Abstracts

Gregory L. Moneta, MD, Abstracts Section Editor

Long-term predictors of descending aorta aneurismal change in patients with aorta dissections

Song J-N, Kim S-D, Kim J-H, et al. J Am Coll Card 2006;50:799-804.

Conclusion: Aneurysmal dilatation as a late manifestation of aortic dissection is most likely to take place in the upper thoracic aorta. Aneurysmal dilatation of the upper thoracic aorta is predicted by a large false lumen diameter on the initial computed tomography (CT) scan.

Summary: After acute aortic dissection, late aneurysmal dilatation of the aorta is a significant complication. The authors sought to demonstrate the long-term natural history of descending aorta dilatation after acute aortic dissection. They also sought to identify early predictors of late aneurysmal change in the dissected aorta. Contrast-enhanced CT scans for acute aortic dissection were performed in 100 patients. There were 51 patients with DeBakey type 1 dissections and 49 patients with DeBakey type 3 dissections. The patients with type 1 dissections underwent ascending aortic surgery ≤24 hours of diagnosis.

Clinical follow-up was for 53 ± 26 months, and CT scans were repeated at a mean of 31 ± 27 months. Aortic dilatation to >60 mm occurred in 14.4% of the upper thoracic descending aortas, 8.2% of the middle descending thoracic aortas, 4.1% in the lower descending thoracic aortas, and in 3.1% of the abdominal aortas. A repeat CT scan was done in 53 patients >2 years after the initial dissection. On the basis of these scans, rates of aortic enlargement per year at the upper, middle, and lower thoracic, and abdominal aorta levels were 3.43 ± 3.66, 3.21 ± 2.70, 2.62 ± 2.19, and 1.93 ± 3.66 mm, respectively ($P < .01$). Aneurysms developed in 28%. Predictors of late aneurysmal change included the initial false lumen diameter of the upper thoracic aorta, aortic diameter in the middle thoracic aorta, and Marfan syndrome. A ≥22-mm initial false lumen diameter of the upper thoracic aorta predicted late aneurysmal degeneration with a sensitivity of 100% and a specificity of 76%. The 42 patients with initial upper thoracic aorta false lumen diameters ≥22 mm also had a higher rate of the combination of aneurysm formation and death ($P < .001$).

Comment: The study suggests patients with acute aortic dissection with large false lumens of their upper thoracic aorta may be ones where prophylactic stent grafting might be beneficial. A European trial that has either just begun, or will begin soon, is investigating the impact of stent grafting on uncomplicated acute type 3 aortic dissections, the ADSORB (Acute Dissection Stenting or Best Medical Treatment study). Results of this trial will, hopefully, help determine the optimal role of stent grafting for acute aortic dissection.

Early results after staged hybrid repair of thoracoabdominal aortic aneurysms

Lee WA, Brown MP, Martin TD, Seeger JM, et al. J Am Coll Surg 2007;2005:420-31.

Conclusion: The hybrid approach of thoracoabdominal aneurysm (TAA) repair can be performed with relatively few technical complications, but morbidity and mortality rates remain significant.

Summary: The authors reviewed the morbidity and mortality associated with the hybrid approach of TAA repair. This is a retrospective review of 17 patients (mean age, 69 ± 15 years, 76% men), who underwent renal and visceral revascularization as a first stage of a hybrid repair of a TAA. The TAAs treated in this study included two Crawford extent type II, eight type III, and seven type IV. Perioperative mortality and complication rates associated with the debranching portion of the procedure were 24% and 25%, respectively. The mean intensive care unit stay and hospital stay were 7 ± 12 days and 22 ± 33 days, respectively. The mean delay between the staged procedures was 27 ± 27 days. The thoracic stent graft (stage 2) was placed in 12 (92%) of the 13 patients who survived the initial portion of the procedure. No additional deaths or postoperative complications were associated with the second stage of the procedure. After the second stage, patients did not require intensive care unit stay, and the overall length of stay after the procedure was 2 ± 2 days. Postoperative follow-up among 11 patients completing both stages was 8 ± 12 months, with no additional deaths during follow-up. Primary patency for renal and visceral grafts was 96% (54 of 56).

