Environmental cardiomyopathy: mechanisms, triggers, and preventive strategies

Aman Aher MBBS[1,2], Netra Shah[3]

[1] University of Missouri-Columbia
[2]Department of Pediatrics
[3]Krishna Institute of Medical Sciences, Karad, India

Abstract

Environmental cardiomyopathy encompasses cardiac dysfunction from exposure to environmental factors such as pollutants, toxins, extreme temperatures, and socioeconomic conditions. Chronic alcohol consumption, exposure to chemotherapy agents, and toxins can directly damage the myocardium, while fine particulate matter (PM2.5) pollution exacerbates risks of heart failure and cardiomyopathy. Psychosocial stressors, high altitudes, and noise pollution further aggravate preexisting cardiac conditions through stress-induced cardiomyopathy, arrhythmias, and hypertension. Climate extremes, including heatwaves and cold weather, impose additional burdens by inducing dehydration and vasoconstriction, leading to myocardial infarction and stroke.

Mechanistically, environmental triggers contribute to cardiovascular mortality via chronic low-grade inflammation, oxidative stress, epigenetic alterations, vascular dysfunction, and direct cardiotoxicity. Air pollutants activate systemic inflammation and disrupt the balance of reactive oxygen species (ROS), resulting in endothelial dysfunction and atherosclerosis progression.

Epigenetic modifications, such as DNA methylation and microRNA expression, impair vascular repair and nitric oxide bioavailability, promoting hypertension and arrhythmias. Direct cardiotoxicity from heavy metals and particulate matter leads to myocardial apoptosis and mitochondrial dysfunction, increasing the risk of heart failure and sudden cardiac death.

Epidemiological evidence links pollutant exposure with elevated cardiovascular mortality, highlighting increased troponin levels and myocardial injury markers in high-pollution areas. Preventive strategies include air quality regulations, antioxidant-rich diets, and biomonitoring for high-risk individuals. Lifestyle interventions, such as stress management, smoking cessation, and regular physical activity, further mitigate risks. This multidisciplinary approach underscores the significance of environmental triggers in cardiovascular health, necessitating targeted policies and public health measures to address these challenges.

Partial reprogramming of adult cardiomyocytes enhances cardioprotective mechanisms in adult heart

Perwez Alam PhD[1,2], Hunter J Bowles[1], Hieu Bui[1], Douglas K Bowles PhD[1,2]

[1] University of Missouri-Columbia
[2]College of Veterinary Medicine

Abstract

Heart disease is the leading cause of death in the U.S., affecting over 28 million adults, with nearly 6.7 million living with heart failure. Traditional strategies to regenerate functional cardiomyocytes (CMs) have been insufficient. Recent research suggests partial reprogramming of adult CMs as a promising strategy to protect the failing heart by secreting rejuvenation-associated paracrine factors that improve the heart's microenvironment and enhance cardioprotection. We previously showed that inhibiting senescence-related genes Rb1 and Meis2 promotes cardiac rejuvenation, improving myocardial infarction (MI) outcomes by enhancing vascular density, reducing fibrosis, and increasing CM survival.

Additionally, transcriptomic analysis identified MCM2 as a key effector, with its overexpression improving cardiac function and angiogenesis post-MI. However, the mechanisms behind MCM2-mediated reprogramming remain unexplored.

To investigate this, we performed

comprehensive omics analysis to identify CM-specific mechanisms responsible for MCM2-mediated cardioprotection. We overexpressed MCM2 in adult CMs in vivo using an adeno-associated viral (AAV9-cTnT-MCM2) vector. One month after injection, CMs were isolated and cultured for 48 hours. Cultured CMs and extracellular vesicles (EVs) from conditioned media were analyzed through transcriptomic and proteomic profiling, respectively. Data were analyzed using Ingenuity Pathway Analysis (IPA). Transcriptomic analysis revealed a set of differentially expressed genes in MCM2-overexpressing CMs compared to controls. When these genes were compared to the expression profile in MI hearts (public data), a significant reversal in gene expression was observed. This suggests that MCM2-overexpression in CMs modulates gene expression to counteract the disease state, offering potential protection against myocardial injury. Furthermore, MCM2-overexpression modulated key pathways involved in fibrosis, CM survival, angiogenesis, immune modulation, and hypoxia response, confirmed by EV proteomics. These findings suggest that MCM2-overexpression activates reprogramming associated pathways in adult CM and induces protective paracrine signaling, which may play a role in cardiac remodeling, angiogenesis, and immune modulation, ultimately contributing to cardioprotection after myocardial injury.

