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Perfusion Augmentation in Acute Stroke Using Mechanical Counter-Pulsation–Phase IIa

Effect of External Counterpulsation on Middle Cerebral Artery Mean Flow Velocity in Five Healthy Subjects

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Background and Purpose—External counterpulsation (ECP) improves coronary perfusion, increases left ventricular stroke volume similar to intraaortic balloon counterpulsation, and recruits arterial collaterals within ischemic territories. We sought to determine ECPs effect on middle cerebral artery (MCA) blood flow augmentation in normal controls as a first step to support future clinical trials in acute stroke.

Methods—Healthy volunteers were recruited and screened for exclusions. Bilateral 2-MHz pulsed wave transcranial Doppler (TCD) probes were mounted by head frame, and baseline M1 MCA TCD measurements were obtained. ECP was then initiated using standard procedures for 30 minutes, and TCD readings were repeated at 5 and 20 minutes. Physiological correlates associated with ECP-TCD waveform morphology were identified, and measurable criteria for TCD assessment of ECP arterial mean flow velocity (MFV) augmentation were constructed.

Results—Five subjects were enrolled in the study. Preprocedural M1 MCA TCD measurements were within normal limits. Onset of ECP counterpulsation produced an immediate change in TCD waveform configuration with the appearance of a second upstroke at the dicrotic notch, labeled peak diastolic augmented velocity (PDAV). Although end-diastolic velocities did not increase, both R-MCA and L-MCA PDAVs were significantly higher than baseline end-diastolic values ($P<0.05$ Wilcoxon rank-sum test) at 5 and 20 minutes. Augmented MFVs (aMFVs) were also significantly higher than baseline MFV in the R-MCA and L-MCA at both 5 and 20 minutes ($P<0.05$).

Conclusions—ECP induces marked changes in cerebral arterial waveforms and augmented peak diastolic and mean MCA flow velocities on TCD in 5 healthy subjects. **(*Stroke*. 2008;39:2760-2764.)**

Key Words: cerebral blood flow ■ cerebral hemodynamics ■ transcranial Doppler ■ external counterpulsation

Early hospitalization after ischemic stroke onset provides an opportunity for treatment with systemic thrombolysis or intraarterial (IA) rescue procedures. However, the majority of stroke patients remain ineligible for these therapies commonly because of late hospital arrival. Because some salvageable brain tissue may exist up to 8 to 24 hours from symptom onset, availability of a low-risk noninvasive intracranial blood flow augmentation device would provide a treatment option to a large number of ischemic stroke patients.

External counterpulsation (ECP) is an approved noninvasive therapy for angina, congestive heart failure, myocardial infarction, and cardiogenic shock that augments blood flow to cardiac and systemic circuits.[1–3] ECP uses ECG-triggered pressure during ventricular diastole delivered by air-filled cuffs around the lower vascular tree. The hemodynamic effects of ECP include 20% to 25% improvement in flow volume in the carotid, renal, and hepatic arteries, with a 20% to 40% improvement in coronary artery blood flow and a 12% increase in left ventricular stroke volume.[4] Direct cardiac catheterization during ECP demonstrates significantly increased diastolic pressure augmentation (71±10 to 137±21 mm Hg; $P<0.0001$) with improved mean intracoronary pressures (88±9 to 102±16 mm Hg; $P<0.006$) and a 28% increase in coronary flow on Thrombolysis in Myocardial Ischemia (TIMI) grading ($P=0.001$).[5]

In angina refractory to medical therapy, ECP has shown similar findings to coronary artery bypass and percutaneous coronary interventions including improvement in cardiac functional class, decreased anginal episodes, and reduction in nitroglycerin use.[6–10] Reduction of anginal episodes and improved quality of life have been sustained to 2 years after ECP in patients with EF <35% and refractory angina.[11] ECP effects have also been studied

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Table 1. Baseline and Postexternal Counterpulsation (ECP) Systemic Hemodynamic Indices

Hemodynamic Indices	Baseline Mean±SD	Post-ECP Mean±SD
Mean arterial pressure (MAP)	86±8 mm Hg	88±9 mm Hg (*P*=ns)
Cardiac output (CO)	7.3±1.5 L/minute	6.7±0.9 L/minute (*P*=ns)
Cardiac index (CI)	3.6±0.7 L/minute	3.3±0.5 L/minute (*P*=ns)
Stroke volume (SV)	98±22 mL/contraction	101±20 mL/contraction (*P*=ns)
SV index (SVI)	48±6.4 mL/contraction	49±6.5 mL/contraction (*P*=ns)
Systemic vascular resistance (SVR)	888±121 dynes/m^2/second	980±64 dynes/m^2/second (*P*=ns)
SVR index (SVRI)	1750±250 dynes/m^2/second	1938±243 dynes/m^2/second (*P*=ns)

