Review

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Is Counterpulsation a Potential Therapy for Ischemic Stroke?

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Key Words
Ischemic stroke · Cerebral blood flow · Counterpulsation

Abstract
Background: Despite the rapid progress in stroke prevention, effective acute stroke treatment except for thrombolysis is still lacking. Hypoperfusion is related to unfavorable functional outcome, further strokes and long-term mortality. Therefore, the need for a safe and effective way of increasing the cerebral blood flow seems obvious. Currently, there is a growing body of evidence to suggest that external counterpulsation (ECP) may enhance the blood supply to the brain and thus may be beneficial to patients with ischemic stroke. ***Methods:*** A MEDLINE search in combination with a search for papers in Chinese literature in the Wan Fang and China Academic Journal databases was carried out. ***Results:*** Preliminary investigations suggested that ECP may improve the clinical outcome of stroke patients. However, well-designed clinical studies exploring the therapeutic effects of ECP in ischemic stroke are very limited. ***Conclusions:*** Randomized-controlled trials with a large sample size are needed to further define the efficacy and safety of ECP in acute stroke management. Future studies should provide insight into the value of ECP in ischemic stroke as well as its possible mechanisms.

Introduction

Despite the rapid progress in stroke management during the past decade, stroke has remained a major cause of death and disability in the world. Ischemic stroke occurs when there is a lack of blood flow to the brain. Abundant evidence shows that poor cerebral perfusion is related to unfavorable functional outcome, further strokes and other vascular events [1–4]. Although a number of major clinical studies have demonstrated the benefit of plaque stabilization [5, 6] and antithrombotic therapy [7, 8], these medications are mainly for secondary stroke prevention. As the main problem of stroke is that there is not enough blood getting to the focal cerebral region, cerebral blood flow (CBF) augmentation may be the first and most important goal in acute stroke management.

Basically, improving the CBF can be accomplished in 2 broad ways: opening arteries directly by mechanical techniques or augmenting the CBF by systemic strategies. Thrombolytic therapy is the only universally accepted acute treatment for ischemic stroke but the limited time window confines its use to very few patients. New strategies to expand the systemic reperfusion including extending the intravenous rt-PA window to 270 min; new fibrinolytic agents (desmoteplase); combination of lytics, antithrombotics as well as neuroprotectans; and externally applied ultrasound to enhance enzymatic fibrinolysis are currently under investigation [9, 10]. Alternative options also include balloon angioplasty with or without

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stenting [11, 12] and mechanical clot retrieval [13, 14] in selected patients who presented after the 3-hour window for intravenous thrombolysis and up to 8 h after symptom onset or did not respond to t-PA. Although the results are enticing, these approaches are invasive and remain experimental. Under such circumstances, the need for a safe, convenient and effective way of increasing cerebral perfusion by systematic strategies seems obvious.

Diastolic counterpulsation is an acceptable method that is known to improve the perfusion of vital organs. Clinically, diastolic counterpulsation has been achieved invasively with an intra-aortic balloon pump (IABP) or noninvasively by external counterpulsation (ECP). In the early 1960s, Moulopoulus et al. [15] developed an experimental prototype of the IABP. The effects of the IABP are based on the intermittent inflation of a balloon in the descending aorta at the beginning of the diastole when the heart is at rest and deflation at the end of the diastole just before the heart begins to beat. The hemodynamic effects of IABP are a reduction in cardiac afterload and an increase in diastolic blood flow to various organs [16]. IABP is now the most widely used mechanical circulatory assist device for patients with cardiogenic shock. However, its clinical application is limited because of the risks (ipsilateral lower extremity ischemia, arterial embolization, infection, trauma to the aorta or pseudoaneurysm and hemolysis) associated with this invasive technique [17].

ECP operates by applying an ECG-triggered diastolic pressure of approximately 250 mm Hg to the calves, thighs and buttocks by means of air-filled cuffs. The diastolic augmentation of the blood flow and the simultaneously decreasing systolic afterload therefore increase the blood flow to the heart, brain and kidneys. As ECP offers a completely noninvasive way of bringing about similar hemodynamic modification, it has become widely used in clinical settings. Consequently, as ECP may improve the cerebral blood blow, it has been proposed as a potential therapy for patients with brain ischemia.

