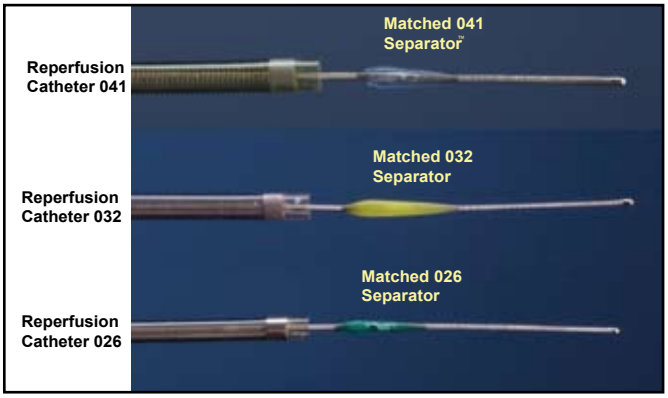
Figure 1. Aspiration System.



Cameron McDougall, MD, Barrow Neurological Institute, Phoenix, AZ, reported results from an international multi-center study that was conducted in 125 stroke patients with occluded vessels. The objective of the trial was to assess the safety and the revascularization effectiveness of this novel clot removal system. Patient inclusion criteria included NIH Stroke Scale (NIHSS) score ~8, presentation within 8 hours of symptom onset, and a Thrombolysis in Myocardial Infarction (TIMI) score of 0 or I. The primary endpoints were TIMI score II or III and device-related serious adverse events (SAE). Secondary endpoints included ≥4 point improvement on the NIHSS at discharge or modified Rankin Scale (mRS) ≤2 at 30 days, all cause mortality, and incidence of intracranial hemorrhage (ICH).

The median time from symptom onset to procedural start was 4.1 hours; the median time required for revascularization was 45 minutes. Using the Penumbra System, 82% of the treated vessels were revascularized to TIMI II or III, with 41.6% of the patients having a favorable outcome at 30 days. None of the SAEs (3%; 2 perforations; 2 ICHs) was device-related. A total of 35 patients (28%) were found to have ICH at 24 hours, of which 14 (11.2%) were symptomatic (CT evidence of a bleed and a 4-point drop on the NIHSS) and 21 (16.8%) were asymptomatic. At the time of discharge, 58% of the patients had a ≥4 point improvement in NIHSS, and 27% had a ≥10 point improvement in NIHSS or NIHSS 0-1. All cause mortality was 26.4%, and 32.8%, respectively, at 30 and 90 days; 25% of patients had a 90-day mRS of ≤2. Due to the effectiveness of the initial aspiration, direct thrombus extraction was used in only 30 of 125 patients.

The Penumbra System was associated with a low rate of serious procedural complications and had an acceptable rate of ICH and all cause mortality. The trend for a better outcome when vessels were opened was consistently observed across all neurological and functional measures.

The US Food and Drug Administration granted clearance of the Penumbra System for revascularization of intracranial vessels in patients with acute ischemic stroke in December 2007. The retrieval ring was used in a minority of patients, and as a result, it was not felt to have been adequately evaluated and therefore was not approved. No complications or adverse events occurred as result of the use of the retrieval ring.

Donepezil in Subcortical Vascular Cognitive Impairment: A Randomized Double-Blind Trial in CADASIL

Cholinergic inhibitors have been shown to provide benefits in cognition, global functioning, and activities of daily living in patients with mild to moderate Alzheimer disease (AD). However, their benefit in cognitive impairment associated with vascular dementia (VaD) remains controversial. One of the limitations of past studies using cholinergic inhibitors has been the inability to determine whether the treatment was affecting AD or VaD. Thus, there is a need for trials involving more narrowly defined subtypes of VaD. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an early-onset genetic form of subcortical ischemic vascular dementia that resembles sporadic small-vessel disease similar to VaD. The underlying pathology of CADASIL is progressive degeneration of the smooth muscle cells in blood vessels that can lead to deficits in executive functioning and cognitive processing speed.

