Final report

on the K120536 grant of the National Research, Development and Innovation Fund of Hungary

Short summary of research results:

I. Apelin regulates skeletal muscle adaptation to exercise

Aging and muscle wasting are associated with reduced plasma levels of apelin. We aimed to investigate the significance of apelin signaling in cardiac and skeletal muscle response to physiologic stress. Apelin knockout (KO) and wild type (WT) mice were subjected to high intensity interval training (HIIT) treadmill running exercise. Primary skeletal muscle myotubes and cardiomyocytes were used to study the direct effects of apelin on energy metabolism. Apelin increased mitochondrial ATP production, mitochondrial coupling efficiency in myotubes and promoted the expression of mitochondrial genes in primary myotubes and cardiomyocytes. HIIT induced mild concentric cardiac hypertrophy in WT mice, whereas apelin KO mice showed eccentric growth of the left ventricles. HIIT did not affect skeletal muscle fiber size in WT mice but decreased the muscle fiber size in apelin KO mice. The decrease in fiber size resulted from a fiber type switch towards smaller slow-twitch type I fibers. The increased proportion of slow-twitch type I fibers in apelin KO mice was associated with increased myosin heavy chain slow isoform mRNA expression, decreased expression of glucose metabolism related genes and increased expression of fatty acid transport related genes. Mechanistically, skeletal muscles of apelin KO mice showed defective induction of insulin-like growth factor-1 expression and signaling in response to HIIT. In conclusion, apelin is required for proper skeletal and cardiac muscle adaptation to physiological stress. High intensity physiological stress in the absence of apelin leads to aged muscle phenotype. Restoring apelinergic signaling may have benefits in treatment of aging- or disease-related muscle wasting.

[Kilpiö et al. 2023; manuscript is under revision in Am J Physiol Cell Physiol.]

II. Apelin as a potential regulator of peak athletic performance

Apelin, as a cardiokine/myokine, is emerging as an important regulator of cardiac and skeletal muscle homeostasis. Loss of apelin signaling results in premature cardiac aging and sarcopenia. However, the contribution of apelin to peak athletic performance remains largely elusive. Herein, we assessed the impact of maximal cardiorespiratory exercise testing on the plasma apelin levels of 58 male professional soccer players. Circulating apelin-13 and apelin-36, on average, increased transiently after a single bout of treadmill exercise; however, apelin responses (Δapelin = peak – baseline values) showed a striking interindividual variability. Baseline apelin-13 levels were inversely correlated with those of Δapelin-13 and Δapelin-36. Δapelin-13 showed a positive correlation with the maximal metabolic equivalent, relative maximal O_2 consumption, and peak circulatory power, whereas such an association in the case of Δapelin-36 could not be detected.

In conclusion, we observed a pronounced individual-to-individual variation in exercise-induced changes in the plasma levels of apelin-13 and apelin-36. Since changes in plasma apelin-13 levels correlated with the indicators of physical performance, whole-body oxygen consumption and pumping capability of the heart, apelin, as a novel exerkine, may be a determinant of peak athletic performance.
[Ligetvári et al. Int J Mol Sci. 2023,24,8195. doi: 10.3390/ijms24098195]

III. Extreme psychological and physical stress differentially regulates plasma apelin levels in professional athletes

Apelin, as a novel exerkine, is emerging as a potential regulator of peak athletic performance. High performance athletes are under considerable physical and psychological stress. We aimed to compare the effects of extreme physical and psychological stress on plasma apelin levels in male professional athletes. A physical stress test was carried out in an exercise physiology laboratory, where subjects completed an incremental treadmill running test to full exhaustion, and a psychological test was performed in a military tactical room, where subjects met a street offense situation. Systolic and diastolic blood pressures and heart rate changed significantly during both stress protocols, with distinct patterns. Circulating levels of apelin-13 and apelin-36 were temporarily elevated after a single bout of maximal treadmill exercise. During psychological stress, peak apelin-13 values did not change from baseline, but showed a significant decrease during recovery. In contrast, apelin-36 levels remained unchanged under mental stress situation. In summary, extreme physical and psychological stress differentially affects plasma apelin levels in professional athletes.
[Manuscript is under preparation.]