All hemodynamic values are reported using standard clinical/instrumentation measures.

using treadmill exercise tests and ^{13}N-ammonia positron emission tomography (PET) at rest and with dipyridamole before/after ECP, alongside measurement of neurohumoral factors and nitric oxide, suggesting that ECP may promote development and recruitment of collateral vessels in ischemic territories.[12]

ECP noninvasive hemodynamic effects are similar to intraaortic balloon pumps (IABP),[13] yet carry less implementation risk. Lastly, ECP has been shown to increase CBF and renal perfusion.[14] As a first step in developing methods for clinical stroke trials, we sought to determine the effect of ECP on MCA blood flow augmentation using TCD in normal controls.

Subjects and Methods

Our primary aim was to determine the effects of ECP on MCA TCD flow velocities, as compared to baseline in normal controls using repeated measures. Our secondary aim was to describe the physiological correlates associated with ECP TCD waveform morphology. Five healthy volunteers were recruited; each subject was screened by medical history to exclude known diagnoses of DVT, dysrhythmias, hypertension, cardiac valvular dysfunction, and use of anticoagulation or antiplatelet agents. Blood pressure was measured, a 12-lead ECG was completed, and heart sounds were auscultated; subjects did not have hypertension, dysrhythmias, or clinically apparent cardiac valvular dysfunction. Carotid and vertebral arteries were scanned by carotid duplex to ensure absence of precerebral occlusions or stenoses.

Once enrolled, continuous ECG and preprocedural systemic hemodynamics were obtained using indirect oscillometric BP and transthoracic bioimpedance cardiac output (CO) to observe for cardiac changes that may affect intracranial blood flow. ECP leg garments were placed and ECP was initiated using model MC-2 (Vasomedical). This equipment consists of an air compressor, a console, a treatment table, and 2 sets of 3 pressure cuffs which are wrapped and Velcro-secured to subjects' lower extremities. Using compressed air, pressure is applied via the cuffs to the lower extremities in a sequence synchronized with the cardiac cycle as follows:

- In early diastole, pressure is applied sequentially from the lower legs to the lower and upper thighs to propel blood back to the heart, producing retrograde aortic blood flow during diastole (diastolic augmentation).
- At end-diastole, air is released instantaneously from all the cuffs to remove the externally applied pressure, allowing the compressed vessels to reconform, thereby reducing vascular impedance.

Bilateral 2-MHz pulsed wave TCD probes were mounted by standard head frame (Marc series, Spencer Technologies) for constant angle of insonation, and M1 MCA waveforms were monitored at 50- to 55-mm depth. Baseline TCD measurements (peak systolic velocity [PSV], end-diastolic velocity [EDV], mean flow velocity [MFV=(PSV−EDV)/3+EDV] and Gosling-King pulsatility index [PI]) were simultaneously recorded in both MCAs. Continuous bilateral TCD monitoring was then initiated for the duration of ECP. Two sets of TCD waveforms were recorded at 5 and 20 minutes, and a third measured immediately after ECP termination. Counterpulsation lasted 30 minutes; settings were adjusted to the level when diastolic velocity increased on spectral TCD waveforms in a manner similar to IABP counterpulsation.[15] Inflation/deflation rhythmic artifact precluded continuous CO measurement, therefore, a panel of systemic hemodynamic measures was recorded after ECP discontinuation. Nonparametric tests (Wilcoxon rank-sum test) were used for all statistical analyses.

ECP waveforms were analyzed in relation to cardiac cycle and baseline measures. Physiological correlates to IABP waveform morphology were identified using the methods we have previously published,[15,16] and knowledge of these characteristics was applied to construct measurable criteria for TCD assessment of ECP flow augmentation.

