The four stages of development: a historical prospective of external counterpulsation

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There are four stages in medical device development. The beginning starts with some new understanding of physiological concepts which evolve into the formation of an innovative idea. The second stage is the technical development phase, from idea to the development of a design to technical reality. At this stage, capital funding and patent applications for the development are necessary but they are not considered here. The third stage is experimental and clinical studies, a data gathering phase to provide evidence of safety and effectiveness of the applications of the device. The final stage is society adaptation and acceptance. These four stages do not occur in series but constantly interact and feedback on each other, evolving on their way to maturity.

Physiological concepts and innovation idea

External counterpulsation (ECP) starts with two ideas: Kantrowitz and Kantrowitz first described the principle of diastolic augmentation (DA) to increase coronary blood flow in 1953 and Sarnoff and colleagues described that myocardial workload is proportional to the pressure generated by the left ventricular and its contraction time.1,2 Then in 1957 Birtwell proposed to design a device that can synthesize the two concepts of DA and systolic unloading to improve ventricular energy supply and demand ratio.3,4 That is the beginning of counterpulsation, a circulatory assist device to help the pumping action of the heart. The clinical objective is to provide a mean to stabilize patients suffering from acute myocardial infarction (AMI) and/or cardiogenic shock.3,4 As experimental and clinical data accumulate, evidence points to the possibility of coronary collateral recruitment due to the greater pressure gradient generated across the stenosis, especially during the diastolic relaxation phase when resistance to flow is minimal. This concept changes the application of ECP as a temporary circulatory assist device to a treatment modality for coronary artery disease. Equipment development for chronic clinical application in the treatment of angina pectoris was carried out in the 1970s-1980s. Numerous papers were published during the 1990s exploring the mechanisms of action, demonstrating ECP increases systemic blood flow and thereby shear stress to the endothelial cell layer,9,10 improves endothelial function,11,12 vascular tone,13 arterial stiffness,14 promotes the release of vascular growth factors15,16 and endothelial progenitor cells,17,18 stimulate the recruitment of collateral circulation,19,20 attenuates inflammatory cytokines activities21 and atherosclerotic process.22 ECP is no longer a treatment device for a single organ, the heart. ECP in the 2000s may be considered to be a therapeutic device for the prevention of progression in cardiovascular disease.

Technical development: from concept to design

The first two classic papers on Assisted Circulation I by Clauss and colleagues in 1961 and Assisted Circulation II by Soroff and coworkers in 1963 described an actuator with a chamber to receive arterial blood via a cannulation of the descending aorta and an electronic triggering circuit using the R wave of the electrocardiogram to initiate withdrawal of a volume of blood during systole and returning the blood during diastole.23,24 These early counterpulsation workers were able to demonstrate a reduction of left ventricular work by 33% and oxygen consumption by 22% with no change in cardiac output. From here onwards, counterpulsation development took two different paths: intra-aortic balloon counterpulsation (IABP) led by Moulopoulos and colleagues at Cleveland Clinics25,26 and external counterpulsation (ECP) by Birtwell, Soroff and coworkers,25 Dennis and coworkers,26 and Osborn and associates.27 Clinical studies of ECP began in late 1960s using a hydraulic actuator consisted of a rigid outer case enclosing a single pant-like bag filled with water put around the lower extremities of the patient. Pressures were applied and released by pumping water in and out of the bag in synchronization the cardiac cycle. The most interesting study at that period is a multicenter prospective randomized control clinical trial in-
volving 258 AMI patients done in 1978-1979, demonstrating that patients treated with 1-4 hours of ECP within the first 24 hours after onset of symptoms the mortal rate was significantly lower than the control group (6.5% versus 14.7%, $P <0.05$). However, clinical results in the early 1970s were not consistent due primarily to the different ways that ECP equipments were constructed. Overall, hydraulic actuators were used because water is incompressible and therefore transmits the externally applied pressure without loss of energy in compressing the medium. On the other hand, water is heavy, exerting a pressure higher than the venous pressure and thereby permanently occluding the venous side of the peripheral circulation. At the same time, a single bag around the lower extremities applying a uniform pressure would produce a bottle-neck effect with the proximal larger arteries collapsed first before the distal smaller arteries, reducing the magnitude of retrograde flow up the aorta to improve diastolic coronary flow. In 1976 Zheng ZS and colleagues in China developed the sequential external counterpulsation (SECP) that solved this fundamental problem. They created a pneumatic system with four cuffs wrapped around the calves and lower. This configuration was later changed in 1983 with the addition of a set of upper-thigh cuffs, and SECP was renamed enhanced external counterpulsation (EECP). Pressures were applied first to the calf cuffs, then the lower-thigh cuffs, and finally the upper-thigh cuffs, "milking" the maximal volume of peripheral blood back up the aorta during diastole, increasing coronary perfusion pressure when the heart is relaxing with minimal coronary flow resistance. Then the pressures were released simultaneously at the onset of systole, leaving behind an empty peripheral vascular bed to receive ejecting blood from the heart, increasing cardiac output. During the 1980s, EECP became a very popular therapeutic procedure in China, available in more than 1,800 medical institutes in 1990; and by 1996, there were 4,000-6,000 systems installed in 3 to 4 thousand facilities.

