

Second Internal Thoracic Artery Versus Radial Artery in Coronary Artery Bypass Grafting: A Long-Term, Propensity Score–Matched Follow-Up Study

Studies of coronary artery bypass grafting have implied that arterial grafts are superior to saphenous venous grafts (SVG). At this time, only the benefit of the single internal thoracic artery (ITA) has been proven by randomized trials. Moreover, observational studies on bilateral ITA use have shown similar results, namely a benefit of a second ITA over SVG. Long-term results, however, are awaited from the Arterial Revascularization Trial (ART). Sternal wound complications have prevented more common bilateral ITA use, and surgeons have been trying to find grafts that act more like ITA and less like SVG. Worldwide, the radial artery (RA) is used more commonly, but results from several studies are conflicting. Studies comparing the outcome of either concomitant RA or second ITA in addition to left ITA are missing. This propensity score–matched study was performed to investigate the outcome of RA compared with second ITA as concomitant arterial graft among 1001 consecutive coronary artery bypass grafting patients. In the study, the use of RA was associated with a significantly higher perioperative major adverse cardiac and cerebrovascular events rate ($P<0.001$) and, additionally, an SVG-like progressive graft failure. Sternal dehiscence rate was similar among both groups (3.2% versus 3.6%, $P=1.0$) and was attributed to the higher rate of skeletonized ITA grafts among patients receiving bilateral ITA. Overall survival (hazard ratio 0.23; $P=0.022$) and major adverse cardiac and cerebrovascular events–free survival (hazard ratio 0.18; $P<0.001$) were significantly improved in patients receiving second ITA. Our study provides strong evidence for the superiority of a second ITA graft compared with RA, indicating that the RA is not an equivalent alternative to a right ITA. See p 1321.

Delayed Postconditioning in the Mouse Heart In Vivo

The major finding of this study is that delayed postconditioning allows infarct size to be reduced in the mouse heart in vivo. This observation emphasizes the fact that the cardioprotection window for postconditioning is wider than initially reported. Such information may be of major importance for clinical applications. Manual thrombectomy, in addition to primary percutaneous coronary intervention, has been shown to improve microvascular reperfusion, with a lower mortality at 1-year follow-up. Unfortunately, routine use of mechanical thrombectomy during primary percutaneous coronary intervention increases procedure time and precludes the application of angioplasty postconditioning in the 1 minute of reflow. Confirmation of the existence of a longer cardioprotection window by postconditioning in a range of animal myocardial infarction models, including larger animals, may justify new clinical trials combining manual thrombectomy and angioplasty postconditioning in patients with acute myocardial infarction in accordance with the recently published recommendations for investigating novel cardioprotective strategies. In addition, demonstration of delayed postconditioning may also be of interest in patients with incomplete reperfusion at hospital admission in whom episodes of brief ischemia/reperfusion may be performed during the percutaneous coronary intervention to further reduce infarct size. However, the translation of cardioprotection from the experiment to the clinic is not obvious, because species differences, age, comorbidities, cotreatments, and the status of the coronary circulation may interfere with postconditioning. We think that our data, which demonstrate the existence of a longer cardio-

protection window, are conceptually relevant for a clinical application and make the case for a pharmacological strategy. See p 1330.

Placental Growth Factor Regulates Cardiac Inflammation Through the Tissue Inhibitor of Metalloproteinases-3/Tumor Necrosis Factor- α -Converting Enzyme Axis: Crucial Role for Adaptive Cardiac Remodeling During Cardiac Pressure Overload

Our results highlight a novel role for placental growth factor (PIGF) in cardiac remodeling to pressure overload by orchestrating the inflammatory response. Important questions of potential clinical importance ensue from these findings. First, the proposed role for PIGF in protection from the development of dilated cardiomyopathy strongly suggests that a pharmacological therapy with recombinant PIGF could be exploited in clinical practice as a promising treatment for heart failure. This will allow maintenance of a balanced positive inflammatory response, necessary to cope with cardiac remodeling in challenging conditions. Another remarkable point that emerges from our findings concerns the clinical impact of antitumor therapies exploiting anti-PIGF antibodies. The conflicting results showed that such clinical studies should now also take into account our study showing a novel role for PIGF in cardiac remodeling and further consideration when deciding on a therapy with anti-PIGF antibodies in patients with increased cardiovascular risk. Finally, the potential importance of PIGF effects on cardiac remodeling in relation to peripartum dilated cardiomyopathy should be considered. Indeed, this condition is associated with different risk factors, notably hypertension and low levels of circulating PIGF. Our model of pressure overload in PIGF-deficient mice may resemble such a situation and suggest a possible reason why pregnancy may lead to dilated cardiomyopathy when concomitant with the presence of risk factors such as hypertension and low levels of PIGF. See p 1337.

Role of Cardiovascular Magnetic Resonance as a Gatekeeper to Invasive Coronary Angiography in Patients Presenting With Heart Failure of Unknown Etiology

Identifying the underlying etiology in patients with new onset heart failure and no overt features of underlying coronary artery disease, eg angina, can be challenging. Invasive coronary angiography (CA) carries tangible risks and does not provide tissue characterization. In this prospective study of 120 patients (powered to display non-inferiority), late gadolinium enhanced cardiovascular magnetic resonance (LGE-CMR) showed equivalence to CA when determined against a gold standard consensus panel who considered data from all the investigations. Diagnoses ascribed by LGE-CMR and CA were also validated against clinical outcomes at a median of 3.7 years. LGE-CMR is ideally placed as a gatekeeper to CA because it is safer, uniquely provides biventricular function and tissue characterization data, and is economically viable. LGE-CMR and CA were equivalent in diagnostic accuracy (97% versus 95%) and the data suggests that 73% of patients would have appropriately avoided CA, being spared the risks and costs of this investigation. Importantly, no patient with prognostically important coronary artery disease would have been denied CA and any subsequent revascularization as LGE-CMR had a negative predictive value of 100%. The data also suggests the need for a paradigm shift in the classification of patients with heart failure to reflect not just coronary anatomy, but also myocardial tissue

characterization. This study therefore challenges the traditional dichotomy of ischemic versus nonischemic cardiomyopathy by revealing subgroups of patients with features of both ischemic and nonischemic etiologies. See p 1351.