IV. Visfatin in peak athletic performance

Visfatin, as an adipokine/myokine, is emerging as a potential regulator of systemic and skeletal muscle glucose homeostasis. The relationship between visfatin and peak athletic performance is largely unclear. Herein, we assessed the impact of maximal cardiorespiratory exercise testing on the plasma visfatin levels of male professional athletes. On average, circulating visfatin increased transiently after a single bout of treadmill exercise; however, visfatin responses (Δ visfatin = peak – baseline values) had considerable cross-individual heterogeneity. Baseline and peak visfatin levels showed a negative correlation with the maximal metabolic equivalent, relative maximal O_2 consumption, and peak circulatory power. Collectively, we observed a pronounced interindividual variability in exercise-induced changes in the plasma levels of visfatin in professional athletes. Further studies are warranted to understand the functional significance of the inverse relationship between visfatin levels and physical performance indicators.
[Manuscript is under preparation.]

V. Influencing factors of cardiac adaptation in adolescent athletes

Endurance training-induced changes in left and right ventricular systolic and diastolic function have been investigated extensively in adult athletes; however, their alterations in adolescent athletes are still elusive. Detailed 2D and tissue Doppler echocardiographic measurements revealed that left ventricular (LV) diastolic function (E/A ratio and e' values) was significantly higher in adolescent athletes compared to age-matched non-athletes and adult athletes. Moreover, significantly higher structural right ventricular (RV) parameters (RV basal/mid/longitudinal diameter) were detected in adolescent athletes compared to those of the age-matched non-athletes. Importantly, corrected TAPSE values were significantly higher in adolescent and adult athletes compared to young non-athletes. In conclusion, supernormal LV diastolic function and significantly higher RV structural and functional parameters are indicative of cardiac adaptation in adolescent athletes.

[Szabó et al. Int J Sports Med. 2021;42:1209-21. doi: 10.1055/a-1386-4805]

VI. Benefits of 4-tiered classification of exercise-induced left ventricular hypertrophy in adolescent athletes

Exercise-induced left ventricular hypertrophy (LVH) is widely investigated in adolescent athletes characterized by 2-tiered classification (2TC). Though, the differentiation of normal adaptive changes from pathological LVH can be challenging. 4-tiered classification (4TC) may discriminate better different forms of exercise-induced LVH providing three-dimensional information of the left ventricle (LV). The main objective of our study was to distinguish alterations between 2TC and 4TC examining 121 adolescent athletes with echocardiography. Moreover, these results were also compared to the matched LV parameters of 114 adult athletes. Examining the 4TC allocation representing parameters (LV mass, LV mass/BSA, LV end-diastolic volume/BSA, concentricity) of the adolescent and adult athletes we identified significant differences between the different LVH groups and normal geometry, suggesting that the applied classification provides proper group distinguishing power. There were no significant differences between the cumulative training times of the different LVH groups. Furthermore, the BSA corrected LV parameters did not show any correlation with training time. Totally 25 athletes (22%) were reclassified in 4TC into completely different groups, highlighted the 6 athletes (5%) reclassified from normal geometry to concentric LVH and the 11 adolescent (9%) reclassified from normal to eccentric LVH. The reclassifications rate showed similar pattern in adult athletes. Based on all these data we assume that training time has no significant impact on the classification. Cardiac remodeling develops already in young age, and further training time has less impact on the adaptive changes. We prefer to apply 4TC in the routine echocardiographic examination of endurance athletes to specify a more sensitive and distinct screening method.

[Manuscript is under preparation.]