Comment: The hybrid approach to TAA repair is difficult operation for both the patient and the surgeon. If complete debranching of the aorta is performed, and a conduit is placed for subsequent placing of the thoracic endograft, operative times of 6 to 9 hours are expected. Mortality and morbidity rates are significant. The hybrid approach to TAA repair, although a tribute to surgical technical expertise, is not likely to be the final word in the surgical treatment of patients with TAAs. We await the availability of an off-the-shelf branched stent graft that can be implanted with a reasonable and not exceptional level of technical expertise.

Effects of torcetrapib in patients at high risk for coronary events

Barter PJ, Caulfield M, Eriksson M, and the ILLUMINATE Investigators. N Engl J Med 2007;357:2109-22.

Conclusion: Torcetrapib therapy, which increases high-density lipoprotein (HDL), results in an increased risk of mortality and morbidity.

Summary: Cholesteryl ester transfer protein (CETP) results in transfer of cholesteryl esters from HDL to other lipoproteins. Inhibiting CETP therefore results in increased HDL cholesterol levels and results in decreased low-density lipoprotein (LDL) cholesterol levels. Given these possible antiatherogenic effects, it would seem reasonable that torcetrapib, an inhibitor of CETP, would have a favorable effect on morbidity and mortality. To test this hypothesis, the authors conducted a double-blind randomized study of 15,067 patients considered at high cardiovascular risk. Patients were treated with atorvastatin alone or torcetrapib plus atorvastatin. The primary outcome was time to the first major cardiovascular event, which was defined as death from coronary heart disease, stroke, or hospitalization for unstable angina or nonfatal myocardial infarction.

In patients receiving torcetrapib therapy, after 12 months, there was an increase of 72.1% in HDL and a decrease of 24.9% in LDL cholesterol compared with baseline ($P < .001$), and there was also an increase in systolic blood pressure of 5.4 mm Hg. Serum sodium, bicarbonate, and aldosterone levels all also increased in patients treated with torcetrapib ($P < .001$). Patients treated with torcetrapib had an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval, 1.09-1.44; $P = .001$) as well as an increase of death from any cause (hazard ratio 1.58; 95% confidence interval, 1.14-2.19; $P = .006$). Post hoc analysis indicated there was an increased risk of death in patients with torcetrapib therapy who had increases in bicarbonate or reductions in potassium levels greater than the median change.

Comment: This study documented a number of off-target pharmacologic effects of torcetrapib. The increase of systolic blood pressure, as well as the metabolic effects, may have negated the effects of improvement in HDL and LDL levels induced by torcetrapib. This study, therefore, neither validates nor invalidates the possibility that raising HDL cholesterol levels by inhibition of CETP can be cardio productive. As the authors point out in the discussion of the article, this hypothesis can only be tested by use of a CETP inhibitor that does not share the off-target pharmacologic effects of torcetrapib.

Childhood body-mass index and the risk of coronary heart disease in adulthood

Baker JL, Olsen LW, Sorensen TIA. N Engl J Med 2007;357:2329-37.

Conclusion: Increases in the body mass index (BMI) during childhood are associated with an increased risk of coronary heart disease (CHD) in adulthood.

Summary: Children are becoming overweight at progressively younger ages, with 19% of children aged 6 to 11 years in the United States considered overweight (Int J Obes Relat Metab Disord 2002;26[suppl 4]:S2-S4, and JAMA 2006;295:1549-55). In this study, the authors sought to determine long-term effects of increased weight in childhood CHD. Authors studied the association between BMI in children aged 7 to 13 years and CHD in adults aged >25 years. Data were analyzed with and without adjustment for birth weight.

Subjects were derived from a cohort of 276,845 school children in Denmark whose height and weight measurements were available. National registries were used to determine CHD events. There were 5,063,622 person-years of follow-up. A total of 10,235 adult men and 4318 adult women had a diagnosis of CHD or died of CHD for whom childhood BMI data were also available. Risk of fatal and nonfatal events and any CHD event in the adults were positively associated with BMI from 7 to 13 years of age for boys and from 10 to 13 years of age for girls. Risk increased across the entire BMI distribution, and associations were linear for each age. Risk also increased as the age of the child increased. Adjustment for birth weight strengthened the results.

Comment: The data provide some quantitative information on the adverse effect of childhood obesity on future health. The magnitude of increased risk of CHD is relatively modestly increased in children at 7 years of age and dramatically increases further by age 13. Parents must somehow

be convinced that helping their child maintain appropriate weight is vitally important to decrease adverse health effects in adulthood.