This review will introduce the development of the technique of counterpulsation, investigate its effect on cerebral circulation, evaluate its potential therapeutic role in cerebrovascular disease and further explore its possible mechanisms.

IABP and Cerebrovascular Disease

Although mainly used in patients with cardiac disease, there is mounting direct or indirect evidence that counterpulsation may enhance the CBF. In 1972, Simeone et al. [18] first reported a progressive rise in CBF after initiation of IABP in adult rhesus monkeys. Animal studies also demonstrated an increase in CBF in experimental cardiogenic shock canines after IABP. Bhayana et al. [19] measured the CBF in 13 dogs by radioactive microsphere technique and found that it increased by 56%, while a rise in CBF by 31% was documented in another evaluation using the same method [20].

An improvement in cerebral perfusion after counterpulsation has been reported by an extended series of studies in both animals and humans suffering from cerebral vasospasm after subarachnoid hemorrhage. Nussbaum et al. [21] reported an average increase in mean CBF of approximately 20% (ranging from 7 to 50) in 10 of 10 dogs after treatment with IABP in a 2-hemorrhage model of cerebral vasospasm. More impressively, the highest value of increase was noted in the dog that developed clinical evidence of focal ischemia. Shortly afterwards, 2 case reports also illustrated the ability of IABP to improve the clinical outcome as well as CBF in patients suffering from vasospam after subarachnoid hemorrhage [22, 23]. Nussbaum et al. [23] reported that in the case of a 60-year-old woman with cerebral vasospam induced by subarachnoid hemorrhage who failed to respond to 3H therapy (hypertension, hypervolemia, hemodilution), the CBF improved by 69.3% on average after IABP.

In 1989, Tranmer et al. [24] investigated CBF changes after IABP in a cerebral ischemia model after internal carotid artery and middle cerebral artery occlusion, which is the first published paper utilizing counterpulsation therapy in acute ischemic stroke. A 15% mean increase in CBF in 4 of 6 dogs was documented and among 4 dogs with significant rises in cardiac output, the local CBF in the ischemic brain increased significantly from 22 ± 12 to 26 ± 11 ml/100 g/min. Although there are compelling data showing the ability of IABP to improve brain perfusion in the situation of cerebral ischemia, most probably due to its invasiveness, there are no published studies evaluating its effect in patients with acute ischemic stroke.

Overview of ECP Therapy

Historical Development of ECP

Taking a cue from IABP, the concept of ECP was originally conceived by Dr. Harry Soroff and Dr. William Birtwell at Harvard University in the 1960s. The early device was built at the beginning of the 1970s and consisted of large steel chambers that housed inflatable cuffs,

which were part of a hydraulic circuit. The device was cumbersome and had a marginal counterpulsation effect. Since then, the machine has been modified several times and its current form is a pneumatic system developed in China in 1983 [25].

During counterpulsation therapy, the patients lie on a treatment table and a series of 3 compressive cuffs are placed on their calves, thighs and buttocks. The machine operates by applying an ECG-triggered diastolic pressure of approximately 250 mm Hg to the vascular bed of the calves, thighs and buttocks by means of 3 pairs of air-filled cuffs. A course of ECP treatment usually consists of 35 daily 1-hour sessions over a 7-week period. To the best of our knowledge, no clinical study or even animal model assessment has ever been carried out to explore whether ECP therapy has a different therapeutic effect under a different duration of treatment. However, in most clinical and animal analyses, 35 h of treatment appears to be a routine practice [26–30].

Clinical Applications and Contraindications of ECP

Clinical trials of ECP date back to the 1960s and most of them have focused on the application of ECP in patients with ischemic heart disease. The benefits associated with ECP include reduction of angina and nitrate use, increased exercise tolerance, prolongation of the time to exercise-induced ST segment depression and an accompanying resolution of myocardial perfusion defects [27–30]. By 1995, enough of a body of research had accumulated for ECP to receive FDA approval as a treatment for chronic stable angina.