Prof. Martin Dichgans, Ludwig-Maximilians-University, Munich, Germany, presented data from an 18-week, double-blind, placebo-controlled, multi-national study evaluating the efficacy and safety of donepezil (10 mg), a cholinesterase-inhibiting drug currently approved for the treatment of AD, in 168 patients diagnosed with CADASIL. Changes in cognitive impairment were assessed using a number of tests, including the vascular AD assessment cognitive subscale (V-ADAS-cog), the mini-mental state examination (MMSE), and executive function tests, eg, trail making test (TMT) A & B time and the executive interview-25 questionnaire (Exit25). Patients aged 27-71 years who had a diagnosis of CADASIL and

cognitive impairment defined by MMSE and TMT B time scores were eligible for the study.

There was no statistical difference in cognitive improvement as assessed by the primary efficacy measure, the V-ADAS-cog scores between donepezil and placebo after 18 weeks of treatment. There was a significant treatment effect favoring donepezil on several executive function tests (TMT B time, p=0.005; TMT A time, p=0.01; Exit25, p=0.02). Donepezil was well tolerated, with patients experiencing typical adverse events associated with cholinesterase inhibition and VaD. Discontinuation due to adverse events was 8.5% in placebo subjects and 11.6% in donepezil subjects.

Although donepezil had no effect on the V-ADAS-cog in CADASIL patients with cognitive impairment, improvements were noted on several scales associated with executive function. This suggests an involvement of cholinergic deficits in executive function, which fits with previous histopathologic data. Further, this trial illustrates the limitations of studies using ADAS-cog tests and similar tests used to study AD, as well as the need to incorporate executive function tests in future trials. The clinical relevance of these findings needs clarification, and further research is warranted.

Genome-Wide SNP Linkage Screen for Intracranial Aneurysm Susceptibility Genes: Results from 333 Multiplex IA Families

Genetic risk factors are considered important in the development, growth, and rupture of intracranial aneurysms (IAs). However, few of these risk factors have been identified. The Familial Intracranial Aneurysm (FIA) Study is a collaborative research effort of neurologists and neurosurgeons throughout the United States, Canada, Australia, and New Zealand that is studying genetic factors in 475 families with multiple IA-affected members.

Prof. Tatiana Foroud, Indiana University, Indianapolis, IN, discussed recent results from this collaboration, in which 6000 single nucleotide polymorphisms were screened in two independent groups of FIA families. This is the largest familial IA sample ever collected. It consisted of 333 families with 1895 members with both ruptured and unruptured IAs. All families had at least two members with an IA.

Subjects were classified using both a 'narrow' (n=705 definite IA cases) and 'broad' (n=866 definite or probable IA) disease definition. Multipoint model-free linkage analysis was performed. One analysis method was performed to identify genes that might have their greatest effect in those families with a high rate of smoking based on average pack-years. Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the 6K Illumina system.

A LOD score (logarithm base 10 of odds) was used to analyze linkage. By convention, a LOD score >3 indicates linkage.

Model-free linkage analyses detected modest evidence of linkage. Parametric analyses yielded an unadjusted LOD score of 2.5 on chromosome 4q (162 cM), with a rare disease allele (0.7%) and reduced penetrance for both heterozygotes and homozygotes. On chromosome 12p (50 cM), an unadjusted LOD score of 3.0 was obtained, under a recessive disease model with a more common disease allele (4% frequency). Significant evidence for a gene x smoking interaction was detected using both the narrow (LOD 4.1; p=0.001) and broad (LOD 3.2; p=0.01) disease definition detected on chromosomes 3, 7, and 12.

This study provides modest evidence of possible linkage of IA to several chromosomes. However, heritable risk for IA can be affected by age of diagnosis and demographic characteristics. Using smoking as a covariate in the linkage analyses allowed for the detection of additional genetic loci that appear to have a strong interaction with this important covariate. Though these data suggest it is unlikely that there is a single common variant with a strong effect in the majority of the IA families, parents, siblings, and children of an IA family member may be at increased risk for this condition.

Subsequent analyses were performed to test whether common susceptibility genes might contribute to the risk of intracranial as well as aortic aneurysms (AA). Analyses employing 29 families having members with either IA or AA confirmed a previously reported linkage to chromosome 11q24-25 and also detected linkage to chromosome 6p.