Revolutionizing cardiology with artificial intelligence and machine learning

Thomas Cartwright DO[1,2],
Mohammad Alkhateeb MD[1,2]

[1] University of Missouri - Columbia
[2] Department of Medicine

Background

Cardiovascular diseases are the leading cause of death worldwide, highlighting the need for innovative solutions to improve patient outcomes. Advances in technology have opened new possibilities for addressing these challenges. Among these, Artificial Intelligence (AI) and Machine Learning (ML) stand out as transformative tools with the potential to revolutionize cardiology and redefine approaches to patient care. This review explores AI and ML driven advancements in cardiology.

Methods

A narrative review was conducted by identifying relevant studies through searches of peer-reviewed journals, review articles, and research databases using terms including "artificial intelligence", "machine learning", "cardiology", "cardiovascular", "diagnostic imaging", "electrocardiography". Studies were selected based on their clinical significance.

Results

AI, ML and deep learning (DL) have shown unparalleled potential in medicine, particularly in cardiology. Predictive algorithms integrate clinical, imaging, and biomarker data to predict cardiovascular events such as myocardial infarction, stroke, and heart failure. In imaging, AI significantly reduces time and operator variability in image interpretation. Convolutional neural networks have automated tasks such as plaque characterization, ventricular function quantification, and myocardial tissue assessment, with diagnostic accuracy on par with expert clinicians. DL models use ECGs to detect arrhythmias and predict left ventricular dysfunction years before clinical manifestation. In electrophysiology, AI refines ablation targeting by mapping arrhythmogenic substrates with precision.

Natural language processing (NLP) tools have also facilitated cardiology related research. Despite advancements, challenges such as data privacy, biases, interpretability issues, and dataset discrepancies hinder clinical adoption. Collaborative initiatives between clinicians, engineers, and policymakers are beginning to address these gaps.

Conclusion

AI is poised to democratize cardiac care, offering high-quality diagnostics, as well as broadening access. Their integration demands multidisciplinary collaboration to address challenges to ensure successful implementation. With ongoing innovation and validation, these technologies can drive the field toward more predictive, preventive, and personalized care.

Repeated autonomic dysreflexia impairs renal function after spinal cord injury

Ruwaida Ben Musa MD, PhD[1,2,3,4],
Olugbenga Michael PhD[5,6,7],
Zhifeng Qi[1,2,3,4],
Fateme Khodadadi-Mericle[1,2,3,4],
Adebowale Adebiyi PhD[5,6,7],
Shaoping Hou PhD[1,2,3,4]

[1] University of Missouri-Columbia
[2]Department of Pathology and Anatomical Sciences
[3]Department of Physical Medicine and Rehabilitation
[4]Dalton Cardiovascular Research Center
[5]Department of Medical Pharmacology and Physiology
[6]Department of Anesthesiology and Perioperative Medicine
[7]NextGen Precision Health

Abstract

Cardiovascular dysfunction is a common complication in subjects with spinal cord injuries (SCI). Autonomic dysreflexia, a life-threatening condition characterized by sudden and severe hypertension often accompanied by bradycardia, occurs in response to somatic or visceral stimuli. Although it has been known that autonomic dysreflexia is harmful to multiple systems, its impact on renal function remains understudied. As the kidneys are particularly vulnerable to hypertension, reduced renal perfusion often leads to progressive renal dysfunction. Accordingly, we posit that repeated episodes of autonomic dysreflexia exacerbate renal dysfunction following SCI. To test this hypothesis, adult female rats underwent a complete transection at the 4th thoracic spinal cord level to interrupt supraspinal control. Two weeks post-SCI, colorectal distension (CRD) was performed twice daily to artificially induce autonomic dysreflexia for three weeks (n = 6), while SCI rats that did not receive CRD and sham-injured rats (laminectomy only) served as 2 controls (n = 6/7). Subsequently, noninvasive and transcutaneous measurement of glomerular filtration rate (GFR) was conducted by injecting fluorescein isothiocyanate (FITC)-sinistrin, as a biomarker, into the tail vein. Blood and urine samples were collected for bioassays to examine kidney injury. Furthermore, renal blood flow (RBF), renal vascular resistance (RVR), and mean arterial pressure (MAP) were recorded in anesthetized rats. After sacrifice, the kidneys were harvested for histological analysis, including H&E staining to evaluate morphological changes and Masson trichrome staining to assess collagen deposition. Compared to the sham group, GFR was significantly reduced in SCI rats exposed to CRD (one-way ANOVA, p = 0.025) but not in SCI rats that did not receive CRD (p = 0.19). In addition, SCI rats treated with CRD exhibited increased RVR (p = 0.026) compared to the sham group. Bioassays and histological assessments are ongoing. Collectively, the results indicate that repeated exposure to autonomic dysreflexia impairs renal function after SCI.

