Conduction Remodeling in Human End-Stage Nonischemic Left Ventricular Cardiomyopathy

Ventricular arrhythmia is one of the primary causes of death in humans with heart failure. Despite major advances in the characterization of ionic and molecular remodeling that occurs during heart failure, the exact role of these changes in the formation of an electrophysiological substrate for arrhythmia and arrhythmogenesis itself is still poorly understood. Numerous animal models of heart failure have thus been developed to investigate the mechanisms of arrhythmogenesis. However, there exists insufficient electrophysiological data from human hearts because of the limited availability of live, human cardiac tissue for basic research in vitro. Our study provides an integrative investigation of arrhythmogenic substrate in end-stage heart failure due to nonischemic cardiomyopathy in humans. We show for the first time in the same human hearts a relation among multiple levels of cardiac signaling: from protein expression and phosphorylation, protein-protein colocalization, to transmural conduction and repolarization. We present evidence that supports some previous animal and human findings at the cellular and molecular levels and contradicts some other findings in animal models. We show that conduction disorder is a critical component of arrhythmogenic substrate in patients with nonischemic cardiomyopathy. We demonstrate that conduction abnormalities lead to nonuniform propagation discontinuities and reentry conditioned by structural disorder. Moreover, we show that connexin 43 downregulation, dephosphorylation, and lateralization are likely causes of such conduction abnormalities. Thus, our findings highlight potential therapeutic targets for predicting and ameliorating the risk of sudden cardiac death in patients with heart failure. See p 1835.

Twenty-Two–Year Trends in Incidence of Myocardial Infarction, Coronary Heart Disease Mortality, and Case Fatality in 4 US Communities, 1987–2008

Community-level event rates are the ultimate measures of successful clinical and public health efforts to reduce major causes of mortality. Studies of acute myocardial infarction (AMI) incidence and survival after AMI provide insight into the relative contribution of prevention and treatment to the decline in coronary heart disease death rates. Evidence of community-level impact on disease occurrence and survival is relevant to practicing physicians who treat patients’ elevated risk factors, provide education on avoiding risk through healthy lifestyles and behaviors, and treat AMI events with surgical and medical interventions. We found that although AMI incidence declined during 1987–2008, the decline was steeper over the past 10 years (1997–2008) than in the preceding 10 years. This is especially true among minority populations. For example, among black men and women, little or no decline in first AMI during 1987–1996 transitioned to statistically significant average annual percent declines in incidence during the more recent period (1997–2008), of −2.5%/y (95% confidence interval, −4.7% to −0.4%) and −3.3%/y (95% confidence interval, −5.8% to −0.8%), respectively. Case-fatality rates after AMI declined steadily for men and women over the past 22 years (−3.9%/y and −2.6%/y average annual change, respectively), suggesting continuing improvements in treatment of AMI patients and/or secular trends toward reduced severity of the AMI itself. Maintaining the decline in AMI incidence that gained momentum in the new millennium will require continued efforts to promote cardiovascular health at the community level. See p 1848.

Global Variation in the Prevalence of Elevated Cholesterol in Outpatients With Established Vascular Disease or 3 Cardiovascular Risk Factors According to National Indices of Economic Development and Health System Performance

The exponential rise in cardiovascular disease over the past decade has placed a tremendous burden on the health and economic development of countries worldwide, with unprecedented demands for an effective response from governments and other stakeholders in global health. From a large, multinational registry of outpatients with established cardiovascular disease or ≥3 risk factors, we used data from 53.570 individuals from 36 countries to examine the relationship between country-level economic and health system factors and the risk of elevated cholesterol (total cholesterol levels >200 mg/dL). The analysis was performed separately for patients with versus without previous history of hyperlipidemia; a higher proportion of the total variability in elevated cholesterol was at the country level for patients with (12.1%) versus without (7.4%) history of hyperlipidemia. Among patients with history of hyperlipidemia, after adjusting for patient-level demographic and clinical characteristics and average fat consumption at the country level, countries in the highest tertile of gross national income or World Health Organization index of health system achievement were found to have significantly lower odds of elevated cholesterol than those in each of the lower 2 tertiles, and the odds of elevated cholesterol was higher for countries in higher versus lower tertile of out-of-pocket health expenditures. No significant associations between country-level factors and elevated cholesterol were found for patients without history of hyperlipidemia. These results support the need for strengthening efforts toward effective cardiovascular disease prevention and control and may provide insight for health policy setting at the national level. See p 1858.