A prospective, randomized study recently investigated the impact of ECP on retinal reperfusion in patients with acute central retinal artery occlusion or branch retinal artery occlusion. A significant increase in perfusion as measured by scanning laser Doppler flowmetry was observed immediately after 2 h of ECP in the ischemic retinal area, whereas there was no significant change in the control group [31]. A case report also showed the clinical benefit of ECP for patients with restless legs syndrome, a disorder assumed to be associated with a decrease in vascular flow to the peripheral or central nervous system [32].

ECP treatment is relatively safe. The main side effects include skin abrasion, low back pain and muscle ache. However, there are certain conditions that require caution when considering the therapy: (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 mm Hg; (4) severe symptomatic peripheral vascular disease; (5) history of varicosities, deep vein thrombosis, thrombophlebitis or stasis ulcer; (6) bleeding diathesis and concurrent warfarin use, and (7) presence of active malignancy.

Possible Mechanisms of ECP

Despite the increasing evidence suggesting the clinical benefits of ECP therapy for angina, the mechanisms behind are largely unknown. The possible factors responsible for its clinical improvement are summarized as follows.

Effects of ECP on Hemodynamic Changes

The sequential cuff inflation at the beginning of the diastole shifts the blood from the lower extremities toward the aorta and at the same time creates a retrograde pressure wave that augments the diastolic blood pressure (diastolic augmentation) as well as the mean arterial blood pressure, 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, the systolic blood pressure (systolic unloading) and cardiac afterload are reduced. The magnitude of hemodynamic changes generated by ECP can be estimated by measuring the diastolic to systolic effectiveness ratio using finger plethysmography (peak diastolic amplitude divided by speak systolic amplitude). Doppler echocardiographic studies found that a ratio of 1.5–2.0 during the procedure may lead to an optimal increase in both diastolic anterograde and diastolic retrograde aortic flow [33]. However, as some patients who had clinical improvement do not achieve a ratio of 1.5–2.0, the clinical significance of this finding is yet uncertain [34, 35]. The magnitude of diastolic augmentation that can be achieved with ECP was found to be comparable to that of the IABP [36]. Unlike IABP, ECP also augments the venous return through the compression of the capacitance vein of the lower limbs, further promoting a 25% increase in cardiac output. These hemodynamic effects result in a rise in blood flow in multiple vascular beds, including the brain, kidneys, liver and myocardium [34, 37, 38].

Effect of ECP on Collateral Circulation

Apart from the hemodynamic changes during ECP, establishing a good collateral circulation may contribute to its long-term benefit. Basically there are 2 ways of enhancing collateral perfusion: one is opening or expand-

ing the preformed vessels, and the other one is the formation of new vessels. It is believed that chronic exposure of the vascular bed to the augmented blood flow may increase vascular shear stress [39, 40], and enhanced shear stress itself plays an important role in the maintenance of a functional endothelium [41]. A recent study found that ECP reduces endothelial damage, arrests vascular smooth muscle cell proliferation and migration, decreases the proliferating cell nuclear antigen proliferative index, suppresses extracellular matrix formation, and eventually inhibits intimal hyperplasia and the development of atherosclerosis by increasing the arterial wall shear stress, which in turn activates the endothelial-derived nitric oxide (NO) synthase/NO pathway and probably suppresses extracellular signal-regulated kinase 1/2 overactivation [42]. In addition, other studies have shown that increased shear stress stimulates the release of NO, which is a vasodilator, and on the other hand, inhibits the release of endothelial endothelin-1 (ET-1), which is a vasoconstrictor. Barsness [26] reported a significant increase in plasma NO levels and a decrease in ET-1 levels after a course of ECP among patients with ischemic heart disease. Another study found the rise in plasma NO levels persist 1 month after the completion of 35 one-hour sessions of ECP [27]. Such changes in the release of shear-dependent vasomediators as well as augmented arterial pressure may help open the preformed collateral channels, which is the simplest way to augment collateral perfusion.