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Evaluation of NIH ImageJ parameters for quantitative analysis of foam cell formation

Anvitha Boosani[1,2], Jonathan A. Green PhD[1]

[1] University of Missouri - Columbia
[2]Division of Animal Sciences
[3]Department of Biochemistry

Abstract

Immune cells are a major contributor to atherosclerotic plaque growth in arteries. The transition of monocytes into macrophages, and macrophages into foam cells (large, obtrusive, lipid-laden macrophages) via oxidized LDL uptake, leads to foam cell accumulation in arterial plaques. This advances disease progression and may cause blockage of blood flow. We have previously investigated the role of the epigenetic protein TET1 (Ten-Eleven Translocation 1) in macrophages and found that modulating its expression may lead to a decrease in oxidized LDL (oxLDL) uptake and subsequent foam cell formation.

Since drugs that inhibit foam cell formation can be tested through in vitro cell culture studies, evaluation of microscopically acquired images

would help in both quantification of foam cells and identification of statistical differences in drug effects. Currently, there are no effective software tools that can identify foam cells and quantitatively measure the extent of inhibition of foam cell formation in acquired images. The goal of this study is to utilize NIH ImageJ parameters for identification of foam cells in microscopic images. In the future, such parameters in the ImageJ software may be integrated in AI-based approaches to analyze large volumes of images acquired using automated microscopes.

The present study evaluated different functionalities in the NIH ImageJ software to assess foam cell formation. U937 monocytes were cultured in T25 flasks and differentiated into macrophages via treatment with phorbol 12-myristate 13-acetate (PMA). Differentiated macrophages were then treated with 33μM Bobcat339 (TET1 inhibitor) and 80μg/mL oxLDL to initiate foam cell formation and evaluate the effects of TET1 inhibition on oxLDL uptake. Images of foam cell populations in different treatment conditions were acquired using an upright light microscope. Different parameters within the NIH ImageJ software were evaluated for effective detection and quantitation of foam cells in the acquired images.

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Chronic Helicobacter pylori infection impairs endothelial function and exacerbates atherosclerosis selectively in male mice

Jingshu Chi[1,2,3,4], Linfang Zhang[1,2,3,4], Xiujuan Xia[1,2,3,4], Feng Chen[1,2,3,4], Caiping Zhang[1,2,3,4], Aiping Lin PhD[1,2,3,4], Qin Zhou[1,2,3,4], Hong Hao PhD[1,2,3,4], Xunlei Kang MD PhD[1,2,3,4], De-Pei Li MD MSC CPM[1,2,3,4], Luis A. Martinez-Lemus DVM PhD[1,2,3,4], Michael A. Hill PhD[1,5], Canxia Xu MD PhD[6,7], Zhenguo Liu MD PhD[1,2,3,4]

[1] University of Missouri-Columbia
[2] Department of Medicine
[3] Division of Cardiovascular Medicine
[4] Center of Precision Medicine
[5] Dalton Cardiovascular Research Center
[6] Central South University, Changsha, China
[7] Department of Gastroenterology

Background

Helicobacter pylori (H. pylori) infection increases the risk of cardiovascular diseases including atherosclerosis. Endothelial dysfunction is closely associated with atherosclerosis. This study aimed to test the hypothesis that chronic H. pylori infection attenuates endothelial function and promotes atherosclerosis selectively in males.

Methods

Male and female wildtype C57BL/6 mice and LDL receptor-deficient (LDL-/-) mice (4 to 6 weeks old) were infected with H. pylori. Mice were fed a regular diet and were euthanized at either 12 or 15 months after H. pylori infection. Aortas were collected from C57BL/6 mice to evaluate endothelial function, and aortas from LDL-/- mice were evaluated for atherosclerotic burden. Blood pressure, blood glucose and lipid profiles were obtained and analyzed. The presence of H. pylori infection was assessed at the end of the experiment using Rapid Urease Test and Giemsa staining of gastric mucosa.

