Role of external counterpulsation in the treatment of ischemic stroke

Jing-Hao Han, Wai-Hong Leung, Ka-Sing Wong

Abstract
Reduced blood flow is the principle pathophysiologic event in acute ischemic stroke. Hence, flow augmentation is the most important goal in stroke management. Improvement of cerebral blood flow can be accomplished by proximal arterial recanalization or by other systemic approaches. Diastolic counterpulsation is a non-invasive method to improve the perfusion of heart, kidneys and brain. This review summarizes the history, possible mechanism and the role of external counterpulsation in ischemic stroke (J Geriatr Cardiol 2010; 7:88-92).

Key words ischemic stroke; external counterpulsation; cerebral blood flow; cerebral perfusion

Introduction
Ischemic stroke is a heterogeneous disease and constitutes 80% of all strokes. Irrespective of the underlying etiology, ischemia or reduced blood flow is the principle pathophysiologic event in acute ischemic stroke. As the main problem of stroke is that there is not enough blood getting to the focal cerebral region, strategies to improve cerebral blood flow (CBF) can play an important role in acute stroke management.

Improvement of cerebral perfusion can be achieved by directly opening arteries or systemically augmenting CBF. Thrombolytic therapy is highly effective but despite recent efforts to expand the window beyond 3 hours, the majority of stroke patients are not suitable for tissue-type plasminogen activator (tPA) treatment due to the limited treatment window. Continuous transcranial Doppler enhanced thrombolysis increases arterial recanalization, along with a trend towards better functional recovery. Other therapies such as balloon angioplasty with or without stenting and mechanical clot retrieval may provide an option for some patients presented after the 3-4.5 hour window for intravenous thrombolysis and up to 8 hours after symptom onset or did not response to tPA. However, these approaches are invasive and their clinical benefits need to be confirmed by large clinical trials. Under such circumstance, the need for a safe, convenient and effective way of increasing cerebral perfusion by systematic strategies is apparent.

Diastolic counterpulsation
Diastolic counterpulsation is an accepted method to improve the perfusion of vital organs, i.e., heart, kidneys and brain. Clinically, diastolic counterpulsation has been achieved invasively with intraaortic balloon counterpulsation (IABC) or non-invasively by external counterpulsation (ECP).

Intraaortic balloon counterpulsation
IABC is a mechanical circulatory-assist device initially used in patients with cardiogenic shock. A balloon is inserted via the femoral artery and positioned in the descending thoracic aorta just distal to the origin of the left subclavian artery and proximal to the renal vessels under X-ray monitoring. The effects of IABC are based on the intermittent inflation of balloon in the descending aorta at the beginning of diastole when the heart is at rest and deflation at the end of diastole just before the heart begins to beat. IABC therefore reduces cardiac afterload, decreases myocardial oxygen consumption, increases systemic tissue perfusion, and improves cardiac performance. The clinical application of IABC is limited probably due to the potential risks of ipsilateral lower extremity ischemia, arterial embolization, infection, pseudoaneurysm associated with this invasive technique.

Besides its clinical use in cardiogenic shock, there is mounting evidence that counterpulsation may enhance brain perfusion. In 1972, Simeone et al first reported a progressive increase in CBF up to 43% after initiation of IABC in rhesus monkeys. Studies also demonstrated an increase in CBF as measured by radioactive microsphere technique in experimental cardiogenic shock canines after IABC. An extended series of studies reported an improvement in cerebral perfusion after counterpulsation in both animal and...
human suffering with cerebral vasospasm after subarachnoid hemorrhage (SAH). Nussbaum et al. reported an average increase of 20% in mean CBF after IABC in a two-hemorrhage model of cerebral vasospasm. Shortly afterwards, two case reports shown that IABC is beneficial to patients with cerebral vasospasm following SAH who failed to respond to hypertension- hypervolemia- hemodilution therapy. The global CBF measured by xenon-enhanced computed tomography was $20.5 \pm 4.4 \text{ ml/100g/min}$ before versus $34.7 \pm 3.8 \text{ ml/100g/min}$ after IABC. Furthermore, CBF enhancement was in parallel with clinical improvement. Wojner found that early balloon deflation results in relatively high resistance flow in the middle cerebral artery (MCA), whereas deflation immediately prior to the next systolic upstroke creates higher positive diastolic flow and low-resistance waveforms in the MCA in patients with vasospasm after SAH. The finding indicates that timing of balloon inflation and deflation also has an influence on the change in CBF.