On the other hand, an increase in shear stress produced by ECP may influence angiogenesis, which may also improve collateral perfusion. Apart from ischemia, a rise in endothelial shear stress produced by ECP due to a chronic exposure of the arterial bed to the augmented blood flow is considered a major stimulus for collateral development [43]. Increased shear stress may upregulate the endothelial production of growth factors, such as vascular endothelial growth factor (VEGF), which plays a key role in angiogenesis [44]. In a case series of 11 patients with stable angina, a significant rise in the plasma level of VEGF was noted [45]. Furthermore, an increase in plasma VEGF levels was reported in 5 patients with chronic angina who achieved a 50% reduction in anginal episodes after a course of ECP, whereas no change was found in 4 patients without response [26]. However, all evidence of biomarker changes now comes from patients with ischemic heart disease. Although stroke patients are most likely to derive clinical benefit through the same mechanisms, evidence of such changes in stroke patients is not available to date.

ECP and Cerebrovascular Disease

Evidence of Improvement in Brain Perfusion

ECP-induced hemodynamic effects result in diastolic augmentation, systemic unloading and also an increase in cardiac output, therefore augmenting the blood flow in multiple vascular beds. Recently, a number of investigations have evaluated the effect of ECP on cerebral circulation by means of carotid duplex or transcranial Doppler ultrasonography. A study from the USA reported that the mean carotid flow velocity integral increased by 22% from 27.7 ± 1.8 to 33.1 ± 2.3 cm/s during ECP, with an average peak carotid diastolic flow velocity of 56 cm/s, which is 75% as high as the systolic wave [46]. Werner et al. [37] noted a 19% rise in flow volume in the carotid artery and a 12% increase in the vertebral artery during ECP. The same research team [47] further reported an augmented flow during the diastole in the middle cerebral artery immediately after the start of ECP in both healthy controls and patients with severe atherosclerosis.

ECP Therapy for Cerebrovascular Disease in China

Because ECP has a potential effect in improving brain perfusion, it is plausible that it will be beneficial for patients with cerebrovascular disease. Physicians in China began treating stroke patients with ECP in the late 1980s. After an extensive search of the MEDLINE (1966–2004) database, no paper published in the English literature was found to evaluate the therapeutic effect of ECP for stroke patients. We then systematically identified and reviewed all articles published in the Chinese literature in the Wan Fang and China Academic Journal databases (2 major national databases in China) during the past 2 decades. Twenty-two papers were identified and all reported a favorable outcome. Table 1 lists the research discussed in this article, together with details of the study design, etc. Apart from the clinical improvement, a number of investigations recorded an increase in brain perfusion after ECP treatment [48, 49]. In a randomized-controlled study, the average CBF was found to be 45.7 ± 6.0 ml/100 g/min before versus 55.6 ± 6.0 ml/100 g/min after ECP in the treatment group (n = 40), while in the non-ECP group no significant change was found (n = 40). In addition, 29 patients (72.5%) in the ECP group, compared to only 22 (55%) in the control group, had a favorable clinical outcome [50].

Studies also show a significant decrease in hematocrit, fibrinogen level and plasma viscosity after 12–35 h of ECP [51–55], which may result in an increase in CBF [56,

