Advances in Stroke

Advances in Interventional Neuroradiology

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With advancement in neuroimaging and biomedical technology as well as growing experience, interventional neuroradiology is increasingly playing an important role in management of stroke. This year's results from well-designed (randomized) trials were available to answer some of outstanding questions, especially in the area of ischemic stroke.

Carotid Disease

For several years carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) in the management of carotid stenosis have been a topic of debate. Initial results of Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S), Stent-protected Percutaneous Angioplasty of the Carotid versus Endarterectomy (SPACE), and International Carotid Stenting Study (ICSS) trials had suggested that CEA was the appropriate technique for the treatment of symptomatic patients with moderate or severe carotid stenosis. However, recent results of a well-designed large trial may change that perception.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was a randomized controlled trial conducted in 108 centers in the United States and 9 in Canada.[1] Patients with symptomatic or asymptomatic carotid stenosis were randomly assigned to undergo CAS or CEA. There was no significant difference in the primary composite end point (stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization) between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; $P=0.51$). The 4-year rate of stroke or death was 6.4% with CAS and 4.7% with CEA. Even if the introduction of the myocardial infarction in the primary composite end point was controversial, CREST was the first study that showed similar results of CEA and CAS in the treatment of carotid stenosis.

Another important result is coming from the meta-analysis of individual patient data from 3 randomized controlled trials (EVA-3S, SPACE, and ICSS) showing that in the first 120 days after randomization, any stroke or death occurred significantly more often in the CAS group (8.9%) than in the CEA group (5.8%, $P=0.0006$).[2] However, age significantly modified the treatment effect. In patients <70 years, the 120-day risk of stroke or death was similar in CAS and CEA groups (5.8% and 5.7%, respectively). In older patients (>70 years), the risk with CAS was twice that with CEA (12.0% and 5.9%, respectively). The conclusion was that stenting might be as safe as endarterectomy in patients <70 years and should be avoided in older patients. Because differences between both treatment options are marginal, patient selection and the local expertise performing CEA and CAS may play a greater role in decision-making and final clinical outcome.

Intracranial Disease

The Stenting versus Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) was a trial in the United States sponsored by the National Institutes of Health/National Institute of Neurological Disorders and Stroke and evaluated the use of aggressive medical therapy alone versus angioplasty and stenting combined with intensive medical therapy.[3] Patients with symptomatic intracranial stenosis of 70% to 99% with a transient ischemic attack or stroke within 30 days were enrolled. Patients in both treatment groups received careful risk factor management (325 mg aspirin/day and 75 mg clopidogrel/day for 90 days postenrollment; systolic blood pressure <140 mm Hg; low-density lipoprotein <70 mg/dL). A low-profile self-expanding stent was used. On April 5, 2011, the trial was stopped by the National Institutes of Health due to a higher risk of stroke and death in the stented arm. Recruitment began in November 2008 and was finalized on April 2011 after 451 (59%) of the planned 764 patients had been enrolled at 50 participating sites in the United States. Two hundred twenty-four patients were assigned to the stenting arm and 227 to medical therapy alone. Despite decreasing the degree of stenosis in the stenting arm, medical therapy alone was superior in preventing recurrent stroke. The 30-day stroke or death rate was 14.7% (nonfatal stroke: 12.5%; fatal stroke: 2.2%) compared with 5.8% (nonfatal stroke: 5.3%; nonstroke-related death: 0.4%; $P=0.002$). These results were unexpected and SAMMPRIS investigators were surprised of such a high complication rate in the

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Wingspan stent group because previously conducted studies in Europe stated a complication rate of approximately 10%. Possible explanation for the higher stroke rate in the stenting arm may be the fact that all patients treated in the SAMMPRIS trial showed recent symptoms that may be due to an unstable plaque that is more likely to cause embolism during stenting. Up to now, only the short-term follow-up data are available. Less than half of the patients enrolled in the SAMMPRIS trial received follow-up examinations for >1 year. It will be important to determine the long-term benefit in the aggressive medical management arm versus stenting group to show if medical therapy alone is sufficient to inhibit the progression of stenosis, which may lead to hypoperfusion or embolic stroke and to which degree an in-stent stenosis has developed that may also cause later stroke events.[4,5] Careful patient selection and appropriate trial design and newer technologies may overcome some of the present issues and resurrect intracranial stenting. It remains also questionable how reasonable in daily life it is to rigorously manage a patient's health as was done in the medical arm of this randomized trial.