Tranmer et al first explore the effect of IABC in a canine cerebral ischemia model. A 15% mean increase in CBF was documented, local CBF in ischemic brain increased significantly from $22 \pm 12$ at baseline to $26 \pm 11$ ml/100 g/min after IABC. A recent randomized-controlled study aiming to determine whether IABC is able to reduce infarct size before mechanical reperfusion for acute myocardial infarction is still ongoing (Clinical Trials.gov Identifier NCT00833612).

**External counterpulsation**

ECP is a method that simulates IABP in a non-invasive manner. The concept of ECP was originally conceived by Dr. Soroff and Dr. Birtwell in the 1960s. The first ECP device consisted of large, steel chambers that housed inflatable cuffs, which were part of a hydraulic circuit. After then, the machine was modified several times and the current model is a pneumatic system developed in China. It operates by applying ECG-triggered diastolic pressure of approximately 250-300 mmHg to the vascular bed of the calves, thighs, and buttocks by means of three pairs of air-filled cuffs. As external pressure is applied from distal to proximal to enhance the efficacy on the circulation, the procedure has become known as EECP. The sequential cuff inflation at the beginning of diastole shifts the blood from the lower extremities toward the aorta and at the same time creates a retrograde pressure wave that augments diastolic blood pressure (diastolic augmentation) as well as mean arterial blood pressure (MAP), while the simultaneous deflation at the end of the diastole removes all the externally applied pressure to allow forward flow of blood, leaving behind an empty vascular bed in the lower limb to receive the output of the heart, therefore reducing systolic blood pressure (systolic unloading) and cardiac afterload. The diastolic augmentation of the blood flow and the simultaneously decreasing systolic afterload therefore increase blood flow to the heart, kidneys and brain. Unlike IABP, ECP also increases venous return through the compression of capacitance vein of the lower limbs, further promoting a 25% increase in cardiac output. The magnitude of diastolic augmentation that can be achieved with ECP was found comparable to that of the IABC.

Clinical application of ECP was approved by FDA as an adjunctive treatment for chronic angina in 1985. It is mainly used in patients with refractory angina unresponsive to medication and those who failed percutaneous coronary intervention or coronary artery bypass surgery. The clinical benefits of ECP therapy include reduction of angina and nitrate use, increased exercise tolerance, prolongation of the time to exercise-induced ST segment depression and improvement in myocardial perfusion. ECP therapy also increases retina perfusion in patients with acute central retinal artery occlusion or branch retinal artery occlusion. Furthermore, clinical benefit of ECP is demonstrated in patients with restless legs syndrome, a syndrome assumed to be associated with a decrease in vascular flow to the peripheral or central nervous system.

A full course of ECP treatment usually consists of 35 daily one-hour sessions over a seven-week period. To the best of our knowledge, no clinical study or animal model assessment has ever been carried out to explore whether ECP therapy has a different therapeutic effect with various duration of treatment. However, in the most clinical studies, 35 hours of treatment appears to be a routine practice.