Results

Over 80% of mice remained infected with H. pylori for up to 15 months. The aortas from male, not female, mice with either 12 or 15 months of H. pylori infection exhibited a significant reduction in acetylcholine-induced endothelium-dependent relaxation, while nitroglycerine-induced endothelium-independent relaxation remained intact along with increased blood pressure. Blood glucose in male, not female, wildtype mice with H. pylori infection for 15 months were also elevated. Additionally, aortic atherosclerotic burden was significantly increased in male, not female, LDL-/- mice with chronic H. pylori infection. Similarly, blood glucose levels, non-HDL cholesterol, total cholesterol, and LDL cholesterol were all significantly increased in LDL-/- male, not female, mice with H. pylori infection.

Conclusion

Chronic H. pylori infection induces significant metabolic abnormalities with increased blood glucose and lipid levels, significantly impairs endothelial function, and promotes atherosclerosis selectively in males. These findings suggest that chronic H. pylori infection could significantly contribute to endothelial dysfunction and cardiovascular diseases such as atherosclerosis in males, not females.

Empowering rural clinics: Enhancing clinical research participation through research readiness training

Background

With the growing emphasis on the importance of rural health, there is a strong need to engage rural practices in generating evidence. Existing programming to train rural practice clinicians and staff to participate in and/or lead research, including clinical trials, is insufficient and overly onerous as an introductory effort. Barriers include a lack of knowledge, anxiety about requirements, and fear of making mistakes. To provide the preparatory training needed to expand rural clinic engagement, we developed a "Research Readiness Training" program. This program is a collaborative effort designed for the rural community clinical team to enhance their ability to support participant recruitment, enrollment, informed consent process, and active partnership with academic partners conducting research. This education may offer rural learners a combined clinical and research experience, reinforcing the importance of adopting a "research embedded in practice" approach to rural healthcare delivery, and perhaps enhancing the rural primary care practice experience.

Methods

Mixed methods using qualitative descriptive approaches in parallel with prospective cohort approach. Participant demographics, practice characteristics, pre- and post-training surveys, engagement metrics, and qualitative feedback data. Clinicians and staff from rural medical practices across Missouri, in non-urban areas, with limited access to larger healthcare facilities and research institutions. Research Readiness Training. Outcome measures: Primary - improved knowledge of, confidence in participating in, and positive attitude toward research. Secondary - Understand barriers to engaging in clinical research.

Results

Development of the Research Readiness Training was informed by a comprehensive approach involving focus groups, town halls, interviews, practical experiences, and literature review. In collaboration with university and external partners, will establish connections with rural sites across Missouri.

Expected Outcomes

Participants will experience increased knowledge of clinical research and confidence to engage in clinical research activities. Additionally, we will gain a better understanding of the barriers that face rural healthcare providers interested in research, with the ultimate goal of increasing rural research collaboration with the academic medical center and inclusion of these underserved populations.

Nitric oxide and endothelin-mediated vasoregulation in the protective mechanisms of renal ischemic postconditioning in neonatal acute kidney injury

Julia E. de la Cruz PhD[1,2,4],
Olugbenga S. Michael PhD[1,2,4],
Ravi Kumar PhD[1,2,4],
Adebowale Adebiyi PhD[1,2,3,4,5]

[1]University of Missouri-Columbia
[2]Department of Medical Pharmacology and Physiology
[3]Department of Anesthesiology and Perioperative Medicine
[4]NextGen Precision Health
[5]University of Tennessee Health Science Center

