Aortic Pathology Determines Midterm Outcome After Endovascular Repair of the Thoracic Aorta: Report From the Medtronic Thoracic Endovascular Registry (MOTHER) Database

Endovascular repair is increasingly being adopted as the treatment of choice for many thoracic aortic conditions. As the application of this technology widens, developing an evidence-based understanding of which patients are most likely to benefit is a priority. A barrier to this has been the relatively few number of procedures that are performed, so that randomized controlled trials on the scale of those performed for infrarenal aortic aneurysm have not been feasible. At present, many published series fail to discriminate between different aortic pathologies when outcomes are reported, making pooled analysis difficult. This first report from the Medtronic Thoracic Endovascular Registry (MOTHER) combines raw data from 5 trials and 1 institutional series, characterizing the difference in early outcomes between the major pathology groups. Regional trends in practice suggest that thoracic endovascular repair has complemented open surgery rather than replaced it and has allowed more patients to be offered therapy than was previously possible. Significantly, some will have been deemed unfit for open surgery because of poor physiological reserve, and although thoracic endovascular aortic repair all but abolishes aortic death, individuals remain subject to an increased risk of mortality from all other causes in comparison with matched controls. Follow-up data collected for the component registries have allowed a description of midterm survival in such patients, and this report serves to highlight the importance of considering all-cause mortality in aneurysm patients and to reinforce the ability of thoracic endovascular aortic repair to prevent aortic-related death in both aneurysm and dissection patients. See p 24.

Low Serum Magnesium and the Development of Atrial Fibrillation in the Community: The Framingham Heart Study

Data from both experimental and human studies suggest that low magnesium may be linked to the development of arrhythmias. Although hypomagnesemia has been associated with the development of atrial fibrillation (AF) after cardiac surgery, it is unknown whether serum magnesium is associated with the development of AF in healthy, ambulatory individuals. In a longitudinal, community-based study of 3530 individuals without known cardiac disease, we identified an association between low serum magnesium and the development of AF over 20 years of follow-up. We found that those in the lowest quartile of serum magnesium were approximately 30% more likely to develop AF than those in the upper 3 quartiles. This association persisted despite adjustment for known AF risk factors and the interim development of heart failure, myocardial infarction, or cardiac surgery. Because magnesium deficiency is relatively common and easily treatable with dietary supplementation, a link with AF in the general population has potential clinical implications. See p 33.

Atrial Giant Cell Myocarditis: A Distinctive Clinicopathologic Entity

Idiopathic giant cell myocarditis (GCM) is a rare and particularly aggressive form of myocarditis, characterized by myocardial destruction attributable to dense lymphohistiocytic inflammation, including abundant giant cells. GCM typically causes fulminant heart failure, arrhythmias, or heart block, and left untreated, is almost universally and rapidly fatal. Current treatment approaches have modestly improved survival, including aggressive immunosuppression and ventricular assist device insertion, but prognosis remains poor and many patients eventually require heart transplantation. We describe a novel variant of GCM, primarily involving the atria, that displays distinctive clinical features and follows a more benign course than ventricular GCM. Clinically, most patients are diagnosed incidentally during routine pathologic evaluation of atrial tissues removed during cardiac surgery for other indications (eg, valve replacement or coronary bypass grafting). Nearly all are in atrial fibrillation. Imaging findings include severe atrial dilatation, mitral/tricuspid regurgitation, atrial mural thrombus, atrial wall thickening, and atrial hypokinesis, with preserved ventricular function. Pathologically, atrial tissues show findings remarkably similar to classical ventricular GCM. Most patients do very well with supportive care, and return to baseline exercise tolerance within weeks to a few months. Atrial GCM represents a distinct clinicopathologic entity with a more favorable prognosis than classic ventricular GCM. This disorder should be included in the differential diagnosis of atrial dilatation, particularly when associated with atrial wall thickening. Although the radiologic and pathologic findings are striking, recognition of this disorder by clinicians, radiologists, and pathologists is important to avoid overtreatment. The utility of immunomodulatory therapy for this condition remains unknown. See p 39.

Penetrance of Hypertrophic Cardiomyopathy in Children and Adolescents: A 12-Year Follow-up Study of Clinical Screening and Predictive Genetic Testing

It has been the general belief that hypertrophic cardiomyopathy (HCM) develops predominantly during the growth spurt in childhood or adolescence. This belief was based on few observations. We report that the vast majority of child carriers of sarcomere gene mutations and child relatives with unknown genetic status did not develop HCM during 12 years of follow-up. However, reports of serious cardiac events in the few children with HCM strongly support the American College of Cardiology/American Heart Association (ACC/AHA) recommendations of repeated clinical screening of children. We suggest that screening be initiated at early school age because affected child relatives have been identified at that age. The new knowledge of a low penetrance of HCM in childhood may be a great relief for affected families. The concern about a negative psychological impact of clinical and genetic screening of children was not confirmed. The low penetrance in children may influence the recommendations for screening of adults; if HCM does not develop primarily in childhood, then screening according to ACC/AHA recommendations of all phenotype-negative adults at 5-year intervals may be insufficient. Echocardiography is the diagnostic tool of choice in the clinical screening; ECG changes seem to be quite unspecific. With contemporary genetic testing, almost half of the relatives can be excluded from being at risk of developing HCM, and follow-up can be limited to the remaining relatives. Thus, our findings add to the importance of increased availability of genetic testing for cardiologists. This relates not only to HCM but also to other inherited cardiac diseases. See p 48.
Hemodynamic Responses to Rapid Saline Loading: The Impact of Age, Sex, and Heart Failure