Table 1. Chinese studies on the effects of ECP in patients with ischemic stroke

Study	Study design	Participants	Intervention	Outcome measurement
Zhao et al. [60], 1988	dual arm, randomized-controlled	ECP (n = 24) non-ECP (n = 24) stroke (n = 48)	12 h ECP	favorable clinical outcome (100 vs. 75%, $p < 0.01$)
Zhen and Gong [61], 1988	dual arm, nonrandomized	ECP (n = 24) non-ECP (n = 24) stroke (n = 48)	12–36 h ECP	favorable clinical outcome (95.8 vs. 75%, $p < 0.05$)
Wu [62], 1990	dual arm, nonrandomized	ECP (n = 75) non-ECP (n = 70) stroke (n = 145)	12–24 h ECP	favorable clinical outcome (78.7 vs. 55.7%, $p < 0.01$)
Zhong et al. [63], 1990	dual arm, randomized-controlled	ECP (n = 22) non-ECP (n = 22) stroke (n = 44)	12 h ECP	favorable clinical outcome (94.1 vs. 64.7%, $p < 0.05$); 95.4% had γ-CBF increase in the ECP group
Li et al. [53], 1994	case series	CAD (n = 20) stroke (n = 8) atherosclerosis (n = 20)	1 h ECP	plasma viscosity ↓ ($p < 0.05$)
Chen et al. [51], 1994	case series	CAD (n = 27) stroke (n = 18) atherosclerosis (n = 48)	1 h ECP	plasma viscosity ↓ ($p < 0.05$)
Chen et al. [64], 1994	dual arm, randomized-controlled	ECP (n = 74) non-ECP (n = 44) stroke (n = 118)	12 h ECP + dextran 40 vs. dextran 40	favorable clinical outcome (64.1 vs. 25%, $p < 0.01$)
Yao et al. [49], 1996	case series	TIA (n = 10) atherosclerosis (n = 12)	24–36 h ECP	72.2% had γ-CBF increase
Xu et al. [65], 1996	dual arm, self-controlled	stroke (n = 20) controls (n = 10)	1 h ECP	t-PA ↑ in both groups, D-dimer ↑ in stroke patients, no change in PAI in both groups
Yang et al. [50], 1996	dual arm, randomized-controlled, assessment-blinded	ECP (n = 40) non-ECP (n = 40) stroke (n = 80)	12 h ECP	favorable clinical outcome (72.5 vs. 55%, $p < 0.01$); γ-CBF increased by 17.8% in the ECP group
He et al. [66], 1996	case series	stroke (n = 184)	12–72 h ECP	95.1% had a favorable clinical outcome
Du et al. [52], 2000	dual arm, nonrandomized	ECP (n = 40) non-ECP (n = 40) stroke (n = 80)	24–36 h ECP	favorable clinical outcome (95 vs. 75%, $p < 0.05$); plasma viscosity ↓ in both groups, HCT ↓ and FIB ↓ in the ECP group
Meng et al. [67], 2000	dual arm, randomized-controlled	ECP (n = 70) non-ECP (n = 68) stroke (n = 138)	24 h ECP + dextran 40 vs. dextran 40	favorable clinical outcome (92.9 vs. 73.5%, $p < 0.05$)
Niu et al. [58], 2000	dual arm, randomized-controlled	ECP (n = 20) non-ECP (n = 22) stroke (n = 42)	12 h ECP + dextran 40 vs. dextran 40	SOD ↓, MDA ↓ and ET-1 ↓ in the ECP group
He and Xu [68], 2000	case series	stroke (n = 20)	12–36 h ECP	60% had a favorable clinical outcome
Ma et al. [69], 2000	case series	stroke (n = 241)	10–50 h ECP	97.1% had a favorable clinical outcome
Liu and Zhou [70], 2001	case series	stroke (n = 30)	defibrase 10 U i.v. for 3 days, followed by 12 h ECP	93.3% had a favorable clinical outcome
Zhang [71], 2001	dual arm, randomized-controlled	ECP (n = 24) non-ECP (n = 24) stroke (n = 48)	12 h ECP + dextran 40 vs. dextran 40	favorable clinical outcome (95.8 vs. 75%, $p < 0.05$)

Table 1 (continued)

Study	Study design	Participants	Intervention	Outcome measurement
Wu et al. [48], 2001	dual arm, randomized-controlled, assessment-blinded	ECP (n = 30) non-ECP (n = 30) atherosclerosis (n = 60)	72 h ECP	γ-CBF increased by 17.2% in the ECP group; no change noted in the control group
Yao [54], 2003	dual arm, nonrandomized, self-controlled	ECP (n = 118) non-ECP (n = 68) stroke (n = 186)	24 h ECP + dextran 40 vs. dextran 40	favorable clinical outcome (96.0 vs. 83.8%, $p < 0.05$) Plasma viscosity ↓ in the ECP group
Liu et al. [72], 2003	dual arm, nonrandomized	ECP (n = 60) non-ECP (n = 63) stroke (n = 123)	35 h ECP	favorable clinical outcome (BI) in the ECP group vs. control ($p < 0.01$)
Zhang et al. [55], 2003	dual arm, randomized-controlled	ECP (n = 70) non-ECP (n = 68) stroke (n = 138)	24 h ECP + dextran 40 vs. dextran 40	favorable clinical outcome* (92.9 vs. 73.5%, $p<0.05$); plasma viscosity ↓ HCT ↓ FIB ↓ in the ECP group