Abstract

Ischemia reperfusion is a major cause of acute

kidney injury (AKI) in infants and occurs in a variety of clinical settings, including sepsis, cardiopulmonary bypass, and kidney transplantation. Rapid ischemic postconditioning (IPostC) involves subjecting an organ to brief periods of ischemia and reperfusion after an ischemic event. Although IPostC has shown potential to alleviate IR injury, its effects on immature kidneys remain unexplored. Nitric oxide (NO) is a potent inducer of heme-oxygenase-1 (HO-1) and inhibits endothelin-1 (ET-1) function. HO-1 has been proposed to be beneficial in AKI and transplantation, whereas ET-1-induced vasoconstriction contributes to renal vascular dysfunction in AKI. We used the neonatal porcine model to investigate NO, HO-1, and ET-1 signaling in the protective mechanisms of renal IPostC in ischemic-AKI. Exposure of primary neonatal pig renal vascular endothelial cells (ECs) to a NO donor increased HO-1 but decreased ET-1 levels. In neonatal pigs, one-hour renal ischemia, followed by six hours reperfusion reduced significantly kidney NO and serum HO-1 levels, which was reversed by 3 cycles of IPostC (5 minutes of reperfusion followed by 5 minutes of ischemia before complete reperfusion). IR-induced increases in urine endothelin converting enzyme-1 (ECE-1) and ET-1 were counteracted by IPostC and the HO-1 inducer cobalt protoporphyrin (CoPP). IPostC and CoPP significantly preserved GFR and renal blood flow while reducing AKI biomarker levels and morphological kidney damage caused by IR. Similarly, the selective ETA receptor antagonist sitaxentan and the ECE-1 inhibitor CGS-26303 mitigated IR-induced AKI. These findings suggest that: (1) Renal IR reduces NO and HO-1 while increasing ET-1 levels; (2) IPostC-induced HO-1 opposes the IR-induced rise in ET-1 biosynthesis; and (3) IPostC mitigates IR injury by stimulating HO-1 production, which counteracts ET-1 synthesis. We conclude that IPostC may lessen neonatal ischemic-AKI by stimulating NO production in the kidneys, which drives HO-1 to reduce ET-1 levels.

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Respiratory responses following H2O2 injections into the nucleus tractus solitarii (nTS) of an Alzheimer's Disease (AD) animal Model and Their Controls

Grace J. Feeney MSC[1],
Daniela Ostrowski MSC PhD[1,2],
Tim D. Ostrowski MSC PhD[1,3]

[1]A.T Still University
[2]Department of Pharmacology
[3]Department of Physiology

Abstract

Besides memory loss, AD often displays respiratory dysfunction possibly due to oxidative damage in respiratory brain areas such as the nTS. We previously identified respiratory dysfunction and oxidative damage in the nTS of the streptozotocin (STZ)- induced AD model, leading to this study about the interplay between these findings.

AD was induced by injecting 6-week-old rats with 2.5 mg/kg of STZ into the fourth ventricle. Two weeks later, we implanted EMG electrodes into the diaphragm to assess respiratory responses to repeated glutamate (20 nL, 40 mM) injections into the caudal nTS before and after a single bolus of H2O2 (40 nL, 37.5 mM) into that same location.

While nTS glutamate injections increased respiratory frequency by 12-15 breaths/min in both CTL and STZ-AD, a single bolus of H2O2 or artificial CSF (aCSF) alone did not change respiration. However, following aCSF, CTL animals had an elevated peak response to glutamate, an effect that was absent following H2O2. Respiratory responses to glutamate in STZ-AD animals did not change following either treatment. Under stress conditions with 10 repetitive glutamate injections, respiratory responses of all experimental groups accommodated by ~40-60%. After aCSF, glutamate stress responses of CTL remained higher than those of STZ-AD. Following H2O2, response magnitudes of CTL were reduced to a level similar to STZ-AD.

The elevated respiratory response of CTL after aCSF may resemble a form of long-term facilitation with repeated and spaced glutamate injections. Inducing an oxidative environment eliminated this

response elevation and CTL responses resembled those of STZ-AD. STZ-AD had no change in response following H2O2, which may reflect an already established oxidative environment from disease progression. Understanding respiratory changes under oxidative stress from STZ-AD may clarify mechanisms involved with respiratory dysfunction in AD patients.

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Clinical hyperpolarized 129Xe MRI for assessment of vascular function in pulmonary hypertension

Gabriela Garcia Delgado[1,2], Isabella Parks[1,2], Ummul Afia Shammi PhD[4,5], Mia Ruppel MS[1,2], Talissa Altes MD[1,3], Robert Thomen PhD[1,2,3]

[1] University of Missouri-Columbia
[2] Department of Chemical and Biomedical Engineering
[3]Department of Radiology
[4]University of Illinois-Chicago
[5]Department of Biomedical Engineering

Introduction

Hyperpolarized Xenon MRI (HPX) of the lung is an imaging tool in which a patient inhales a bolus of xenon gas which is then directly imaged via MRI. The inhaled xenon can be separately imaged in the alveolar airspaces, lung parenchymal tissue (membrane) and red blood cells (RBCs) all within a single 10-15 second breath-hold. HPX is used to quantify the percentage of the lung with inadequate ventilation (common in obstructive disease), impaired gas transfer (common in fibrotic disease), and defective perfusion (common in pulmonary vascular disease). This information is invaluable to clinicians who desire quantitative physiologic markers of disease status, progression, and response to treatment. Pulmonary hypertension (PH) in particular is a disease in which HPX can help delineate disease etiology and improve patient management. Here we present HPX images and results in a healthy control subject, a pre-capillary PH patient, and a post-capillary PH patient.