Prevention of perioperative thromboembolism in patients with atrial fibrillation

Beldi G, Beng L, Siegel G, Fisch-Knaden S, et al. Brit J Surg 2007;94: 1351-5.

Conclusion: Compared with postoperative anticoagulation with low-molecular-weight heparin (LMWH), postoperative anticoagulation with therapeutic unfractionated heparin (UFH) in patients receiving long-term anticoagulation is associated with an increased risk of bleeding and does not reduce the risk of thromboembolism.

Summary: This was a retrospective study designed to test the safety and efficacy of two methods of prophylaxis for perioperative thromboembolism in patients with atrial fibrillation (AF), which was present in 1.9% of patients undergoing 14,801 operative procedures. Patients with AF who were not receiving oral anticoagulation (n = 146) were placed on the LMWH nadroparin before and after surgery (40 U/kg). Those patients with AF who were on anticoagulation before surgery (n = 136) were placed on intravenous UFH postoperatively at a dose to maintain therapeutic levels.

Arterial or venous thromboembolism occurring in the perioperative period was independent of pre-existing risk factors. Atrial or venous thromboembolism occurred in 4.6% of patients, without significant differences between the perioperative use of LMWH or UFH ($P = .78$). Thromboembolism was significantly associated with increased perioperative mortality (odds ratio, 9.5; 95% confidence interval, 2.5-35.8, $P = .001$). Postoperative bleeding occurred in 4.8% of patients treated with LMWH and in 17.6% of patients treated with UFH ($P < .001$).

Comment: Patients on long-term anticoagulation for AF often must have anticoagulation interrupted for an operative procedure. During this time, anticoagulation is generally "bridged" with heparin until vitamin K antagonists can be restarted. The study is important in that it indicates this "bridging" of anticoagulation is probably best performed with LMWH, rather than UFH. Although this was a study of general surgical patients, it is likely that differences may be even more dramatic in patients undergoing vascular surgery.

Preoperative cerebral hemodynamic impairment and reactive oxygen species produced during carotid endarterectomy correlate with development of postoperative cerebral hyperperfusion

Suga Y, Ogasawara K, Saito H, et al. Stroke 2007;38:2712-2717.

Conclusion: Reactive oxygen species, which are produced during carotid endarterectomy (CEA), and preoperative cerebral hemodynamic impairment correlate with development of cerebral hyperperfusion after CEA.

Summary: The authors sought to determine the relationship between production of reactive oxygen species and preoperative cerebral hemodynamic impairment with postoperative cerebral hyperperfusion in CEA patients. Malondialdehyde-modified low-density lipoprotein (MDA-LDL) is a marker of oxidative damage that can be measured in serum samples. Cerebral hemodynamic impairment can be measured using single-photon emission computed tomography (SPECT) to assess cerebral blood flow and cerebrovascular reactivity with acetazolamide. In this study, 90 patients who underwent carotid endarterectomy for ipsilateral internal carotid artery stenosis >70% were assessed with MDA-LDL levels, as well as preoperative SPECT. Hyperperfusion was defined as a cerebral blood flow increase of >100% compared with preoperative values.

After CEA, hyperperfusion was documented by increased cerebral blood flow in 12 patients (13%). Logistic regression analysis determined that reduced preoperative cerebrovascular reactivity (95% confidence interval, 1.053-1.453; $P = .0097$) and an increase in MDA-LDL after internal carotid artery clamping (95% confidence interval, 0.862-0.980; $P = .0098$) were associated with development of postoperative cerebral hyperperfusion. Of the 11 patients with reduced preoperative cerebrovascular reactivity and increased MDA-LDL after internal carotid artery clamping, post-CEA hyperperfusion developed in 10, and two of these had cerebral hyperperfusion syndrome.

Comment: It is known post-CEA hyperperfusion syndrome correlates with reduced preoperative cerebrovascular reactivity. However, hyperperfusion syndrome does not develop in all patients with reduced preoperative cerebrovascular reactivity (52% in this study). The addition of MDA-LDL levels to the preoperative assessment of cerebral blood flow in patients at risk for post-CEA hyperperfusion syndrome may help more precisely identify patients at risk for postoperative CEA hyperperfusion syndrome.