PAI = Plasminogen activator inhibitor; CAD = coronary artery disease; HCT = hematocrit; SOD = superoxide dismutase; MDA = malondialdehyde; FIB = fibrinogen. Favorable clinical outcome: assessed by Chinese stroke scale (4th version).

57]. More importantly, these changes in biomarkers were accompanied by a clinical improvement [52, 54, 55]. It is of interest that 1 study found a decrease in plasma ET-1 level after ECP treatment among acute stroke patients as previously seen in subjects with angina [58]. ET-1-mediated vasoconstriction further reduced the blood flow in collateral circulation and aggravated the ischemic effect of an existing cerebral lesion, thus, a significant decrease in the ET-1 level may consequently lead to a better clinical outcome. Although the reason behind is unclear, a decrease in the plasma markers of oxidative stress was also shown in these patients [58].

In summary, ECP may improve the neurological outcome by enhancing brain perfusion [48–50], lowering blood viscosity [51–55], as well as regulating vasomediators [58] and oxidative stress [58]. Although the results appeared promising and no serious adverse complications were documented, most of the evidence was based on the findings of observational studies, case series and research with poor design. The methodological issues found in these studies include: the relatively small sample size, the lack of an appropriate control group, the variation in the treatment duration, the use of nonstandard outcome measurements and the lack of information on the method of blindness in the study design. The treatment duration varied from trial to trial, ranging from 1 to 50 h, even in the same study the treatment sessions were not identical. In addition, instead of using standard outcome measurements, such as NIHSS and modified Rankin Scale, most studies used the Chinese Stroke Scale or other surrogate biomarkers to assess the outcome. These shortcomings of the existing literatures greatly weaken the credibility of the therapeutic effect of ECP on ischemic stroke. Therefore, these studies could only be used as evidence to support the clinical benefit of ECP among stroke patients in anything more than a very general way.

Conclusions

From the results of the studies to date, there is evidence to suggest that ECP may enhance the blood supply to the brain. Therefore, we feel there is a rationale that ECP may be beneficial to patients with ischemic stroke. Currently, ECP is a well-established adjunctive treatment for chronic angina, but there have been very few experiences in stroke treatment. Although the quality of the studies done in China is generally poor, the preliminary data suggested that ECP might improve the clinical outcome of ischemic stroke. Well-designed clinical trials exploring the therapeutic effects of ECP in ischemic stroke are very limited at the current stage. Our randomized, crossover, assessment-blinded pilot study showed that ECP was safe and feasible for stroke patients with large artery disease [59]. Randomized-controlled trials with a large sample size are definitely needed to define the efficacy and safety of ECP in acute stroke management. Also, it is important to identify which patients benefit the most from ECP treatment as well as the time window for initiating the therapy after symptom onset. Further, we should be aware that in a device-related clin-

ical trial, it is impossible to fully blind the patients as well as the personnel carrying out the treatment. In the Multicenter Study of Enhanced External Counterpulsation trial, a pressure of 75 mm Hg was applied to the sham control group, whereas the active group used a pressure of 300 mm Hg. The mask is not effective as some of the patients correctly guess their form of treatment [28]. The only way to conduct the trial is to have a blinded rater, who assesses the patients independently during the follow-up period, as was done in the t-PA trials. Finally, more has to be learned about the mechanisms responsible for its clinical benefit, especially the real-time CBF during ECP, as well as changes in biomarkers that may help establish a good collateral circulation in the long term.

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