VII. The role of neuronal nitric oxide synthase in the regulation of cardiac function

The impact of neuronal nitric oxide synthase (nNOS) on cardiac contractility has been extensively studied but the results are controversial. We revealed that the positive inotropic response to endothelin-1 (ET-1) is counterbalanced by concurrent stimulation of NO release from nNOS in the intact rat heart. The sGC–cGMP–PKG pathway appears to be implicated in the NO-mediated regulation of contractility. In addition, cGMP catabolism by PDE5A may also control the inotropic effect of ET-1 via modulating ERK1/2 signaling. Additionally, bioinformatic analysis is in progress to investigate whether components of the signaling module are differentially expressed in dilated and hypertrophic cardiomyopathy. Overall, these observations support the hypothesis that the nNOS–NO–sGC–cGMP–PKG pathway is critical for limiting contractile function under inotropic stress.

[Manuscript is under preparation.]

VIII. Automatic daily remote monitoring in heart failure patients implanted with a cardiac resynchronisation therapy-defibrillator

Remote monitoring (RM) is an undoubtedly useful and guideline recommended technology in the clinical follow-up of cardiac resynchronization defibrillator (CRT-D) implanted patients; however, its clinical importance is controversial regarding morbidity and mortality in this patient group. This study sought to evaluate the performance of an RM follow-up protocol using modified criteria of PARTNERS HF trial in comparison with a conventional follow-up scheme. We compared cardiovascular (CV) mortality (primary endpoint), and hospitalization events for decompensated HF, and the number of ambulatory in-office visits (secondary endpoint) in CRT-D implanted patients with automatic RM utilizing daily transmissions (RM group, n=45) and conventional follow-up (CFU group, n=43) in a single-center, observational study. After a median follow-up of 25 months, a significant advantage was seen in the RM group in terms of CV mortality (1 vs. 6 death event, p=0.04), although RM follow-up was not an independent predictor for CV mortality (HR: 0.882; 95% CI 0.25-3.09; P=0.845). Patient CV mortality was independently influenced by hospitalization events for decompensated HF (HR: 3.24; 95% CI 8-84; P=0.022) during follow-up. We observed significantly fewer hospitalization events for decompensated HF (8 vs. 29 events, P=0.046) in the RM group. Furthermore a decreased number of total (161 vs. 263, P<0.01) and unnecessary ambulatory in-office visits (6 vs.19, P=0.012) were seen in RM group as compared to CFU group. Follow-up of CRT-D patients using automatic RM with daily transmissions based on a novel detection algorithm enabled more effective ambulatory interventions leading indirectly to improved CV survival. Moreover, RM directly decreased the number of HF hospitalizations and ambulatory follow-up burden compared to CRT-D patients with conventional follow-up.

[Ezer et al. Arch Med Sci. 2023;19(1):73-85. doi: 10.5114/aoms/131958]

IX. Single centre experience with the balloon-expandable Myval transcatheter aortic valve system with the first 100 patients: 30-day and 1-year follow-up

Transcatheter aortic valve replacement (TAVR) has evolved from a novel technology to an established therapy for high-risk patients with symptomatic severe aortic valve stenosis. Herein, we report our single centre data, regarding the first 100 patients who underwent TAVR procedure with the new balloon-expandable MYVAL system. We report 30-day and 1 year outcome in low to high risk TAVR patient population. Patient outcome was classified according to the Valve Academic Research Consortium-2 (VARC-2) definitions. The device performance was assessed using transthoracic echocardiography. The mean age was 74.7 years, 63% were male. The mean Euroscore II was 4.8±4.9 and the mean STS score was 5.6±3.9. VARC-2 outcomes were as follows: device success 99%, STROKE 1%, major and minor vascular complication was 1% and 11%, respectively, the rate of new permanent pacemaker implantation was 30.7%. At discharge, the incidence of grade I, grade II aortic regurgitation was 39% and 1%, respectively, without relevant paravalvular leak. In-hospital mortality was only 1% (complication of vascular surgery). At one year, the all-cause mortality rate was 7% (only 2 due to cardiac event) and only a single patient had valve-related dysfunction requiring surgical aortic replacement. TAVR procedure with MYVAL transcatheter heart valve system shows excellent 30-day and 1-year outcomes regarding patient survival, technical success and valve-related adverse events.