Methods

A healthy control patient (28/F) and two PH patients – one pre-capillary PH (63/M) and one post-capillary PH (52/F) – were imaged on a 3T Siemens Vida MRI scanner using a 3D-radial-DIXON sequence which allows for separate reconstruction of xenon in airspaces, lung membrane, and RBCs.

Results

Ventilation was normal in all patients, but gas-exchange was impaired in the PH cases: 5% of the lung volume had reduced RBC signal in the control compared with 39% and 31% in the pre- and post-capillary PH patients respectively. The post-capillary PH patient exhibited more extensive and complete defects concentrated in the lower lobes. In contrast, the pre-capillary PH patient showed less severe defects that were distributed across a larger lung volume.

Conclusion

Gas exchange can be utilized to evaluate pulmonary vascularity in PH and may aid in clinical management of these patients.

Cerebrovascular reactivity to hypoxia and hypercapnia: role of β-adrenergic receptors

Amaris Hairston[1], Brian Shariffi PhD[1,2], Megh Patel[1], Dain W. Jacob PhD[1,2], Anna M. Gonsalves[1,2], Jennifer L. Harper[1], Brian P. Bostick[1,3], Jacqueline K. Limberg PhD[1,2]

[1] University of Missouri - Columbia
[2] Department of Nutrition and Exercise Physiology
[3] Department of Medicine

Background

β-adrenergic receptor (β-AR) antagonists are prescribed to patients experiencing migraines. Although the mechanisms behind the efficacy of their treatment remain unclear, data suggest β-AR antagonists may exert a vascular action within the cerebral circulation. We assessed resting cerebral perfusion as well as cerebrovascular reactivity to a hypoxic and a hypercapnic stress with and without

β-AR antagonism via oral propranolol. We hypothesized cerebrovascular reactivity would be reduced after propranolol administration compared to placebo.

Methods

Middle cerebral artery velocity (MCAv, transcranial Doppler ultrasound) was assessed in 21 healthy young adults (12M/9F, 27.1±7.8 yrs; 24.3±2.6 kg/m2). Individuals completed two study visits randomized and blinded to oral placebo or propranolol (1 mg/kg). At each visit, participants completed a quiet resting period followed by two study conditions separated by a 10-min washout: 1) 5-min steady-state hypoxia (10.7±0.6 FiO2, 81.7±4.3% SpO2), 2) 5-min hyperoxic hypercapnia (+7.9±2.4 mmHg partial pressure of end-tidal CO2).

Results

MCAv increased in response to both steady-state hypoxia (main effect of hypoxia, p=0.0005) and hypercapnia (main effect of hypercapnia, p<0.0001). The MCAv response to hypoxia was augmented with propranolol compared to placebo (main effect of propranolol, p=0.0279; interaction of hypoxia and propranolol, p=0.0371). In contrast, the MCAv response to hypercapnia was unaffected by propranolol (main effect of propranolol, p=0.4362; interaction of hypercapnia and propranolol, p=0.7949).

Conclusion

Reductions in oxygen delivery (hypoxia) or retention of metabolic byproducts like carbon dioxide (hypercapnia) both elicit increases in cerebral perfusion in an attempt to restore homeostasis. Contrary to our hypothesis, the non-specific β-AR antagonist propranolol had no effect on hypercapnic reactivity and resulted in a paradoxical increase in the cerebrovascular response to hypoxic stress. These findings support a role for the β-AR in restraining cerebral blood flow during hypoxia, but not hypercapnia.

Low circulating FGF-21 after high protein intake likely mediates the adverse effect of high protein intake on endothelial function

Hunter Hollomon[1,2,3], Alan Fappi PhD[1,2,3], Bettina Mittendorfer PhD[1,2,3]

[1] University of Missouri-Columbia
[2] Department of Nutrition and Exercise Physiology
[3] Department of Medicine

Introduction

Endothelial dysfunction is an early marker of cardiovascular disease (CVD). A Western-type diet is a major risk factor for CVD, presumably because of high intake of simple sugars and red and processed meats with high salt, saturated fat, and cholesterol contents. Results from animal models and population studies suggest high protein intake as part of a Western-type diet also contributes to CVD burden, but the mechanisms involved are unknown. We tested the hypothesis that high protein intake adversely affects endothelial vasodilator function, and this effect is partially mediated by the inhibitory effect of high protein intake on FGF21 production.