Results

The 5 subjects averaged 35±9 years of age, were in sinus rhythm, and were normotensive throughout ECP (Table 1). Preprocedural TCD measurements were normal (Table 2). The onset of ECP was marked by an immediate change in TCD waveform configuration with the appearance of a second upstroke in the arterial flow pattern initiated at the point of the

Table 2. Baseline Transcranial Doppler Flow Velocities in Comparison to Augmented Flow Velocities on External Counterpulsation

Velocities	Baseline Velocities (cm/sec)	Velocities at 5 Minutes Augmentation (cm/sec)	Velocities at 20 Minutes Augmentation (cm/sec)
Right middle cerebral artery median (range) values			
Mean flow velocity	48 (33–80)	58* (34–94)	61* (35–95)
End-diastolic velocity	34 (23–52)	36† (24–54)	40‡ (24–63)
Peak diastolic augmented velocity	NA	66‡ (39–118)	70‡ (40–112)
Left middle cerebral artery median (range) values			
Mean flow velocity	56 (36–68)	67* (41–99)	68* (41–98)
End-diastolic velocity	44 (26–46)	43† (25–54)	39† (29–53)
Peak diastolic augmented velocity	NA	78‡ (35–120)	73‡ (45–122)

*$P<0.05$ (Wilcoxon ranks test) vs baseline mean flow velocity (MFV).
†*P*=ns (Wilcoxon ranks test) vs baseline end-diastolic velocity (EDV).
‡$P<0.05$ (Wilcoxon ranks test) vs baseline EDV.
NA indicates not applicable.

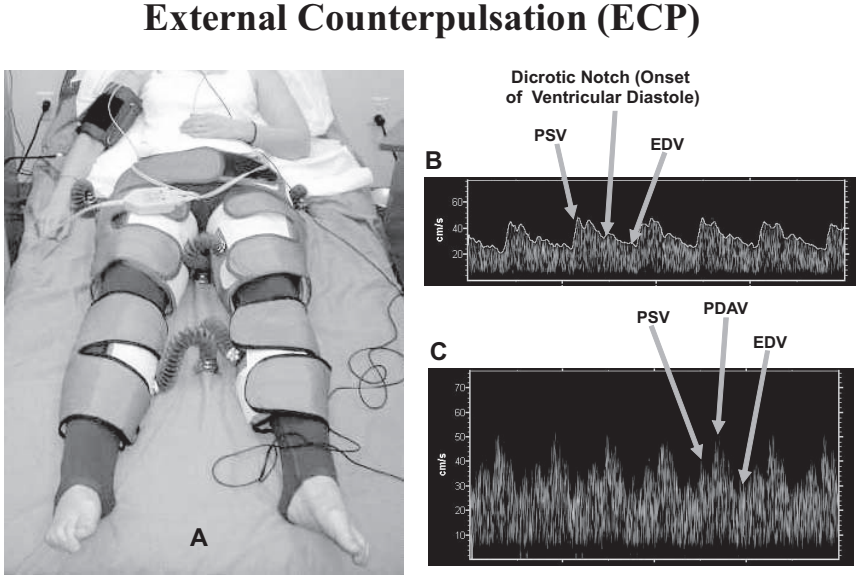


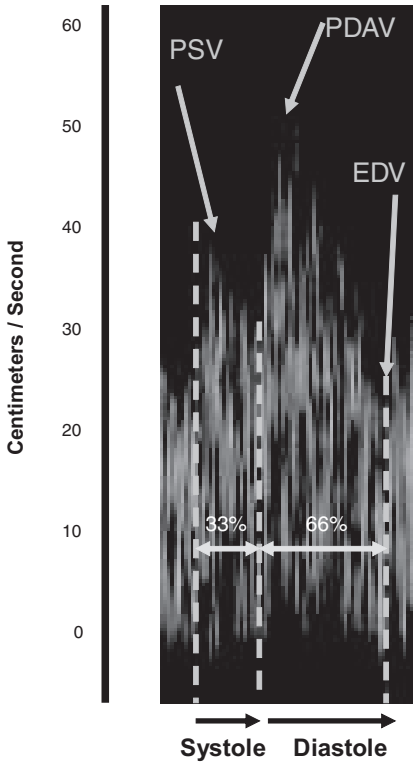
Figure 1. ECP device and normal transcranial Doppler (TCD) waveform compared to ECP TCD waveform.

dicrotic notch (Figure 1), labeled peak diastolic augmented velocity (PDAV), with maximum amplitude in early ventricular diastole at a flow velocity that was similar to, and in some cases slightly higher than, subjects' peak systolic velocity (PSV) values (right PSV_{ECP} mean 73±21 cm/s, PDAV mean 72±29 cm/s, P=NS; left PSV_{ECP} mean 77±20 cm/s, left PDAV mean 78±30 cm/s, P=NS). ECP diastolic augmentation terminated just prior to the next systolic upstroke in the EDV period and deflation cycles were not associated with loss of end-diastolic flow or flow reversal.

