Paradigm of Genetic Mosaicism and Lone Atrial Fibrillation: Physiological Characterization of a Connexin 43–Deletion Mutant Identified From Atrial Tissue

Atrial fibrillation is the most common sustained cardiac arrhythmia and is a common cause of stroke. Epidemiological studies project an exponential rise in the prevalence of atrial fibrillation in Western societies, coincident with the increasing age of the population. Management strategies for atrial fibrillation are not highly efficacious. Pharmacological therapies may lead to intolerable side effects and often become refractory over time. Success rates from catheter ablation procedures vary considerably between institutions and may lead to major complications, and long-term success (>24 months) in large cohorts has not been reported despite the use of this procedure for more than a decade. Thus, a further understanding of the molecular mechanisms promoting vulnerability to fibrillation of the atria is critical in facilitating the development of more efficacious therapies. In this study, we provide data implicating a loss-of-function mutation in the gene encoding the gap junction protein connxin 43 as a mechanism leading to augmentation of heterogeneous myocardial electrical coupling, predisposing atrial myocardium to reentrant arrhythmias. Specific drug development enhancing gap junction function may attenuate arrhythmia vulnerability. See p 236.

Relationship of Intraoperative Cerebral Oxygen Saturation to Neurodevelopmental Outcome and Brain Magnetic Resonance Imaging at 1 Year of Age in Infants Undergoing Biventricular Repair

This study explored whether intraoperative cerebral oxygen saturation (rSO2) measured by near-infrared spectroscopy was associated with neurodevelopmental outcomes at age 1 year among infants undergoing biventricular repair without aortic arch reconstruction. Lower Psychomotor Development Index of the Bayley Scales was modestly associated with lower rSO2 during the 60-minute period after cardiopulmonary bypass and at the time points of 10 minutes of cooling, off-cardiopulmonary bypass, and 60 minutes after cardiopulmonary bypass. Lower rSO2 from postinduction to 60 minutes after cardiopulmonary bypass and for the 60-minute period after cardiopulmonary bypass was associated with hemosiderin foci on brain magnetic resonance imaging, even after adjustment for age ≤30 days or diagnosis group, suggests that periods of intraoperative and early postoperative decreased cerebral oxygen delivery are associated with adverse longer-term neurodevelopmental outcomes. See p 245.

B-Type Natriuretic Peptide Signal Peptide Circulates in Human Blood: Evaluation as a Potential Biomarker of Cardiac Ischemia

The clinical diagnosis of acute coronary syndromes relies heavily on circulating diagnostic biomarkers such as troponin. However, delays in detectable changes in circulating troponin, combined with their absence in ischemia short of infarction, result in clinical uncertainty in a significant number of patients presenting with suspected acute coronary syndromes. Thus, identification of novel biomarkers that may provide early information on acute myocardial infarction and cardiac ischemia is of major importance. We provide here the identification of a novel potential biomarker of acute coronary syndromes, namely a peptide fragment derived from the signal peptide region of B-type natriuretic peptide (BNPsp). BNPsp is present as a distinct peptide in explant human cardiac tissue and is secreted into the circulation in normal health. Furthermore, detectable elevations in BNPsp were observed in ST-elevation myocardial infarction patients significantly earlier than myoglobin, creatine kinase-MB, and troponin. BNPsp thus presents as a novel class of potential biomarker in acute coronary syndromes, and further studies to determine its assay specificity and diagnostic potential in the complete spectrum of acute coronary syndromes are clearly warranted. See p 255.

Potential Effects of Aggressive Decongestion During the Treatment of Decompensated Heart Failure on Renal Function and Survival

Previous studies of acute decompensated heart failure have demonstrated a strong association between worsening renal function and increased mortality. Similarly, high-dose loop diuretics have been associated with decreased survival, and aggressive diuresis has been proposed as a possible cause for worsening renal function. However, it has also been suggested that incomplete relief of congestion during acute decompensated heart failure may contribute to heart failure disease progression and worse survival. The aim of this study was to examine the relationship between aggressive decongestion, worsening renal function, and survival in relation to hemoconcentration. Hemoconcentration occurs when the rate of diuresis exceeds the refill rate of extravascular fluid into the intravascular space, causing concentrations of hemoglobin and plasma proteins to increase. This study demonstrated that hemoconcentration was associated with higher doses of loop diuretics, greater rates and quantities of diuresis and weight loss, greater reductions in cardiac filling pressures, and worsening renal function. However, patients who developed hemoconcentration had substantially improved survival despite a higher incidence of worsening renal function. These observations suggest that aggressive decongestion of patients with acute decompensated heart failure may improve survival, even when high diuretic doses are required or renal function deteriorates. See p 265.