Adolescents With d-Transposition of the Great Arteries Corrected With the Arterial Switch Procedure: Neuropsychological Assessment and Structural Brain Imaging

Advances in the management of congenital heart disease have improved the survival of individuals with even the most complex heart lesions, unmasking significant neurodevelopmental risk among survivors. Assessments conducted in early childhood have provided early data on the frequency and severity of neurodevelopmental morbidity. However, few studies have evaluated the neuropsychological and neuroimaging outcomes of adolescents with congenital heart disease. We evaluated 139 children 16 years of age with d-transposition of the great arteries who were enrolled as infants in the Boston Circulatory Arrest Study, a randomized trial comparing the outcomes associated with 2 vital organ support strategies: deep hypothermia with total circulatory arrest or with continuous flow cardiopulmonary bypass. Adolescents in the 2 groups generally performed similarly. However, compared with the general population, adolescents in the combined treatment groups had lower, and more variable, scores on academic achievement, memory, attention, executive functions, visual-spatial skills, and social cognition. Almost two thirds had received remedial academic or behavioral services. Postoperative seizure, detected clinically or by continuous EEG recording, was the strongest predictor of poor outcomes. Structural MRI abnormalities were found in one third of the adolescents and were more frequently focal than diffuse, consisting of mineralization or iron deposits. Greater exposure to catheterization and longer time on cardiopulmonary bypass were independent risk factors for brain mineralization. Although most adolescents had satisfactory neuropsychological outcomes, a significant minority performed below the expected level. Our results suggest that children with d-TGA should remain under surveillance into adolescence to permit identification of neurocognitive and behavioral difficulties. See p 1361.

Lysozyme M-Positive Monocytes Mediate Angiotensin II-Induced Arterial Hypertension and Vascular Dysfunction

Arterial hypertension represents the most important risk factor for cardiovascular disease and death. Activation of the renin-angiotensin-aldosterone system is central to the pathomechanism of hypertension, and the vasoconstrictor angiotensin II very potently initiates an inflammatory and an oxidative stress response within the vasculature. With the present studies, we provide experimental evidence

that proinflammatory monocytes and macrophages are mediators of angiotensin II-induced vascular dysfunction and may be causally involved in the development of high blood pressure in this particular animal model. Ablation of lysozyme-positive myelomonocytic cells markedly attenuated angiotensin II-induced blood pressure increases and vascular dysfunction *in vivo*. These experimental data highlight the important role of angiotensin II as a proinflammatory promoter of atherosclerosis and provide incremental mechanistic evidence for the positive vascular effects of angiotensin-converting enzyme inhibitors and angiotensin II type I receptor blockers in the prevention of cardiovascular diseases. Identification of the molecular targets of the proinflammatory monocytes/macrophages that are specific for the angiotensin II-induced effects and that are accessible to pharmacotherapy might potentially open up new therapeutic options to treat arterial hypertension and atherosclerosis. See p 1370.

Pharmacologic Suppression of Hepatic ATP-Binding Cassette Transporter 1 Activity in Mice Reduces High-Density Lipoprotein Cholesterol Levels but Promotes Reverse Cholesterol Transport

Plasma levels of high-density lipoprotein cholesterol (HDL-C) do not always reflect the dynamic process of reverse cholesterol transport (RCT) from macrophage to bile and feces and the risk of atherosclerosis. For example, mice lacking the hepatic HDL receptor scavenger receptor class B type I have markedly elevated HDL-C levels but impaired RCT and increased atherosclerosis. The ATP-binding cassette transporter 1 (ABCA1) is expressed in the liver, and by exporting cholesterol out of the liver to the HDL protein, apolipoprotein A-I plays a critical role in maintaining plasma HDL-C levels. However, the relationship of hepatic ABCA1 to RCT and atherosclerosis remains poorly understood. Because hepatic ABCA1 pumps cholesterol from the liver into the blood instead of the bile, it might reduce the rate at which the liver excretes HDL-derived cholesterol. Probucol is a drug that reduces HDL-C levels but also, paradoxically, reduces atherosclerosis and xanthomas. We tested the hypothesis that probucol inhibits hepatic ABCA1 activity, thereby reducing HDL-C levels but promoting RCT from macrophages. In studies in mice lacking the hepatic HDL receptor scavenger receptor class B type I, probucol substantially reduced HDL-C but significantly increased macrophage RCT. Furthermore, probucol significantly enhanced the excretion of HDL-derived cholesterol into the feces. Probucol markedly inhibited ABCA1-dependent cholesterol efflux from mouse primary hepatocytes, and this effect was shown to be responsible for the effect of probucol on increasing the fecal excretion of HDL-derived cholesterol *in vivo*. These results provide an explanation for the beneficial effects of probucol on atherosclerosis despite its HDL-lowering effects and suggest that inactivation of hepatic ABCA1 leads to increased RCT despite reducing plasma HDL-C levels. See p 1382.

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