Acute Ischemic Stroke

With expansion of stroke service and introduction of sophisticated devices, acute ischemic stroke is playing a key role in interventional neuroradiology training.[6,7] Intra-arterial mechanical thrombectomy is increasingly used in the management of acute ischemic stroke.[8] The recent introduction of stent retrievers (nondetachable microcatheter-based stent-like devices) by several companies seems to be a very important step, but only small single-center series so far have been published.[9] The industry-sponsored SWIFT trial (Solitaire FR With the Intention for Thrombectomy include the Solitaire device; Covidien/eV3, Maple Grove, MN) and TREVO (Thrombectomy Revascularization of Large Vessel Occlusion include the Trevo device; Stryker Neurovascular, Fremont, CA) to name a few are now undergoing clinical evaluation in the United States and Europe and results are expected early next year.[10,11]

Brain Aneurysm

Since International Subarachnoid Aneurysm Trial (ISAT) and Analysis of Treatment by Endovascular approach of Nonruptured Aneurysms (ATENA), the endovascular treatment is established as a first-line treatment in the management of ruptured and unruptured aneurysms. However, technical refinements are needed to expand endovascular treatment to complex aneurysms (wide neck, large and giant, fusiform) as well as improve durability. The safety of the remodeling technique, initially designed for the treatment of wide neck aneurysms, was recently confirmed in the large ATENA and CLARITY (Clinical and Anatomical Results In the Treatment of ruptured intracranial aneurYsms) series (unruptured and ruptured aneurysms).[12,13] Several strategies have been proposed to reduce aneurysm recanalization after endovascular treatment. Surface-modified platinum coils, proposed to reduce aneurysm recanalization, underwent scrutiny in the industry-sponsored randomized MAPS (Matrix And Platinum Science; Stryker Neurovascular) and HELPS (Hydrocoil Endovascular aneurysm occLusion and Packing Study; MicroVention-Terumo Inc, Tustin, CA) trials.[14,15] Trial results showed that overall Matrix detachable coils are as effective as bare platinum GDC detachable coils with target aneurysm recurrence rates of 13.3% versus 14.6%, respectively. In aneurysms with good occlusion at the treatment point, Matrix detachable coils demonstrated a statistically significant, superior long-term target aneurysm recurrence rate of 2.7% compared with the GDC detachable coils' rate of 9.6%. HELPS included coil embolization of ruptured and unruptured aneurysms conducted in 24 centers in 7 countries (249 patients in the Hydrocoil group and 250 in the bare-platinum coil, control group).[15] The adverse composite primary end point (major aneurysm recurrence and procedure-related deaths and morbidity that resulted in patients not having follow-up angiography) was lower but not significantly in Hydrocoil group (30.7% compared with 37.7% in the control group, $P=0.13$). Major recurrences were less frequent in Hydrocoil group (27.2%) than in the control group (35.8%, $P=0.049$), but unexplained hydrocephalus in nonrecently ruptured aneurysms, although not statistically significant, was more frequent in Hydrocoil group (4.5%) than in the control group (0.9%). According to these results, widespread use of Hydrocoils cannot be recommended. Overall results from currently available surface-modified coils remain disappointing and may not justify their use.

In the field of aneurysm treatment, flow diverters are probably one of the actually most promising and innovative ways of treating aneurysms. Based on previous extensive experimental studies and clinical data presented, the first generation of a flow diverter (Pipeline Embolization Device; Covidien/eV3, Mansfield, MA) was approved this year by the Food and Drug Administration for a selected group of aneurysms otherwise difficult or impossible to treat.[16,17] Flow diverters induce disruption of the flow at the level of the neck, promoting intra-aneurysmal thrombosis. Flow diverters also provide a support for the development of endothelial tissue across the aneurysm neck. In preliminary small clinical series, feasibility of the treatment with a flow diverter was high and associated with low morbidity and mortality.[18,19] However, in a subset of large and giant aneurysms, delayed rupture has been described after treatment for initially unruptured aneurysms.[20] This may be related to a large clot burden generated after the treatment and inflammatory aneurysmal wall response. In the coming year we may see expansion of flow diverter technology to a wider range of aneurysms and accumulating number of publications.

Brain Arteriovenous Malformations

Onyx (Covidien/eV3) has established itself as the most widely used liquid embolic agent for dural arteriovenous shunts and brain arteriovenous malformations with excellent results. In a recent series, a high rate of complete obliteration (51%) has been described with acceptable low morbidity and mortality rates of 7.1% and 1.4%, respectively.[21] Excellent clinical and anatomic results have been reported in the preoperative use of Onyx followed by surgery or radiosurgery.[22,23]

Imaging

Since the introduction of flat-panel C-arm systems in the neuroangiography suite 6 years ago, a wide range of imaging