As ECP offers a completely non-invasive way of bringing about similar hemodynamic modification, it has become widely used in clinical settings. ECP therapy is relatively safe. The main side effects are skin abrasion, low back pain and muscular ache in the lower extremities. However, there are certain conditions that require additional caution: 1) severe aortic insufficiency or aortic dissection; 2) atrial fibrillation or frequent ventricular premature beats that would interfere with ECP triggering; 3) blood pressure persistently >180/110 mmHg; 4) severe symptomatic peripheral vascular disease; 5) history of varicosities, deep vein thrombosis, thrombophlebitis or stasis ulcer; 6) bleeding diathesis and concurrent warfarin use with International Normalized ratio (INR)>2; and 7) presence of active malignancy.

**Mechanism of ECP** Despite the growing body of evidence supporting the clinical benefits of ECP therapy, the mechanisms behind are poorly understood. Possible mechanisms include an increase in blood flow in multiple vascular beds during the procedure, and enhancement of the collateral circulation through preexisting channels or by angiogenesis. Previous evidence suggests that physical exercise may improve coronary collateral function. As ECP mimics physical exercise in a standardized way, a prospective, single-blinded, sham-controlled trial which measures absolute collateral flow by calculating the collateral...
flow index and myocardial perfusion before and after ECP in patients with coronary artery disease is now underway and the results are awaited (Clinical Trials.gov Identifier NCT00414297).

Besides the acute hemodynamic changes during ECP which has been reviewed earlier in this article, a good collateral circulation may contribute to its long term clinical benefit. Collateral perfusion could be improved either by opening the preexisting vessels or through the formation of new vessels. Chronic exposure of the vascular bed to the augmented flow may increase vascular shear stress, and enhanced shear stress itself plays an important role in maintaining the normal endothelial function. ECP therapy reduces endothelial damage, arrests vascular smooth muscle cell proliferation and migration, decreases proliferating cell nuclear antigen proliferative index, suppresses extracellular matrix formation, and eventually inhibits atherosclerosis by increasing the arterial wall shear stress, which in turn activates the endothelial derived nitric oxide (NO) synthase pathway. Several studies found that increased shear stress stimulates endothelial NO (vasodilator) release and on the other hand, inhibits endothelial endothelin-1 (vasoconstrictor) release. A significant increase in plasma NO levels and a decrease in endothelin-1 (ET-1) levels were recorded after a course of ECP in patients with ischemic heart disease, and the increase in NO levels remained 1 month after the completion of ECP. An elevation in arterial pressure together with an increase in the release of shear-dependant vasodilators may increase organ perfusion via opening of preformed collateral channels, which is the simplest way to improve collateral circulation.

On the other hand, an increase in shear stress induced by ECP may influence angiogenesis. ECP therapy was associated with an increase in the plasma level of vascular endothelial growth factor (VEGF) in patients with stable angina, a factor which plays a key role in the process of angiogenesis. Furthermore, an increase in plasma VEGF levels was reported in chronic angina patients who have been responsive to ECP, whereas no change was found in patients without clinical improvement. However, evidence in biomarker changes mainly derived from patients with ischemic heart disease, although ischemic stroke patients may achieve clinical benefit through the same mechanisms, no changes in stroke patients are reported to date.

External counterpulsation in the management of ischemic stroke
There is accumulating evidence that ECP therapy may improve CBF. A study showed that the mean carotid flow velocity integral increased by 22% during ECP, with an average peak carotid diastolic flow velocity of 56 cm/sec, which is 75% as high as the systolic wave. Werner et al documented a 19% increase in flow volume in the carotid artery and a 12% increase in the vertebral artery during ECP. Studies also demonstrated an augmented flow during diastole in the MCA immediately after the start of ECP in both healthy controls and patients with severe atherosclerosis.

