Dietary Fish and ω-3 Fatty Acid Consumption and Heart Rate Variability in US Adults

Consumption of fish and ω-3 fatty acid reduces risk of cardiac death, but mechanisms are not well established. Heart rate variability (HRV) predicts cardiac death and reflects specific electrophysiological pathways and influences. To elucidate electrophysiological influences and support effects on clinical risk, we evaluated the associations between habitual consumption of fish and marine ω-3 fatty acids and HRV, assessed by both 12-lead ECG (n=4263) and 24-hour Holter monitoring (n=1152), in a population-based cohort of older US adults. After multivariable adjustment, consumption of tuna or other broiled/baked fish was associated with specific HRV components, including indices suggestive of greater vagal predominance and moderated baroreceptor responses (eg, higher root mean square successive differences of normal-to-normal intervals, higher normalized high-frequency power, and lower low-frequency/high-frequency ratio) and less erratic sinoatrial node firing (eg, lower Poincaré ratio and higher short-term fractal scaling exponent). Findings were similar for estimated dietary consumption of marine ω-3 fatty acids. For the magnitudes of the observed differences in HRV comparing the highest with the lowest category of fish intake, the differences in relative risk of coronary heart disease death during 10.8 years of follow-up ranged from 1.1% lower risk for the differences in standard deviation of normal-to-normal intervals to 5.9% and 8.4% lower risk for the differences in the Poincaré ratio and short-term fractal scaling exponent, respectively. Thus, habitual consumption of tuna/other fish and marine ω-3 fatty acid are associated with specific and clinically relevant differences in HRV in older adults, including indices of more favorable vagal activity, baroreceptor responses, and sinoatrial node function. Cellular mechanisms and implications for clinical risk deserve further investigation. See p 1130.

Association of Leukocyte Telomere Length With Circulating Biomarkers of the Renin-Angiotensin-Aldosterone System: The Framingham Heart Study

Leukocyte telomere length (LTL) reflects the cumulative burden of oxidative stress and inflammation experienced over a life course. Activation of the renin-angiotensin-aldosterone system is associated with increased oxidative stress and inflammation. We tested the hypothesis that LTL may be related to circulating biomarkers of the renin-angiotensin-aldosterone system by examining the cross-sectional relations of LTL and circulating renin and aldosterone concentrations in 1203 Framingham Heart Study participants. In multivariable analyses adjusting for confounders, LTL was inversely related to renin and the renin-to-aldosterone ratio but directly related to aldosterone. Relations of LTL to renin-angiotensin-aldosterone system biomarkers and to the renin-to-aldosterone ratio were stronger in those with hypertension. Participants with hypertension who were in the top tertile of the renin-to-aldosterone ratio had an LTL that was 182 base pairs shorter relative to those in the lowest tertile. These observations raise the hypothesis that the renin-to-aldosterone ratio may be a biomarker of the cumulative exposure to oxidative stress and inflammation, especially in people with high blood pressure. Additional investigations are warranted to confirm our observations. See p 1138.

Rural Interhospital Transfer of ST-Elevation Myocardial Infarction Patients for Percutaneous Coronary Revascularization: The Stat Heart Program

When a door-to-balloon time of ≤90 minutes can be achieved, primary percutaneous coronary intervention (PPCI) is preferred over intravenous fibrinolytic therapy as a reperfusion strategy for ST-elevation myocardial infarction (STEMI). Unfortunately, only 25% of US hospitals have PPCI-capable facilities. Interhospital transfer of STEMI patients from non–PCI-capable (STEMI-referral) to PCI-capable (STEMI-accepting) facilities has been suggested as a strategy (transfer PCI) to enhance the generalizability of PPCI. In rural US communities, unexpected impediments to interhospital transport may contribute to reperfusion delays, necessitating alternative “backup” treatment strategies (ie, full-dose intravenous fibrinolysis). We established a regional transfer PCI STEMI consortium (Stat Heart) in rural central Illinois consisting of 6 STEMI-referral hospitals, which were within 28 to 88 miles of our 2 STEMI-accepting facilities. We used a 4-step, guideline-based STEMI protocol that empowered the STEMI-referral emergency department physician to initiate treatment and to expedite interhospital transfer for primary or rescue PCI if needed, after fibrinolysis. Among the first 230 Stat Heart patients, the median door-to-balloon time among those receiving PCI was 117 minutes. Unexpected interhospital transport delays (usually resulting from inclement weather) required the use of intravenous fibrinolysis in 19 patients (8.3%; 9 requiring rescue PCI) with achievement of a median door-to-needle time of 27 minutes. In Stat Heart, we observed that universal reperfusion strategies for all STEMI patients at all times are not always feasible (ie, “one size does not fit all”) and demonstrated that interhospital transfer for timely primary and rescue PCI can be achieved safely in rural US communities when incorporated within coordinated healthcare networks. See p 1145.