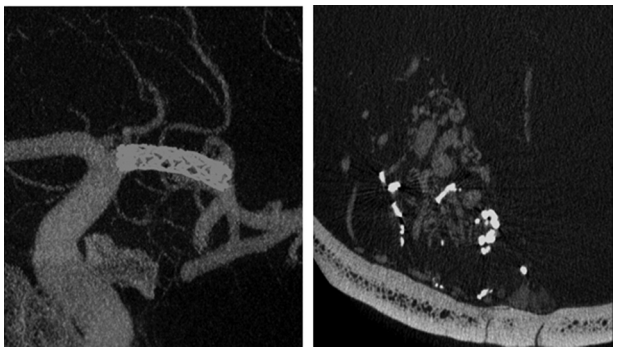

Figure. Left, Maximum intensity projection (MIP) of a contrast-enhanced flat-panel cone-beam CT (FP-CBCT) data set of a patient after the placement of an intracranial balloon-expandable stent. High-resolution image shows apposition of stent struts to the vessel wall and the relationship with lenticulostriates and the middle cerebral artery bifurcation. **Right**, MIP of contrast-enhanced FP-CBCT data of a patient with a large brain arteriovenous malformation acquired during the procedure and after partial embolization with Onyx.

and postprocessing techniques have been developed that led to valuable peri-interventional patient data. Due to the high image quality of flat-panel cone-beam CT (FP-CBCT), approximating the quality of conventional CT, C-arm systems have proven to provide more than just fluoroscopy and 2-dimensional/3-dimensional angiographic imaging (Figure).

Tremendous advances on the assessment of cerebral blood volume using C-arm CT has been reported throughout the last years, enabling functional imaging into the neuroangiography room.[25] In the last year, the applicability of this technique was evaluated on 10 patients with acute ischemic stroke and 8 patients with an intracranial hemorrhage.[26] Based on their observations, the authors found that cerebral blood volume obtained with FP-CBCT was helpful in assessing hemodynamic changes directly before and after the endovascular treatment. In addition, a quantitative analysis of absolute lesion volumes determined from FP-CBCT-based cerebral blood volume in an animal model showed that lesion volumes correlated with histology but that improvement in terms of image signal-to-noise is required.[27]

Although cerebral blood volume is believed to be a valuable parameter for brain infarction, cerebral blood flow is generally thought to offer improved discrimination between lesion and salvageable tissue. Assessment of cerebral blood flow using FP-CBCT is not a trivial task, because its acquisition time generally exceeds the time resolution needed to sample cerebral blood flow. To overcome this limitation, an interesting imaging protocol has been presented that uses multiple aortic arch injections in combination with multiple bidirectional sweeps of the C-arm to obtain enough data to reconstruct the time-intensity curves within brain tissue.[28] Although this method may require too many FP-CBCT acquisitions and thus a too high radiation dose for it to be clinically implemented, the results show great potential for future time-resolved brain perfusion measurements in the angiographic suite.

The high-spatial resolution of FP-CBCT enables visualization of relatively small structures that may not be easily depicted by conventional CT. For instance, the size and high blood flow of an arteriovenous malformation nidus can impede visualization with CT or MRI angiography. By using a contrast-enhanced FP-CBCT imaging protocol, multiple arteriovenous malformation nidi were successfully depicted, providing suitable data sets for radiation treatment planning (Figure).[29] Furthermore, the optimization of an injection and imaging protocol and implementation of an adapted reconstruction algorithm led to visualization of intracranial stents in relation to surrounding vascular anatomy with great detail, which even showed cases of intimal hyperplasia at follow-up (Figure).[30,31]

In pursuing to minimize the invasiveness of follow-up imaging after placement of endovascular devices, the feasibility of intravenous administered contrast-enhanced FP-CBCT was investigated.[32,33] The visibility of vascular anatomy and devices was compared with that with conventional intra-arterial digital subtraction angiography and the grade of restenosis was measured on both modalities. It was concluded that the image quality of intravenous contrast-enhanced FP-CBCT was adequate to distinguish between the stent and lumen and to recognize potential (re-)stenosis. In addition, the grade of stenosis within stents measured on intravenous contrast-enhanced FP-CBCT was not statistically different from grading performed on intra-arterial digital subtraction angiography. These reports show that intravenous contrast-enhanced FP-CBCT has the potential of replacing intra-arterial digital subtraction angiography in follow-up imaging after endovascular treatment. What remains a challenge is the metal artifact caused by radiodense materials such as aneurysm clips and coils. Recently, great advancements have been made in reducing the metal artifact in FP-CBCT data; however, more research is mandatory to assess its validity for clinical diagnosis.[34]

Disclosures

Dr Pierot is a consultant for Johnson & Johnson/Codman, Covidien/EV3, Microvention/Terumo, Penumbra, and Sequent. Dr Wakhloo is consulting for Johnson & Johnson/Codman, Stryker Neurovascular, Philips Healthcare Surpass Medical Ltd.

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