Feasibility and Safety of Using External Counterpulsation to Augment Cerebral Blood Flow in Acute Ischemic Stroke—The Counterpulsation to Upgrade Forward Flow in Stroke (CUFFS) Trial

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Background: External counterpulsation (ECP) increases perfusion to a variety of organs and may be helpful for acute stroke. *Methods:* We conducted a single-blinded, prospective, randomized controlled feasibility and safety trial of ECP for acute middle cerebral artery (MCA) ischemic stroke. Twenty-three patients presenting within 48 hours of symptom onset were randomized into one of two groups. One group was treated with ECP for 1 hour at a pressure of up to 300 mmHg ("full pressure"). During the procedure, we also determined the highest possible pressure that would augment MCA mean flow velocity (MFV) by 15%. The other group was treated with ECP at 75 mmHg ("sham pressure"). Transcranial Doppler MCA flow velocities and National Institutes of Health Stroke Scale (NIHSS) scores of both groups were checked before, during, and after ECP. Outcomes were assessed at 30 days after randomization. *Results:* Although the procedures were feasible to implement, there was a frequent inability to augment MFV by 15% despite maximal pressures in full-pressure patients. In sham-pressure patients, however, MFV frequently increased as shown by increases in peak systolic velocity and end diastolic velocity. In both groups, starting ECP was often associated with

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contemporaneous improvements in NIHSS stroke scores. There were no between-group differences in NIHSS, modified Rankin Scale Scores, and Barthel Indices, and no device or treatment-related serious adverse events, deaths, intracerebral hemorrhages, or episodes of acute neuro-worsening. *Conclusions:* ECP was safe and feasible to use in patients with acute ischemic stroke. It was associated with unexpected effects on flow velocity, and contemporaneous improvements in NIHSS score regardless of pressure used, with a possibility that even very low ECP pressures had an effect. Further study is warranted. **Key Words:** External counterpulsation—Ischemic stroke—Transcranial Doppler—Cerebral blood flow velocity.

Introduction

External counterpulsation (ECP) increases blood flow in organs such as the brain, eye, kidney, skin, and liver[1-4]; improves outcome in heart disease[5-7]; and has potential as a perfusion-optimization treatment for ischemic stroke. The procedure has been approved for use in ischemic heart disease and congestive heart failure. It utilizes electrocardiogram-triggered inflations of cuffs to apply pressures ranging from 75 to 300 mmHg sequentially to the lower extremities and buttocks, inducing retrograde aortic blood flow and increased diastolic blood flow.[2,3,8-10] ECP augmented mean flow velocity (MFV) on transcranial Doppler (TCD) in a study in 5 healthy human volunteers,[11] and in another study—when used as a 14-week-long regimen of daily 1-hour treatments—was feasible, safe, and improved functional outcome in subacute ischemic stroke patients.[12] However, the safety and utility of ECP as an acute treatment for ischemic stroke has not been established. The Counterpulsation to Upgrade Forward Flow in Stroke (CUFFS) trial was designed to evaluate the safety and feasibility of instituting a 1-hour treatment with ECP in adult patients presenting within 48 hours of onset of a middle cerebral artery (MCA) stroke while exploring its impact on MCA flow velocity and acute neurological deficit.

Materials and Methods

Study Design

CUFFS was a prospective, randomized, controlled, single (patient)-blinded study in which adults with acute strokes were randomly assigned to either full-pressure or sham-pressure ECP. TCD was performed prior to, during, and immediately after ECP to assess changes in MCA flow velocity, with National Institutes of Health Stroke Scale (NIHSS) scores evaluated at the same time points. Subsequent NIHSS scores were obtained during each patient's hospital stay and again at 30 days post randomization, with adverse events (AEs) and serious adverse events (SAEs) monitored for a duration of 2 days and 30 days post randomization, respectively. The study was performed at 3 urban comprehensive stroke centers. All study procedures were supported by a U.S. Food and Drug Administration investigational device exemption and approved by the Institutional Review Board at each of the participating site.

Procedures and Assessments

Screening, Enrollment, and Randomization

We enrolled awake patients 18 years of age and older with acute MCA distribution strokes[13] to optimize the uniformity and interpretation of results (because having a narrower distribution of potential deficits would allow for a more robust comparison between treatment groups). Inclusion criteria were an ability to initiate ECP within 48 hours of stroke onset, in a patient in whom no acute reperfusion therapy or other experimental therapy was planned. The exclusion criteria included rapidly resolving symptoms; an NIHSS score of more than 22; current or prior intracranial hemorrhage; brain tumor or abscess; a presentation consistent with subarachnoid hemorrhage; vascular anomalies such as known or suspected aortic dissection, aneurysm, or other anomalies of the heart or great vessels; cardiac issues such as nontrivial aortic regurgitation, symptomatic valvular heart disease, acute symptomatic congestive heart failure, or a known left ventricular ejection fraction less than 30%; issues that would interfere with ECP triggering such as a pacemaker, rapid atrial fibrillation, or frequent premature ventricular contractions (PVCs); conditions that might be affected by or limit repeated cuff inflations, such as known collagen vascular disease, significant obesity, a history of significant chronic low back pain, ongoing lumbar radiculopathy, symptomatic lower extremity peripheral vascular occlusive disease, phlebitis, stasis ulcer, severe varicosities, or a diagnosis of deep vein thrombosis (DVT) within the past month; known coagulopathy such as thrombocytopenia with a platelet count of less than 100 K or an international normalized ratio (INR) greater than 2.0; blood pressure of more than 180/100 despite treatment; and an inadequate temporal window for TCD imaging.

Written consent was obtained prior to initiating study procedures. After enrollment but before randomization, all patients underwent duplex ultrasound scanning of the lower extremities so DVT could be ruled out and