Comparative Outcomes for Patients Who Do and Do Not Undergo Percutaneous Coronary Intervention for Stable Coronary Artery Disease in New York

Little is known about the relative frequencies of different treatments that patients receive after being diagnosed with stable coronary artery disease and what the comparative outcomes are for routine medical treatment (RMT) versus percutaneous coronary intervention (PCI) with RMT for patients not in randomized controlled trials. Consequently, patients with stable coronary artery disease undergoing cardiac catheterization in New York State between 2003 and 2008 were followed up to determine the treatment they received. Patients receiving RMT and patients receiving PCI with RMT were propensity matched through the use of 20 factors that could have a bearing on outcomes. The resulting cohort of 933 matched pairs was used to compare mortality/myocardial infarction (MI), mortality, MI, and subsequent revascularization rates. Most of the patients (89%) underwent PCI. PCI/RMT patients had significantly lower adverse outcome rates at 4 years for mortality/MI (16.5% versus 21.2%; P=0.003), mortality (10.2% versus 14.5%; P=0.02), MI (8.0% versus 11.3%; P=0.007), and subsequent revascularization (24.1% versus 29.1%; P=0.005). Adjusted RMT/PCI hazard ratios were 1.49 (95% confidence interval, 1.16–1.93) for mortality/MI and 1.46 (95% confidence interval, 1.08–1.97) for mortality. There were no differences in treatment outcomes for patients <65 years of age or for patients with single-vessel disease. Most patients with stable coro-
Cardioprotection Through S-Nitrosylation of Macrophage Migration Inhibitory Factor

Macrophage migration inhibitory factor (MIF) is the first identified cytokine, discovered almost half a century ago by David, Bloom, and Bennett. Molecular knowledge about this protein mediator has recently grown tremendously, and a pivotal role has been attributed to MIF as a key regulator of innate and acquired immunity, as well as numerous pathophysiological functions involving its inflammatory cytokine and chemokine. There is emerging evidence that MIF also plays a central role in cardiovascular diseases and myocardial ischemia and reperfusion (I/R) injury. Despite an improved understanding of the pathophysiology of I/R injury and numerous preclinical trials, most of the clinical trials to prevent I/R injury have been disappointing. The present study now provides the first evidence that protein modification by means of S-nitrosylation of MIF increases the cardioprotective properties of this factor in the early phase of I/R injury. This reveals the first-described posttranslational regulatory modification of MIF and thus opens up a novel role of this ancient protein. This study further identifies the precise site of this modification and uncovers a key function of the reactive cysteine 81 residue. S-nitrosylation distinctly affects MIF properties and leads to decreased apoptosis and infarct size in vivo. Beyond the background that the precise pathophysiology of I/R injury is still not entirely understood, targeted regulation of MIF functions by S-nitrosylation might deliver a new therapeutic approach in the treatment of myocardial infarction. See p 1880.

Systemic and Pulmonary Vascular Dysfunction in Children Conceived by Assisted Reproductive Technologies

Assisted reproductive technology (ART) has been used for 3 decades, and the children born after ART now make up for 1% to 4% of the births in developed countries. ART involves the manipulation of early embryos at a time when they may be particularly vulnerable to external disturbances. Environmental influences during the embryonic and fetal development influence the individual’s susceptibility to cardiovascular disease, raising concerns about the potential consequences of ART on the long-term health of the offspring. Here, we show for the very first time that apparently healthy children born after ART show systemic and pulmonary vascular dysfunction, as evidenced by endothelial dysfunction, increased arterial stiffness, and carotid intima-media thickness in the systemic circulation and exaggerated hypoxic pulmonary hypertension during short-term high-altitude exposure. This vascular dysfunction does not appear to be related to parental factors or hormonal stimulation of the ovulation in the mother but to the ART procedure itself. For the practicing physician, this study indicates that ART children who live at high altitude or suffer from diseases associated with chronic hypoxia are at risk for exaggerated pulmonary hypertension and need to be monitored for this problem. In the systemic circulation, it is not known yet how this vascular dysfunction, which is similar in magnitude to that in children suffering from type 1 diabetes mellitus, will evolve. Although future mechanistic studies in ART mice may reveal possibilities for targeted intervention to improve or prevent ART-induced vascular dysfunction in humans, avoiding additional cardiovascular risk factors in this population appears to be important now. See p 1890.

Body Mass Index, Surgery, and Risk of Venous Thromboembolism in Middle-Aged Women

Obesity and surgery are established risk factors for venous thromboembolism, but there is limited information about the independent effects of excess body weight on the incidence of postoperative venous thromboembolism. We linked questionnaire data from a large cohort study (the Million Women Study) with hospital admission and death records to examine the risk of venous thromboembolism in relation to body mass index, both in the absence of surgery and in the first 12 weeks following surgery. In the absence of surgery, there was a clear trend of increasing risk of venous thromboembolism with increasing body mass index. We also found that the risk of being admitted to hospital for surgery increased with increasing adiposity. Following surgery, both overweight and obese women had higher risks of venous thromboembolism, when compared with women of a healthy weight. This relationship between adiposity and postoperative venous thromboembolism risk was seen for both day and inpatient surgery, although the excess incidence was much greater following inpatient surgery. Clinical guidelines identify obesity as an additional risk factor for postoperative venous thromboembolism. Our findings suggest that venous thromboembolism prophylaxis is important for overweight, as well as obese, women undergoing either day or inpatient surgery. The observed progressive increase in venous thromboembolism incidence with increasing body mass index also suggests that the avoidance of further weight gain and even small reductions in body size are likely to be beneficial for those who are overweight and obese. See p 1897.
Practicing Clinician: Clinical Summaries: Original Research Put Into Perspective for the Practicing Clinician

Circulation. 2012;125:1825-1826
doi: 10.1161/CIR.0b013e318257cae8
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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