Activatable Magnetic Resonance Imaging Agent Reports Myeloperoxidase Activity in Healing Infarcts and Noninvasively Detects the Antiinflammatory Effects of Atorvastatin on Ischemia-Reperfusion Injury

Myeloperoxidase is a signature enzyme of inflammatory cells (neutrophils, monocytes, and macrophages) and can serve as a surrogate marker for the extent of tissue inflammation in myocardial infarction. Here, we present a novel approach to noninvasive imaging of myeloperoxidase activity locally in the myocardium. Using an “activatable” paramagnetic myeloperoxidase substrate with magnetic resonance imaging, the approach could be used to identify patients at risk for adverse remodeling after myocardial infarction and may guide novel therapeutic strategies to prevent heart failure. Because neutrophils and/or monocytes/macrophages play key roles in inflammation and tissue repair, the imaging agent also could be used to assess atherosclerosis, myocarditis, or transplant rejection. See p 1153.

Endothelial Cilia Are Fluid Shear Sensors That Regulate Calcium Signaling and Nitric Oxide Production Through Polycystin-1

Patients with polycystic kidney disease exhibit an enhanced propensity for hypertension. Studies have revealed that mutations which result in abnormal ciliary proteins such as polars and polycystin-1 lead to the development of polycystic kidney disease in mice. These findings
suggest an association between ciliary function and the development of hypertension. Kidney cells that exhibit abnormal ciliary proteins fail to sense fluid shear stress. Within endothelial cells, this hemodynamic fluid flow can regulate blood pressure by altering calcium signaling and nitric oxide production. Here, we show that embryonic mouse aortic endothelial cells possess primary cilia, specialized organelles that sense and convert fluid shear stresses into changes in intracellular calcium and nitric oxide production. Polars and polycystin-1 were shown to mediate these effects. In addition, prolonged activation of cilia by high shear stress would induce proteolytic cleavage of polycystin-1, thereby desensitizing endothelial cells to these mechanical stimuli. Overall, these findings suggest that dysfunction of endothelial cilia could interfere with normal shear-induced regulatory mechanisms that may contribute to abnormal vascular control in polycystic kidney disease patients and hence may lead to hypertension. Furthermore, hypertensive patients who exhibit ciliary desensitization resulting from continuous exposure to high levels of fluid shear might be unable to respond normally to changes in blood pressure. This might increase the likelihood of localized blood vessel injury, aneurysm, hemorrhage, edema, atherosclerosis, vascular ectasia, dissection, and other abnormalities. Greater insight into this novel mechanism of endothelial flow sensing by cilia may lead to advanced understanding of focal cardiovascular diseases and development of novel forms of “ciliary therapy” in the future. See p 1161.

Cardioprotection by \( \text{N}-\text{Acetylglucosamine Linkage to Cellular Proteins} \)

Despite decades of intensive effort, our understanding of the mechanisms of myocardial cell injury and survival remains limited. In this report, we take a unique approach to the problem and illustrate a potential new paradigm of ischemic cardiobiology. The present study identifies one of the first enzymatically reversible posttranslational modifications, other than phosphorylation, to figure prominently in myocardial ischemia/reperfusion injury in vivo. Previous data suggest that the posttranslational modification \( \text{O-linked } \beta\text{-N-acetylglucosamine (O-GlcNAc)} \) may act as an intracellular metabolic or stress sensor, linking glucose metabolism to cellular function. Considering this, we hypothesized that augmentation of \( \text{O-GlcNAc} \) levels represents an endogenously recruitable mechanism of cardioprotection. From a mechanistic vantage point, \( \text{O-GlcNAc} \) levels waned synchronously with events related to mitochondrial permeability transition pore formation. Proteomic analysis identified several potential targets of \( \text{O-GlcNAc} \) modification, including a putative mitochondrial permeability transition pore member, voltage-dependent anion channel. Thus, \( \text{O-GlcNAc} \) signaling represents a unique endogenously recruitable mechanism of cardioprotection in vivo that may involve direct modification of mitochondrial proteins critical for survival (eg, voltage-dependent anion channel). Identification of all of the potential targets of \( \text{O-GlcNAc} \) modification in the heart, particularly in the human myocardium, and the question of whether augmentation of \( \text{O-GlcNAc} \) levels during ischemic preconditioning is necessary for the infarct-sparing effects of preconditioning will be the focus of future studies. See p 1172.