A volume challenge unMASKS left ventricular diastolic dysfunction and therefore has been proposed as a way to identify heart failure with preserved ejection fraction. However, the normal hemodynamic response to a volume challenge and how age and sex affect this relationship remain unknown. In the present study, we assessed age- and sex-related normative responses of pulmonary capillary wedge pressure to rapid saline infusion (100–200 mL/min) in 60 healthy subjects. Hemodynamic responses to saline infusion in 11 patients with heart failure with preserved ejection fraction were then compared with those in healthy young and older subjects. Rapid saline infusion significantly increased pulmonary capillary wedge pressure from 10±2 to 16±3 mm Hg with ~1 L saline and to 20±3 mm Hg with ~2 L saline in healthy subjects. More than 90% of the healthy subjects exhibited pulmonary capillary wedge pressure values previously considered to define heart failure with preserved ejection fraction (>15 mm Hg) with ~2 L saline. In older women, a greater increase in pulmonary capillary wedge pressure relative to volume infused was observed compared with men and younger women, suggesting more dramatic loss of diastolic reserve in older women. The greatest increase in pulmonary capillary wedge pressure relative to volume infused was noted in patients with heart failure with preserved ejection fraction, consistent with the most severely impaired diastolic reserve. These data could constitute an important step for the development of diagnostic protocols for the invasive evaluation of patients with dyspnea. Future studies will assess how effectively saline loading differentiates patients with heart failure with preserved ejection fraction from patients with other cardiovascular diseases such as systemic and pulmonary arterial hypertension. See p 55.

CXC-Chemokine Receptor 4 Antagonist AMD3100 Promotes Cardiac Functional Recovery After Ischemia/Reperfusion Injury via Endothelial Nitric Oxide Synthase–Dependent Mechanism

Numerous clinical trials with cell therapy focusing on cardiac functional recovery after cardiovascular diseases, including myocardial infarction, have been performed over the past decade. Despite a certain extent of favorable outcome by the evolutional compared with conventional therapies, the trials have been required to overcome ethical, technical, and medical expense issues that may hinder the development of a novel therapeutic strategy. We have shown here that single administration of the CXC-chemokine receptor 4 antagonist AMD3100 exhibited sufficient therapeutic effect on cardiac functional recovery via mobilizing bone marrow–derived endogenous progenitor cells, including endothelial progenitor cells, by an endothelial nitric oxide synthase–dependent mechanism in a mouse ischemia/reperfusion injury model. The easy-to-handle, low-invasiveness, and inexpensive therapy with AMD3100 that we proposed in the present study can avoid the above-described hurdles to be cleared in clinical trials for cell therapy. AMD3100 treatment may not be able to restore cardiac function after myocardial infarction completely but could be a potent supplemental option after the established coronary recanalization/reperfusion technique with percutaneous transluminal coronary angioplasty balloons and stents. Clinical trials of autologous stem/progenitor cell therapy are ongoing, and positive outcomes have emerged, specifically in nononpation patients suffering from severe cardiovascular disease. Our data suggest that AMD3100, an endogenous stem/progenitor cell mobilizer, has the potential to be a simple but promising additional therapy, taking the place of stem/progenitor cell transplantation therapy for ischemic heart diseases. See p 63.

A Glucagon-Like Peptide-1 Analog Reverses the Molecular Pathology and Cardiac Dysfunction of a Mouse Model of Obesity

This study reveals the heretofore unrecognized ability of a glucagon-like peptide-1 analog to reverse multiple molecular mechanisms underlying the pathophysiology of obesity-induced cardiovascular dysfunction. Although this class of antidiabetic drug is under Food and Drug Administration–mandated evaluation for long-term cardiovascular safety, it will be many years before these data are reported. Meanwhile, this drug class is also being tested for its ability to reduce body weight, with a very limited understanding of how it affects the vulnerable cardiovascular systems of obese subjects. In this context, the findings of direct cardiovascular benefit of liraglutide in an animal model of obesity in vivo and cell culture models of inflammatory cell adhesion and lipotoxicity in vitro have promising implications for the clinical use of these agents in obesity. See p 74.

Protein Kinase C-β Contributes to Impaired Endothelial Insulin Signaling in Humans With Diabetes Mellitus

Atherosclerotic vascular disease in patients with type 2 diabetes mellitus is a pressing health problem. Abnormal endothelial function contributes to cardiovascular disease development and manifestation in diabetic patients. Experimental studies link insulin resistance and endothelial dysfunction. We demonstrated that endothelial cells collected directly from patients with diabetes mellitus have impaired activation of endothelial nitric oxide synthase in response to insulin. Further, we observed evidence of increased oxidative stress and inflammatory activation in the endothelial cells from patients with diabetes mellitus. This study provides evidence that patients with diabetes mellitus have endothelial insulin resistance and supports the possibility that treatments aimed at restoring insulin action in the endothelium may be a novel strategy to reduce vascular disease burden in this high risk group. See p 86.