Impaired Autonomic Regulation of Resistance Arteries in Mice With Low Vascular Endothelial Growth Factor or Upon Vascular Endothelial Growth Factor Trap Delivery

Vascular endothelial growth factor (VEGF) is a key angiogenic factor, and blocking of VEGF signaling in cancer patients inhibits angiogenesis, thereby preventing tumor progression. One of the side effects of anti-VEGF therapy is the hand-foot syndrome, which is characterized by dilated blood vessels in hands and feet, leading to dysesthesia, erythema, and tingling of extremities, which may progress to burning pain with dryness, cracking, and ulceration of the skin. Here, we show that knock-in mice with reduced VEGF levels display abnormal regulation of resistance arteries, resulting in defects in thermoregulation and redistribution of blood flow in response to hypoxia. The abnormal vascular regulation was attrib-
ated to reduced vascular smooth muscle cell contractility associated with reduced expression of contractile proteins, as well as to dysfunction of neuroeffector junctions as a result of their abnormal structural development. Furthermore, short-term treatment of wild-type mice with a VEGF trap also induced thermoregulation defects and neuroeffector dysfunction with structural remodeling of neuroeffector junctions, indicating that VEGF is necessary for maintenance of the structural and functional integrity of adult neuroeffector junctions. These findings may provide mechanistic insights into the cause of the hand-foot syndrome. See p 273.

**Impaired Macrophage Migration Inhibitory Factor–AMP-Activated Protein Kinase Activation and Ischemic Recovery in the Senescent Heart**

Cardiovascular disease remains the most frequent single cause of death among persons >70 years of age. The aged heart is inherently more susceptible to injury during myocardial ischemia. However, the cause(s) of this increased susceptibility remain poorly understood. On the basis of both in vitro and in vivo observations, AMP-activated protein kinase (AMPK) has emerged as an important component of the cardioprotective response against ischemic injury. The present study provides the first evidence that the senescent heart manifests an impaired AMPK activation in response to ischemic stress, which is associated with more severe myocardial damage during ischemia and reperfusion. This study also showed that cardiomyocyte production of an upstream activator of AMPK, macrophage migration inhibitory factor, is impaired in the aged heart. Importantly, supplementary administration of macrophage migration inhibitory factor by pharmacological or genetic approaches restored AMPK function in the aged heart, limited ischemic damage, and improved cardiac function after ischemia and reperfusion. Evidence is also provided that defective hypoxia-inducible factor-1, α subunit (HIF-1α) in the senescent heart may account for the impairment in macrophage migration inhibitory factor expression. An aging-associated decrease in the function of the HIF-1α–macrophage migration inhibitory factor axis may play a causative role in the intolerance of the senescent heart to ischemic injury. Pharmacological interventions that restore migration inhibitory factor signaling and AMPK activity in the senescent heart may be a useful means to reduce cardiac damage caused by ischemic injury in older individuals. See p 282.

**Bystander-Initiated Rescue Breathing for Out-of-Hospital Cardiac Arrests of Noncardiac Origin**

Little is known about the difference in the effectiveness of bystander-initiated conventional cardiopulmonary resuscitation (CPR) with rescue breathing and chest compression–only CPR for adult out-of-hospital cardiac arrests (OHCAs) of noncardiac origin, which account for 20% to 40% of adult OHCAs. The large, prospective, population-based registry covering all of Japan enabled us to evaluate the effectiveness of each type of bystander CPR for OHCAs of noncardiac origin. Although this study demonstrated the actual benefits of the addition of rescue breathing for OHCAs of noncardiac origin, the absolute survival was very low regardless of type of CPR, and the number of OHCAs needed to treat with conventional CPR versus compression-only CPR to save a life with favorable neurological outcome was 290. Even among the >43 000 OHCAs of noncardiac origin over 3 years in an entire large country, <10 additional patients survived with better neurological outcome after conventional CPR compared with compression-only CPR. On the basis of the findings of this investigation and other studies supporting the effectiveness of compression-only CPR for OHCAs of cardiac origin, we suggest a 2-pronged CPR training strategy: chest compression–only CPR training for most people and conventional CPR with rescue breathing for individuals who are likely to witness cardiac arrests such as medical professionals and lifeguards. Efforts to teach and encourage laypersons to perform any bystander-initiated CPR (especially compression-only CPR) would improve survival after OHCAs. See p 293.
Clinical Summaries

Circulation. 2010;122:227-228
doi: 10.1161/CIR.0b013e3181e8eb30

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