[Magyari et al. 2023; manuscript is under revision in Catheter Cardiovasc Interv.]

X. IL10 levels in patients with ST-elevation myocardial infarction and chronic coronary syndrome

Inflammatory processes play key roles in the pathogenesis of acute myocardial infarction (AMI). Interleukin-10 (IL-10) belongs to the family of anti-inflammatory cytokines. Previously, elevated IL-10 serum levels were reported to provide independent favorable prognostic information in patients with acute coronary syndromes. However, it is unexplored whether alterations in IL-10 levels are confined to the culprit lesion, or represent a widespread systemic response. Plasma samples were collected from coronary and radial arteries from patients with ST-segment–elevation myocardial infarction (STEMI group: 11 patients, 8 males/3 females, 64±17 years) undergoing primary percutaneous coronary intervention (pPCI), and from patients with chronic coronary syndrome (CCS group: 6 patients, 6 males/0 females, 67±8 years) undergoing elective percutaneous coronary intervention (ePCI). Cytokine levels were quantitated using a multiplex microbead immunoassay (Procarta® Immunoassay Kit - Polystyrene Beads) on a LUMINEX® photometer. Peripheral arterial plasma IL-10 levels were significantly higher in STEMI group than in CCS group prior to PCI (median (IQR): 2.51 (1.46-4.32) pg/mL vs. 0.53 (0.08-2.11) pg/mL, $P<0.05$). IL-10 levels tended to be lower at the site of culprit lesion in comparison with the periphery in STEMI patients ($P=0.054$). Levels of IL-10 tended to be higher at the site of culprit lesion in comparison with the periphery in CCS patients ($P=0.063$). In conclusion, our results demonstrate that peripheral arterial plasma IL-10 levels are elevated in STEMI compared to CCS.

[Manuscript is under preparation.]

XI. The role of CXCR3 and associated chemokines in the development of atherosclerosis and the progression of myocardial infarction

The chemokine receptor CXCR3 and associated CXC chemokines have been extensively investigated in several inflammatory and autoimmune diseases as well as in tumor development. Recent studies have also highlighted the role of these chemokines in cardiovascular disease. Our aim was to present the current knowledge on the role of CXCR3-binding chemokines in the pathogenesis of atherosclerosis and in acute myocardial infarction.

[Szentes et al. Front Immunol. 2018;9:1932. doi: 10.3389/fimmu.2018.01932]

XII. The effect of magnesium on reperfusion arrhythmias in STEMI patients, treated with PPCI

Restoration of coronary blood flow is crucial in treating ST-segment elevation myocardial infarction (STEMI); however, reperfusion with primary percutaneous coronary intervention (PPCI) may induce life-threatening arrhythmias. The impact of periprocedural magnesium administration on reperfusion arrhythmias is elusive. Search in scientific databases identified 3 randomized-controlled trials with 336 STEMI patients who have undergone PPCI and received either magnesium or a placebo before reperfusion. The incidence of ventricular tachycardias was not significantly increased in the placebo control group, whereas ejection fraction and infarct zone wall motion index showed a trend for a decrease in the magnesium treatment group. Based on Trial sequential analysis, these is no firm evidence supporting these observations. Our meta-analysis indicates, that magnesium on reperfusion arrhythmias after PPCI is ineffective with a very weak evidence, due to the small number of patients and the biases of the included studies, and a well-designed clinical trial is needed.

[Szapáry et al. Front Cardiovasc Med. 2021;7:608193. doi: 10.3389/fcvm.2020.608193]