As ECP therapy enhances brain perfusion, there is rational to assume that patients with cerebrovascular disease might benefit from this treatment. Physicians from China began treating stroke patients with ECP in the late 1980s and the clinical outcomes were generally promising. Besides its clinical improvement, two studies have shown an improvement in cerebral perfusion after ECP. In a randomized controlled study, the average CBF increased from 45.7 ± 6.0 ml/100 g/min to 55.6 ± 6.0 ml/100 g/min in the ECP treated group, whereas no significant change was found in the control group. Moreover, 29 (72.5%) patients in the ECP group whereas 22 (55%) patients in the control group had a favorable clinical outcome. Studies also have shown a significant decrease in hematocrit, fibrinogen level and plasma viscosity after ECP, which may be associated with the improvement in cerebral circulation. More importantly, these changes in biomarkers were accompanied with a clinical improvement. Niu et al found a similar reduction in plasma ET-1 level after ECP in acute stroke patients, as previously seen in angina patients. As ET-1 mediated vasoconstriction may further reduce blood flow in the collateral circulation, a significant decrease in ET-1 may consequently lead to a better clinical outcome of stroke patients. Although the results were promising and no serious adverse complication was documented, the most of the evidence was based on results of studies without appropriate design and the sample size is rather small. Another major drawback is instead of using standard outcome measurements, such as the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Score (mRS), the most studies used the less widely known Chinese Stroke Scale.

These shortcomings greatly weaken the reliability of the evidence for a therapeutic effect of ECP on ischemic stroke. A recent randomized, crossover, assessment-blinded pilot study demonstrated ECP is safe and feasible for stroke patients with large artery disease. Fifty patients were randomized to either early (ECP week 1-7 and no ECP week 8-14) or late group (no ECP week 1-7 and ECP week 8-14). At end of week 7, there was a significant change in NIHSS (early 3.5 vs late 1.9; P=0.042). ECP was associated with a favorable trend of change in NIHSS of 2.1 vs 1.3 for non-ECP (P=0.061) after adjusted for treatment sequence. At week 14, a favorable functional outcome was found in 100% of early group patients compared to 76% in the late group (P=0.022). Changes in brain perfusion as measured by color velocity imaging quantification (CVIQ) in bilateral common carotid arteries and vertebral arteries were not significant, but tended to increase with ECP. In a case serials of 8 patients with acute MCA territory infarct, mean CBF volume increased by 4.5% on the relevant side, and 4.8% on the irrelevant side during ECP under a cuff inflation pressure of 225 mmHg.
Randomized-controlled trials with large sample size are needed to further define the efficacy and safety of ECP in acute stroke management. Our research team is now carrying out a multi-center randomized-control study to evaluate the therapeutic effects of ECP in patients with acute ischemic stroke and large artery disease. Another randomized, single blind (subject), placebo control study to assess whether or not 1 h of ECP increases blood flow to the brain and improve stroke symptoms is activated and will open for participant recruitment soon (Clinical Trials gov Identifier NCT00983749).

Conclusion

The majority of research in acute ischemic stroke has focused on proximal recanalization by tPA or clot retrieval techniques in the past two decades. However, only a small proportion of patients might benefit from these treatments due to the limited therapeutic window. Evidence for the effectiveness and safety of enhancing CBF by ECP is emerging. Thus, ECP therapy holds great promise for the treatment of ischemic stroke and more has to be learned about the mechanism responsible for its clinical benefits. In the future, it is important to identify the subtype of ischemic stroke patients whom may benefit most from ECP treatment. Secondly, the treatment window needs to be determined. Furthermore, it should be appreciated that in a device-related clinical trial, it is impossible to fully blind the patients as well as personnel applying the treatment, hence the need for a blinded rater, who assesses the patients independently during the follow-up period is apparent.

References

2. Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic retrieval techniques in the past two decades. However, only a small proportion of patients might benefit from these treatments due to the limited therapeutic window. Evidence for the effectiveness and safety of enhancing CBF by ECP is emerging. Thus, ECP therapy holds great promise for the treatment of ischemic stroke and more has to be learned about the mechanism responsible for its clinical benefits. In the future, it is important to identify the subtype of ischemic stroke patients whom may benefit most from ECP treatment. Secondly, the treatment window needs to be determined. Furthermore, it should be appreciated that in a device-related clinical trial, it is impossible to fully blind the patients as well as personnel applying the treatment, hence the need for a blinded rater, who assesses the patients independently during the follow-up period is apparent.