Effect of Statins on Skeletal Muscle Function

Many clinicians believe that statins cause muscle pain, but this has not been observed in clinical trials, and the effect of statins on muscle performance has not been carefully studied. The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study assessed symptoms and measured creatine kinase, exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo was administered for 6 months to 420 healthy, statin-naive subjects. No creatine kinase value exceeded 10 times normal in any subject during the trial, kinase performance has not been carefully studied. The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study assessed symptoms and measured creatine kinase, exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo was administered for 6 months to 420 healthy, statin-naive subjects. No creatine kinase value exceeded 10 times normal in any subject during the trial, but average creatine kinase increased 20.8±14.1 U/L (P<0.01) with atorvastatin. There were no significant changes in several measures of muscle strength or exercise capacity with atorvastatin, but more atorvastatin than placebo subjects developed myalgia (19 versus 10; P=0.05). Myalgic subjects on atorvastatin or placebo had decreased muscle strength in 5 of 14 and 4 of 14 variables, respectively (P=0.43). These results indicate that high-dose atorvastatin treatment for 6 months does not decrease average muscle strength or exercise performance in healthy, previously untreated subjects. Nevertheless, this blinded, controlled trial confirms the undocumented impression that statins increase muscle complaints. Atorvastatin also increased average creatine kinase, suggesting that statins produce mild muscle injury even among asymptomatic subjects. This increase in creatine kinase
Pivotal Role of Rho-Associated Kinase 2 in Generating the Intrinsic Circadian Rhythm of Vascular Contractility

The cardiovascular system displays circadian rhythms in some physiological parameters, including blood pressure. The occurrence of pathological events, such as myocardial infarction and angina pectoris, also exhibits circadian variation. The circadian changes in vascular contractility underlie these physiological and pathological circadian events. The present study elucidated the details of the vascular intrinsic clock mechanism that regulate vascular contractility. The most prominent achievement of the present study is the identification of ROCK2 as a clock-regulated gene. The circadian oscillation of the expression of a clock gene, ROR$\alpha$, is translated to the oscillatory expression of ROCK2, which in turn generates the oscillation of myofilament Ca$^{2+}$ sensitivity and vascular contractility. ROCK2 plays an important role in the regulation of smooth muscle contraction, especially under pathological setting. Furthermore, ROCK2 regulates smooth muscle growth and contributes to the development of vascular lesions. Therefore, it remains to be investigated how this intrinsic vascular clock is, if at all, modified under pathological conditions and how it contributes to the pathogenesis and pathophysiology of cardiovascular diseases, such as hypertension, coronary vasospasm, or atherosclerosis. In addition, vascular function is regulated by the interplay between the central and peripheral clocks. How these 2 clock systems cross-talk to each other and how they regulate vascular function as an integrated system remain to be elucidated. The present study thus provides a novel conceptual insight into vascular biology regarding the circadian regulation of vascular contractility and thereby contributes to understanding the pathogenesis of cardiovascular disease and developing new therapeutic strategies. See p 104.

Attenuating Endoplasmic Reticulum Stress as a Novel Therapeutic Strategy in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) carries poor prognosis despite aggressive medical interventions. The reason for the failure of current therapies is 2-fold. First, most approved therapies (endothelin antagonists, phosphodiesterase type V inhibitors, and prostacyclin analogs) are vasodilators that were originally developed for systemic vascular diseases, not PAH, and are limited by systemic side effects. Second, the elevated pulmonary pressures in PAH are more a result of vascular remodeling than of vasoconstriction, particularly at the time of clinical presentation. Thus, agents that reverse this vascular remodeling and are specific to the pulmonary circulation are desperately needed. In addition, an efficacious therapy must address the many diverse triggers of PAH, both acquired and genetic, and because multiple triggers often occur within the same patient, identification of a “bottleneck” target is important. Many PAH-associated conditions are linked to endoplasmic reticulum stress, and although early pathology reports described dysmorphic endoplasmic reticulum in PAH plexiform lesions, the involvement of endoplasmic reticulum stress in PAH was only recently proposed. Here, we show that the orally administered generic chemical chaperone 4-phenylbutyrate (PBA) reduces endoplasmic reticulum stress, preventing/reversing pulmonary vascular remodeling and lowering pulmonary pressures in 2 animal models of PAH without apparent effects on the systemic vasculature. PBA and tauroursodeoxycholic acid (a chemical chaperone with a function similar to PBA) also normalized the cellular “PAH phenotype” in pulmonary artery smooth muscle cells in vitro. Our work supports targeting endoplasmic reticulum stress as an effective and selective strategy for the treatment of PAH. Because both PBA and tauroursodeoxycholic acid are used clinically, mostly under research protocols, translation to human PAH is possible. See p 115.