cardiac protection against I/R injury remain unclear. Therefore, we aim to elucidate the role of HIF-1α in CH-induced cardioprotection.

Adult male wild-type (WT) and heterozygous Hif1a knockout (Hif1a+/−) mice were exposed to chronic hypoxia (CH; 7000 m, 8 h/day for 4 weeks) or kept in normoxia. Isolated hearts were subjected to global ischemia/reperfusion (I/R) to determine infarct size. Expression analyses, mitochondrial respiration and electron microscopy were performed to evaluate mitochondrial characteristics. Oxidative stress was assessed by various assays, while mitochondrial permeability transition pore (mPTP) opening was evaluated by calcium retention capacity. The expression and subcellular distribution of selected proteins were further assessed by proteomics and Western blotting. In parallel, the role of HIF-1α in protection was examined in transfected human AC16 cardiomyocytes.

CH reduced infarct size in a HIF-1α-dependent manner, as this protection was absent in $Hif1a^{+/-}$ mice. HIF-1α deficiency altered mtDNAcontent, mitochondrial morphology, respiration, and protein expression, indicating that HIF-1α contributes to mitochondrial dynamic and quality control. Inhibition of mitochondrial fission abolished the infarct size-limiting effect of CH, supporting an essential role for HIF-1α-mediated mitophagy in CH-induced cardioprotection. Proteomic analysis further revealed extensive CH-induced remodeling, a substantial proportion of which was dependent on HIF-1α. CH enhanced antioxidant defense, attenuated oxidative stress, and promoted the protective translocation of hexokinase-2 to mitochondria, consistent with modulation of mPTP susceptibility. In line with these findings, HIF-1α overexpression increased AC16 cell survival during H_2O_2-induced oxidative stress, whereas its pharmacological inhibition reduced cell viability.

Together, these findings demonstrate that HIF-1α is a key mediator of CH-induced cardioprotection, improving mitochondrial dynamics, antioxidant defense, and mitochondrial mechanisms involving mPTP opening.

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Two sides of the same heart: Genetic and functional differences between the human right and left ventricle

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Content:

Cardiac cyclic nucleotide signalling has long been studied in ventricular myocardium in animal models. Many experimental studies utilise cardiomyocytes isolated from mixed ventricular preparations without distinguishing between chambers. The right ventricle (RV) and left ventricle (LV) differ markedly in structure, workload and sensitivity to haemodynamic stress, pointing towards chamber-specific signalling mechanisms playing a role in cardiac physiology. To investigate this, we quantified the expression of genes involved in cyclic nucleotide signalling pathways and the levels of cAMP and cGMP n human RV and LV using quantitative RT-qPCR and fluorescence resonance energy transfer (FRET).

Our results suggest a potential enhancement of cGMP signalling in the RV. Expression of both soluble guanylyl cyclase subunits (sGCα and sGCβ), key components of the nitric oxide–dependent pathway, was increased in the RV compared with the LV. In contrast, components of the natriuretic peptide axis, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and the clearance receptor NPR3, were reduced. Enzymes involved in cyclic nucleotide degradation, including neprilysin (NEP) and phosphodiesterases, were also differentially expressed, supporting increased cGMP signalling capacity in the RV.

In parallel, most of the genes involved in cAMP pathways were not changed, but β1-adrenergic receptor expression was elevated in the RV, suggesting greater sensitivity to sympathetic stimulation.

Interestingly, cGMP levels were similar in myocytes from both ventricles upon SNAP and CNP stimulation. However, cAMP production in the two chambers differs. In the RV in fact, cAMP reaches higher levels compared to the LV. Additionally, the kinetics of response to adrenergic stimulus appear to be faster compared to the LV. In line with this, the expression level of b1 adrenergic receptors is significantly increased in the RV.

Given the thinner RV wall and its greater sensitivity to afterload, this signalling profile may support both protective cGMP signalling and rapid adrenergic-mediated inotropic adaptation.

"Novel approaches in stem cell therapies for cardiovascular repair - focus on extracellular vesicles"

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Content:

Growing evidence indicates extracellular vesicles (EVs) released by mammalian stem cells (SCs) of various origin as important mediators of cell-to-cell communication, transferring their bioactive components including mRNAs, miRNAs, proteins and lipids between cells, which may provide pro-regenerative effects in injured tissue repair. Several SC fractions have been indicated as valuable donor cells releasing EVs with therapeutic potential, such as mesenchymal stem/ stromal cells (MSCs) and induced pluripotent stem cells (iPSCs).

Recent studies including the findings from our research laboratory indicate that iPSC-derived EVs (iPSC-EVs) and MSC-EVs may be enriched in several mRNAs, miRNAs and proteins supporting regeneration of injured tissues, including infarcted myocardium. It has been demonstrated that the SC-EVs are capable to effectively transfer their bioactive cargo to mature somatic cells in places of tissue injury and significantly impact on functional properties of such target cells including on their proliferation activity, survival, metabolic status and differentiation potential both in in vitro and in vivo conditions. By using several ischemic tissue injury in vivo, we have demonstrated that administration of MSC-EV or iPSC-EVs with specific molecular cargo including specific miRNAmolecules, may safely and effectively provides beneficial effects in tissue repair by stimulating angiogenesis and increasing cell survival and proliferation in place of injury. Thus, the SC-EV- based strategies represent a safe therapeutic approach with no side effects related to the administration of entire stem cells such as e.g. pluripotent iPSCs.