Effect of the Italian Smoking Ban on Population Rates of Acute Coronary Events

The adverse health effects of environmental tobacco smoke are well established; they include lung cancer and respiratory and cardiovascular diseases. Coronary artery disease has been clearly associated with exposure to passive smoking, and the physiopathological mechanisms of this association are well understood. In several countries around the world, laws banning smoking in public places have been implemented to protect people’s health, but the evidence of their beneficial health effects has remained limited. The aim of this study was to evaluate the effect of the national comprehensive smoking ban on population rates of acute coronary events in Rome, the largest Italian city. Both out-of-hospital cardiac deaths and hospitalizations were considered. During the first year of implementation of the law, fewer coronary events than in previous years were observed in subjects 35 to 64 years old (an 11.2% decrease) and in subjects 65 to 74 years old (a 7.9% decrease). No evidence was found of a reduction in acute coronary events in the population over 74 years of age, possibly because their exposure levels were less influenced. Subjects of low socioeconomic position had the greatest reduction in acute coronary events after the smoking ban. These data strengthen preliminary findings from the United States and Europe and show that smoking bans are simple and effective interventions for improving public health. Because coronary heart disease is the leading cause of death, even a small proportional reduction could have tremendous public health implications. See p 1183.

The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) Trial: First Randomized Placebo-Controlled Study of Myoblast Transplantation

The recognition that heart failure is caused largely by the irreversible loss of a substantial number of cardiomyocytes has led to the concept that implantation of contractile cells in postinfarction myocardium could improve left ventricular function. Preclinical studies showing that skeletal myoblasts met this objective have paved the way for early-phase clinical trials, which were not able to establish the efficacy of the procedure. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial is the first to address this issue. Using the rigorous standards of randomized, controlled, double-blind studies, it enrolled 97 patients with severe left ventricular dysfunction scheduled for bypass surgery and allocated them to receive in-scar injections of a placebo medium or autologous myoblasts. After 6 months, neither global nor regional function improved in treated patients beyond that seen in the placebo group. However, the highest dose of myoblasts was associated with a significant antiremodeling effect. Recordings of internal defibrillators showed that the 6-month incidence of ventricular arrhythmias did not differ significantly among groups despite a trend toward a greater number of early postoperative events after myoblast grafting. These results lead to 3 main conclusions: (1) Implanted myoblasts may exert some therapeutic benefits, possibly through paracrine signaling; (2) it remains uncertain whether these effects have an impact on patient outcomes; and (3) to move the field from proof of concept to active therapy requires the optimization of the best cells matching the target clinical setting (acute infarction or heart failure), their method of delivery, and strategies enabling the enhancement of graft survival and its functional integration. See p 1189.

Aortic Valvuloplasty in Pediatric Patients Substantially Postpones the Need for Aortic Valve Surgery: A Single-Center Experience of 188 Patients After up to 17.5 Years of Follow-Up

Aortic valvuloplasty (AoVP) of congenital aortic valve stenosis is an established procedure regarded as a valid alternative for surgical management. However, its long-term efficacy in preventing or postponing aortic valve surgery remains uncertain for the individual patient. Therefore, the aim of this study was to examine the long-term results of AoVP in pediatric patients and its efficacy in preventing or postponing aortic valve surgery. This study reviewed up to 17.5 years of follow-up data of all 188 patients who received AoVP at the Deutsches Herzzen- trum München in Munich, Germany. The patients were divided into those <1 month of age (group <1 month; n=68) and those ≥1 month of age (group ≥1 month; n=120) at the time of AoVP. After the first and second AoVP, moderate and severe aortic regurgitation developed...
in 29% and 14%, respectively, of the patients in group <1 month and in 19% and 29%, respectively, of the patients in group ≥1 month. Survival after 10 years free from aortic valve surgery was 59% (95% confidence interval, 45 to 73) in group <1 month and 70% (95% confidence interval, 59 to 81) in group ≥1 month. This study shows that the long-term results of AoVP of congenital aortic valve stenosis in pediatric patients and its efficacy in preventing or postponing aortic valve surgery are very good. About two thirds of the patients are free from aortic valve surgery 10 years after AoVP. See p 1201.

A Quantitative Trait Locus (LSq-1) on Mouse Chromosome 7 Is Linked to the Absence of Tissue Loss After Surgical Hindlimb Ischemia

When occlusions are present in the large arteries to the lower extremity, the result is the most common form of peripheral arterial disease (PAD). PAD, a major healthcare problem, has 2 major clinical presentations: intermittent claudication and critical limb ischemia. Despite the significant overlap in risk factors leading to the development of both clinical presentations, patients with critical limb ischemia frequently have ongoing or imminent tissue loss and thus have a higher rate of amputation and mortality. Patients with intermittent claudication rarely develop tissue loss. Therefore, we hypothesized that underlying genetic differences may influence the clinical outcomes in PAD. In the present study, we used a preclinical model of PAD and identified a chromosomal region in mice, termed LSq-1, that, when present, was associated with absence of tissue loss. This is the first identification of such a quantitative trait locus in PAD. This study can serve as a valuable foundation for future studies to identify specific gene(s) involved in PAD in patients. We describe how these results can be used to rapidly identify human orthologs of the mouse genes. Such information has the potential to advance our understanding of the pathophysiology of PAD, as well as new treatment options. See p 1207.
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