PDAVs in the right and left MCA were statistically higher than baseline end-diastolic values (Table 2). Overall augmented mean flow velocity (aMFV) was calculated using the formula in Figure 2, to capture the increased flow of ECP during diastole similar to IABP counterpulsation. Augmented MFVs were significantly higher than baseline MFVs in the right and left MCA (Table 2). Post-ECP measures were not significantly different from baseline (Table 1), and all subjects completed the 30 minute counterpulsation period without difficulty or complications.

Discussion

We showed that ECP induces marked changes in cerebral arterial waveforms and augments MCA flow velocities on



Step One:

$$\frac{PDAV + EDV}{2} = ADV$$

Step Two:

$$\frac{PSV - ADV}{3} + ADV = aMFV$$

Note: PDAV=peak diastolic augmented velocity; EDV=end-diastolic velocity; ADV=augmented diastolic velocity; PSV=peak systolic velocity; aMFV=augmented mean flow velocity.

Figure 2. Calculation of ECP TCD augmented mean flow velocity (aMFV).

TCD in 5 healthy subjects. PDAVs doubled compared to baseline end-diastolic velocities. This velocity augmentation was detected at a steady angle of insonation and presumably unchanged arterial territory perfusion. If these conditions are met, TCD augmented velocities may indicate, at least initially, an increased ECP blood flow volume during ventricular diastole. Because the effect of ECP is particularly evident during ventricular diastole, overall MFVs also increased and remained stabile during 30 minutes of counterpulsation.

The forerunner to ECP, IABP, is a well established therapy for the management of many cardiac conditions.[17,18] Others have documented deflation flow gaps during IABP counterpulsation,[16,19–21] but our ECP methods did not produce these on TCD spectra. Additionally, IAB use requires significant staff education and training on both cardiac and systemic arterial hemodynamic waveform morphology to ensure safe use of the device with appropriate prescription of inflation/deflation sequences in relation to the cardiac cycle.

ECP carries few risks and is likely to be more feasible in stroke treatment than either invasive IAB or intra-aortic inflation devices (Neuroflo),[22] and comparison of ECP and IAB counterpulsation has demonstrated equivalent hemodynamic effects.[13] ECP has greater potential for widespread use and is less expensive than invasive technology, in that catheterization procedures and central access devices/monitoring are unnecessary.

ECP cardiac therapy is prescribed as a course of 35 sessions applied as 1, 1-hour daily session, 5 days a week, for 7 weeks; it has been used in both hospital and outpatient settings. We provide formulas and magnitude of expected response in normal subjects, enabling incorporation of TCD into future ECP stroke feasibility and dose finding studies. The cardiac arteriogenesis effects of ECP should be studied in neurovascular patients, as a therapy for management of complete/chronic carotid occlusions, Moya Moya and TIA.

Certain limitations of the present report need to be acknowledged. For one, our study was limited to only 5 healthy subjects, and it may be beneficial to replicate this experiment using a larger subject pool. Secondly, the increase in MFV observed in our study was modest, and straightforward extrapolation of velocity increases to actual blood flow increases cannot be assured by our methods in this small sample of subjects. Moreover, to the best of our knowledge, no beneficial effects have been associated with improved cerebral perfusion in patients with completed infarct, and the utility of these methods on recruitment of collaterals and preservation of at-risk ischemic tissue remains unknown. In addition, further research is required to determine the potential beneficial effects of ECP in relation to stroke mechanism (eg, embolism versus thrombosis). Finally, we developed and used new measurable criteria for TCD assessment of ECP flow augmentation. Further validation of these criteria by independent groups is necessary.

Medical exclusions for ECP include arrhythmias interfering with ECG-triggering, bleeding diathesis, active thrombophlebitis, severe lower extremity vasoocclusive disease, aortic aneurysm, and pregnancy. Additional precautions include control of pretreatment BP and tachycardia, and cautious use with cardiac valvular insufficiency.[2,3] Stroke patients are vasculopaths and will require vigilant assessment for candidacy in any ECP study. IABP counterpulsation has been shown to augment intracranial blood flow even in high resistance states such as cerebral circulatory arrest.[23] The ability of counterpulsation devices such as ECP to overcome resistance to blood flow attributable to partial arterial occlusions remains unknown, but given our previous findings suggesting a high prevalence of acute ischemic strokes with partial occlusions,[24] investigation of the safety and efficacy of ECP as a mechanism for improving blood flow in patients outside the window for intravenous thrombolysis or IA rescue is warranted.

Disclosures

None.

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