Methods

First, we evaluated the effect of consuming a high-protein (HP) mixed meal (22% of energy as protein), compared with an isocaloric standard protein (SP) meal (15% of energy as protein), on plasma FGF21 concentration and reactive hyperemia, an established marker of endothelial function, in nine middle-aged (49±14 years-old) people with overweight/obesity (body mass index: 28±3 kg/m2). Secondly, we evaluated the effect of escalating doses (0-50 ng/ml) of FGF21 on endothelial nitric oxide synthase (eNOS) phosphorylation at Ser1177 (stimulatory) and Thr495 (inhibitory), and nitric oxide (NO) production in cultured human umbilical vein endothelial cells (HUVEC).

Results

Plasma FGF21 concentration and the reactive hyperemia index were not different after ingesting the SP meal compared with basal conditions (before meal). After the HP meal, plasma FGF21 concentration decreased by 70±2 % (mean ± SEM) and the reactive hyperemia index decreased by 21±3 %. Recombinant human FGF-21 treatment of HUVECs significantly increased Ser1177 eNOS phosphorylation, decreased Thr495 eNOS phosphorylation, and stimulated NO production in

a dose-dependent manner.

Conclusion

In conclusion, high protein intake impairs endothelial function, at least in part by lowering circulating FGF-
21. These findings provide a potential mechanism f or the increased CVD risks associated with high protein intake.

Differential effects of particulate matter exposure on macrophage populations in different tissues in an age-dependent and sex-independent manner

Aiping Lin PhD[1,2,3,4], Jing Zhang[1,2,3,4], Jingshu Chi[1,2,3,4], Feng Chen[1,2,3,4], Bo Peng[1,2,3,4], Dan Ni[1,2,3,4], Caiping Zhang[1,2,3,4], Qin Zhou[1,2,3,4], Yue Guan[1,5], Hong Hao PhD[1,2,3,4], Xunlei Kang MD PhD[1,2,3,4], De-Pei Li MD MSC CPM[1,2,3,4], Luis A. Martinez-Lemus DVM PhD[1,2,3,4], and Zhenguo Liu MD PhD[1,2,3,4]

[1]University of Missouri-Columbia
[2]Department of Medicine
[3] Division of Cardiovascular Medicine
[4] Center of Precision Medicine
[5] Flow Cytometry Core

Background

Fine particulate matter (PM) triggers a systemic inflammation, and macrophages are critical to the initiation and maintenance of inflammation. Both sex and age have significant impact on inflammatory responses. The present study aimed to test the hypothesis that PM exposure differentially alter macrophage populations in different tissues in a sex- and age-dependent manner.

Methods

Young (8-10 weeks old) and aged (20-24 months old) male and age-matched female C57BL/6 mice were exposed to PM or PBS (control) via intranasal instillation every other day for six weeks. Peripheral blood was collected at baseline (before exposure), 4 weeks, and 6 weeks of PM exposure, and lung, liver, peritoneal cells, bone marrow, and spleen were harvested at the end of PM exposure. Macrophage populations (M1 and M2) were analyzed using flow cytometry.

Results

The M1/M2 ratio in peripheral blood exhibited a time-dependent increase in both young male and female mice with PM exposure at both week 4 and 6 of exposure, compared to controls. The M1/M2 ratio was also significantly elevated in the lungs in both young male and female mice with PM exposed at week 6 of exposure. However, no significant difference in macrophage populations were observed in the liver, spleen, bone marrow or peritoneal cells between the mice with PM and their controls. Interestingly, there was no significant change in the M1/M2 ratio in peripheral blood or any of the analyzed tissues in aged mice with PM exposure as compared with their controls.

Conclusion

Chronic PM exposure increases pro-inflammatory M1 macrophage population in peripheral blood and lung tissue in both young male and female mice, while no change was observed in aged mice with PM exposure. These data suggest that PM exposure led to an increase in M1 macrophages in circulation and lung in an age-dependent and sex-independent mechanism.