Involvement of MMPs in the outward remodeling of collateral mesenteric arteries

Haas TL, Doyle JL, Distasi MR, et al. Am J Physiol Heart Circ Physiol 2007;293:H2429-37.

Conclusion: Matrix metalloproteinase (MMP) activity is essential to the remodeling process that leads to luminal expansion associated with collateral vessel enlargement.

Summary: Shear stress is important in collateral enlargement. Elevations in shear stress within resistance or conduit arteries result in luminal expansion. The result is normalization of shear stress and maintenance of flow to the downstream vasculature. This process involves remodeling of the extracellular matrix and cellular proliferation; however, specific cellular events leading to these events are poorly understood. It is known that MMPs contribute to the remodeling of the extracellular matrix in vein grafts and conduit vessels exposed to high flow rates. This study sought to evaluate the role of MMPs in remodeling of small collateral arteries exposed to increases in shear stress.

The authors used an established model of outward remodeling of mesenteric collateral arteries that utilizes ileal arteries of male Wistar rats that are surgically ligated to produce a collateral-dependent region. They sought to determine whether MMPs were up-regulated during remodeling and to test whether MMP activity was required for luminal expansion. After 2 to 7 days, arteries were harvested and MMP9 and MMP2 levels determined using standard gelatin zymography and immunostaining. At 4 days, membrane type 1 MMP (MT1-MMP) and MMP2, but not MMP9, protein levels were elevated in collateral arteries. The elevated MMP proteins, along with their respective transcriptional activators, were predominately localized to the smooth muscle layer of the collateral arteries. Doxycycline, a general MMP inhibitor, prevented luminal expansion of collateral arteries but did not affect medial growth responses or endothelial cell proliferation.

Comment: This study may serve as the basis of a new approach to improving distal circulation in situations where the primary conduit arteries are stenosed or occluded. Perhaps enlargement of collateral vessels through an MMP mechanism can serve as an alternative to angiogenesis in patients with severe intermittent claudication or critical limb ischemia.

Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery

Murphy GJ, Reeves BC, Rogers CA, et al. Circulation 2007;116:2544-52.

Conclusion: In patients having cardiac surgery, red blood cell (RBC) transfusion is associated with increased rates of ischemic postoperative morbidity, infection, and early and late mortality, as well as increased hospital lengths of stay and hospital costs.

Summary: The authors sought to quantify clinical outcomes and costs with RBC transfusion in patients having cardiac surgery. Databases for clinical hematology and blood transfusions were linked with the United Kingdom population register. Hematocrit information was obtained from intensive care unit charts. Prespecified primary end points were composite infection (wound infection, septicemia, or respiratory infection) and ischemic outcomes (renal impairment from ischemic injury, myocardial infarction, or stroke). Resource use, cost, and survival were secondary outcomes. Regression modeling with adjustment for potential confounding variables was used to determine associations between transfusion and the primary and secondary outcomes.

Patients were derived from the Bristol Royal Infirmary database of adult cardiac surgery patients. This included patients having cardiac surgery from April 1, 1996, to December 31, 2003. Adjusted odds ratio for ischemic outcomes (832 of 8518) and for composite infections (737 of 8516) were 3.35 (95% confidence interval [CI], 2.68-4.35) and 3.38 (95% CI 2.60-4.40) respectively. Relative cost of admission was increased by any transfusion at a rate of 1.4 times for transfusion (95% CI 1.37-1.46), varying from 1.11 for 1 U to 3.35 for >9 U transfused. At any time after operation, patients with transfusion were less likely to have been discharged from the hospital (hazard ratio [HR] 0.63; 95% CI, 0.60-0.67) and more likely to have died (0 to 30 days: HR, 6.69; 95% CI, 3.66-15.1; 31 days to 1 year: HR, 2.59; 95% CI, 1.68-4.17; >1 year: HR, 1.32; 95% CI, 1.08-1.64).

Comment: Transfusion is known to be strongly associated with infection. In this study however, transfusion was also strongly associated with increased hospital costs and poorer long-term prognosis. A most surprising finding was that ischemic outcomes were made worse by transfusion, inconsistent with a widely held belief that RBC transfusion improves tissue oxygenation. It appears another accepted truth in medicine is once again no more than a half-truth and probably less than that. In fact, we have a very poor understanding of the indications for RBC transfusion. These data certainly imply that we are transfusing too many patients and not only wasting money but also adversely affecting the patients.