Moreover, it has been demonstrated that the bioactive and pro-regenerative potential of SC-EVs of various origin may be enhanced by genetic modifications enriching their bioactive molecular composition, which gives new opportunities for future more effective and optimized use of SC-EVs in clinical applications, including in pro-regenerative therapies of ischemic cardiovascular tissue injuries.

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Unraveling the Physiological Cascade of Atherosclerotic Remodeling in Coronary Arteries

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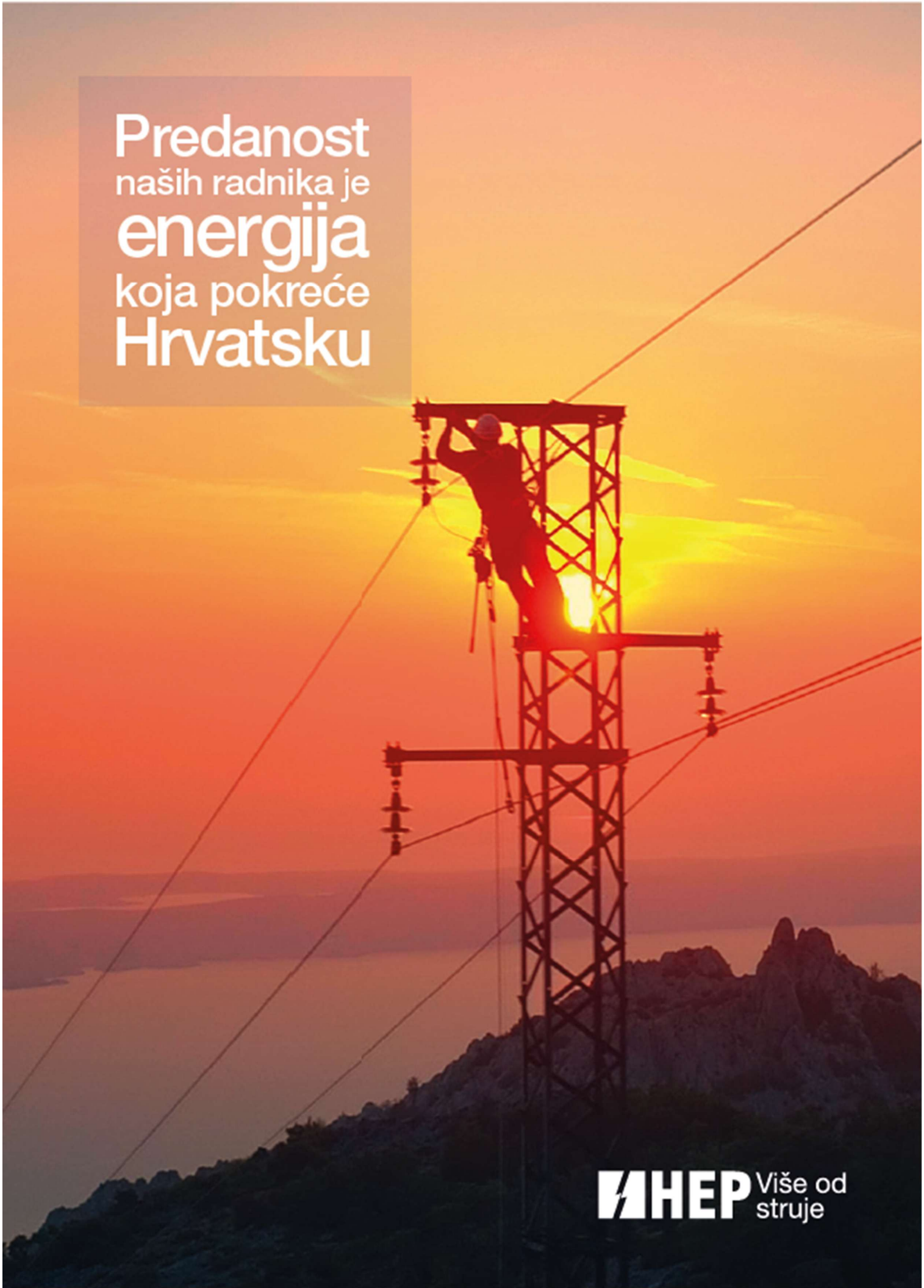
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Coronary artery remodeling in atherosclerosis is not a sudden pathological event, but rather a highly orchestrated physiological cascade that originates at the endothelial interface. Understanding the early biophysical and chemical triggers of this process is crucial for developing targeted preventive strategies.

This lecture aims to delineate the step-by-step physiological cascade that initiates coronary remodeling, focusing on how early endothelial barrier dysfunction facilitates the transition from lipid accumulation to structural vessel modification. The process begins with localized endothelial dysfunction, often triggered by disturbed hemodynamic shear stress. This disruption compromises the tight junctions of the endothelial monolayer, drastically increasing vascular permeability.

Consequently, low-density lipoproteins (LDL) readily penetrate and become trapped within the subendothelial space. Isolated from plasma antioxidants, these retained LDL particles undergo chemical modification by reactive oxygen species (ROS), yielding oxidized LDL (ox-LDL). As a potent pro-inflammatory stimulus, ox-LDL triggers the recruitment of circulating monocytes, which differentiate into macrophages and transition into foam cells upon lipid engulfment. This inflammatory microenvironment ultimately signals vascular smooth muscle cells to undergo phenotypic switching, migrating and synthesizing extracellular matrix to form a fibrous cap—marking the definitive structural remodeling of the coronary wall.

By dissecting this physiological cascade from barrier disruption to matrix reorganization, this presentation highlights the critical early windows of intervention where preserving endothelial integrity can stop adverse coronary remodeling before irreversible structural changes occur.


Predanost
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