Conclusion

The majority of research in acute ischemic stroke has focused on proximal recanalization by tPA or clot retrieval techniques in the past two decades. However, only a small proportion of patients might benefit from these treatments due to the limited therapeutic window. Evidence for the effectiveness and safety of enhancing CBF by ECP is emerging. Thus, ECP therapy holds great promise for the treatment of ischemic stroke and more has to be learned about the mechanism responsible for its clinical benefits. In the future, it is important to identify the subtype of ischemic stroke patients whom may benefit most from ECP treatment. Secondly, the treatment window needs to be determined. Furthermore, it should be appreciated that in a device-related clinical trial, it is impossible to fully blind the patients as well as personnel applying the treatment, hence the need for a blinded rater, who assesses the patients independently during the follow-up period is apparent.

References

2. Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic retrieval techniques in the past two decades. However, only a small proportion of patients might benefit from these treatments due to the limited therapeutic window. Evidence for the effectiveness and safety of enhancing CBF by ECP is emerging. Thus, ECP therapy holds great promise for the treatment of ischemic stroke and more has to be learned about the mechanism responsible for its clinical benefits. In the future, it is important to identify the subtype of ischemic stroke patients whom may benefit most from ECP treatment. Secondly, the treatment window needs to be determined. Furthermore, it should be appreciated that in a device-related clinical trial, it is impossible to fully blind the patients as well as personnel applying the treatment, hence the need for a blinded rater, who assesses the patients independently during the follow-up period is apparent.

Conclusion

The majority of research in acute ischemic stroke has focused on proximal recanalization by tPA or clot retrieval techniques in the past two decades. However, only a small proportion of patients might benefit from these treatments due to the limited therapeutic window. Evidence for the effectiveness and safety of enhancing CBF by ECP is emerging. Thus, ECP therapy holds great promise for the treatment of ischemic stroke and more has to be learned about the mechanism responsible for its clinical benefits. In the future, it is important to identify the subtype of ischemic stroke patients whom may benefit most from ECP treatment. Secondly, the treatment window needs to be determined. Furthermore, it should be appreciated that in a device-related clinical trial, it is impossible to fully blind the patients as well as personnel applying the treatment, hence the need for a blinded rater, who assesses the patients independently during the follow-up period is apparent.

References

2. Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic retrieval techniques in the past two decades. However, only a small proportion of patients might benefit from these treatments due to the limited therapeutic window. Evidence for the effectiveness and safety of enhancing CBF by ECP is emerging. Thus, ECP therapy holds great promise for the treatment of ischemic stroke and more has to be learned about the mechanism responsible for its clinical benefits. In the future, it is important to identify the subtype of ischemic stroke patients whom may benefit most from ECP treatment. Secondly, the treatment window needs to be determined. Furthermore, it should be appreciated that in a device-related clinical trial, it is impossible to fully blind the patients as well as personnel applying the treatment, hence the need for a blinded rater, who assesses the patients independently during the follow-up period is apparent.

Conclusion

The majority of research in acute ischemic stroke has focused on proximal recanalization by tPA or clot retrieval techniques in the past two decades. However, only a small proportion of patients might benefit from these treatments due to the limited therapeutic window. Evidence for the effectiveness and safety of enhancing CBF by ECP is emerging. Thus, ECP therapy holds great promise for the treatment of ischemic stroke and more has to be learned about the mechanism responsible for its clinical benefits. In the future, it is important to identify the subtype of ischemic stroke patients whom may benefit most from ECP treatment. Secondly, the treatment window needs to be determined. Furthermore, it should be appreciated that in a device-related clinical trial, it is impossible to fully blind the patients as well as personnel applying the treatment, hence the need for a blinded rater, who assesses the patients independently during the follow-up period is apparent.

References