A cyclic stretch-operated mechnotransdunction to maintain contractile phenotype of vascular smooth muscle cells

Yixiao Liu PhD[1,2,3], Jianxin Yan MD, PhD[1,2,3], Xue Jiang[1,2], Minna Huang[1,2], Mahsa Saheb Farmanabadi[1,2], Nathan Schwartz[1,2], Michael J. Davis PhD[1,3], Taixing Cui MD PhD FAHA[1,2,3]

[1]University of Missouri-Columbia
[2]Dalton Cardiovascular Research Center
[3]Department of Medical Pharmacology and Physiology

Abstract

Cyclin stretch-induced mechanotransduction plays a crucial role in vascular homeostasis and

disease. However, the underlying mechanisms remain poorly

understood. Herein, we established a physiological cyclin stretch which drives vascular smooth muscle cell (vSMC) phenotype switch from a dedifferentiated state to differentiated one and identified a novel signaling pathway for the physiological stretch-operated mechanotransduction. Using a mouse aortic SMC-derived cell line (MOVAS), we demonstrated that uniaxial cyclic stretch (12.9%, 1Hz) alone induced a phenotype switching from a dedifferentiated state to differentiated one, characterized by reduced growth and enhanced expression of a multitude of SMC contractile markers. Combined analysis of multi-omics data revealed an indispensable role of cyclin-dependent kinase 8/19 (CDK8/19) associated with downregulation of piezo-type mechanosensitive ion channel component 2 (Piezo2) in driving vSMC dedifferentiation, illustrating the mechanical origin of the discovered CDK8/19 signaling in vSMCs. In completely ligated mouse carotid arteries with reduced cyclic stretch, we found that the expression of CDK8/19 was dramatically upregulated in medial and neointima SMCs, underscoring a CDK8/19-operating mechanotransduction for vSMC dedifferentiation. Conversely, knockout of CDK8/19 in vSMCs and perivascular delivery of CDK8/19 inhibitors strongly suppressed neointimal formation in completely ligated carotid arteries in mice. Taken together, our results indicate that CDK8/19 are essential mediators of the mechanotransduction for vSMC dedifferentiation and may be potential therapeutic targets for occlusive vascular disease.

Role of β2-Adrenergic Receptor in CD4+ T Cells in Modulating Vascular Stiffness During Hypertension

Soraya Nekouian[1], Miles A. Tanner[1], Chastidy A. Bailey[1], Shawn B. Bender PhD[1-3], Laurel A. Grisanti[1-3]

[1] University of Missouri-Columbia
[2]College of Veterinary Medicine
[3]Dalton Cardiovascular Research Center

Background

Hypertension is a major global health concern, contributing to cardiovascular events such as stroke and heart failure. Immune cells, particularly T cells, have emerged as key players in the inflammatory mechanisms underlying hypertension. Recent evidence indicates that β2-adrenergic receptor (β2AR) signaling alters CD4+ T cell function but its role in hypertension remains unexplored. This study aims to investigate how the deletion of β2AR in CD4+ T cells impacts immune responses and vascular remodeling in an angiotensin (Ang) II-induced hypertension model. We hypothesize that β2AR deletion will reduce the recruitment and activation of pro-inflammatory T cells, leading to decreased vascular stiffness and fibrosis.

Methods

We employed a murine model with a CD4+ T cell-specific β2AR knockout (tKO) and induced hypertension using Ang II infusion. Wild-type mice were compared to tKO mice to assess changes in blood pressure, vascular stiffness, and immune cell populations. Vascular stiffness was measured through pressure myography, while immune responses were analyzed using flow cytometry and molecular assays.

Results

Deletion of β2AR in CD4+ T cells significantly influenced both immune responses and vascular function in Ang II-induced hypertension. β2AR-deficient mice exhibited reduced recruitment and activation of pro-inflammatory T cells within the aorta, resulting in less vascular stiffening and fibrosis compared to controls. This reduction was associated with a dampened Th1/Th17 response and fibrosis markers in vascular tissues. β2AR-deficient mice had a less pronounced increase in blood pressure, suggesting a protective effect of β2AR deletion against the hypertensive response. Pressure wire myography demonstrated greater arterial compliance and reduced stiffness in these mice, highlighting the role of β2AR in modulating vascular remodeling during hypertension.

Conclusion

β2AR signaling in CD4+ T cells plays a crucial role in regulating vascular stiffness and inflammation during hypertension. Targeting

β2AR signaling could offer new therapeutic strategies for managing hypertension-induced vascular remodeling.