In 1988, Zheng and Lawson, Hui and Soroff began their EECP studies in the United States to treat patients with refractory angina pectoris using a protocol of 1 or 2 hours of EECP daily with 35 hours as a complete treatment course. Their studies provided evidence that EECP is effective in both short-term and sustained relief of angina symptom, increasing exercise capacity and quality of life in approximately 70-80% of treated patients, and provide sustained improvements in perfusion to ischemic areas of the myocardium. Currently, outside of China, there are more than 1,200 EECP systems in 23 countries with more than 120,000 patients benefited from EECP treatment.

Future development of EECP will improve design of the cuffs to fit more tightly around patient body to reduce the volume of compressed air required to empty the peripheral vascular bed, reducing the size and electrical power consumption of EECP systems and provide more comfort to the patients. Improvement should also be made to provide automation timings for inflation and deflation with several safety features to reduce the risk of inflation during systole, with appropriate inflation and deflation pressures.

**Clinical evidence of safety and effectiveness**

Even though EECP is noninvasive, it does not mean that it is without risk, especially for patients with coronary heart disease. Safety of EECP depends on proper timings in compressing the peripheral vasculature with appropriate pressures. The trigger signals should truly be in synchronization with cardiac cycle, the inflation pressure wave should reach the aortic valves at the end of systole, the deflation should start before isovolumetric contraction, inflation pressure should be at least 50 mm Hg higher than arterial pressure and deflation pressure should be lower than venous pressure. Fortunately there are very few reports of major adverse cardiovascular events in the literature. It is reasonable to conclude that with caution in selecting and treating patients, EECP is safe.

In the 1960s to 1970s, there were many papers using ECP in the treatment of AMI and cardiogenic shock in the United States, with definitive hemodynamic effects but mixed clinical results. This variability may be due to technical difficulties of using hydraulic systems. ECP took a hibernation period in the United States while the technical problems were solved in China with the introduction of sequential pneumatic activated EECP systems. During the 1980s to 1990s there were numerous case reports documenting EECP therapeutic effectiveness in China treating many different types of ischemic diseases, from coronary heart disease, renal, cerebral, retinal, hearing dysfunction, to treatment of risk factors such as hypertension and diabetes. Unfortunately many of these case reports had no control groups, lack in strict criteria in selecting patients, including inclusions and exclusions. Further studies to confirm the results of these case reports are necessary.

In 1992, the first paper using EECP in the treatment of angina pectoris patients documented by improvement in radionuclide perfusion stress tests and exercise tolerance was published in the United States. Since then there were more than 150 papers published with approximate 200 presentations in major scientific meetings. There were two major randomized control studies, the MUST-EECP for angina pectoris patients and the PEECH trial for heart failure patients. In addition, there were two registries with 5,000 and 3,000 patients documenting the demographics, medical history, risk factors and changes in Canadian Cardiovascular Society (CCS) functional class, nitroglycerin usage and quality of life pre- and post- EECP with 2-3 year follow-up. EECP is used in the United States mainly for the treatment of patients suffering from refractory angina. EECP has been proven to be effective in reducing at least 1 CCS class in 80% of the patients and the effects sustained...
for up to three years.

During the past five years, extensive research efforts were carried out in search of the mechanisms of action of EECP globally. Investigators in China have completed some fundamental animal studies demonstrating long term application of EECP produces vasculoprotection effects by improving endothelia function in releasing nitric oxide to control vascular tone, balancing neurohormonal factors, promote microcirculation development, reduces inflammatory reaction and attenuates atherosclerotic process. Investigators in Switzerland and Germany reported 30-35 hours of EECP treating patients with chronic stable angina improves coronary collateral growth.19, 20 Investigators in the United States and Israel reported EECP therapy in angina patients reduces arterial stiffness, blood pressure and stimulated the release of endothelial progenitor cells.17, 18 These mechanisms provide evidence paving the path of EECP as a preventive therapy for cardiovascular disease in the future.

Society adaptation and acceptance

EECP therapy has a long history of development, with evidence to support its safety and effectiveness, and has been very popular in China in the 1990s, the critical question is why then EECP has not been accepted as a routine clinical treatment of cardiovascular disease globally? The answer to this question is not readily available, and analysis of some of the circumstances surrounding this issue may be helpful:

Clinical applications

The popular rise of EECP therapy in China during the 90's using it to treat not only coronary heart disease but many other diseases such as cerebral thrombosis, transient ischemic attack, embolism of retinal artery, ischemic optical neuropathy, traumatic optic nerve atrophy, idiopathic deafness, etc.31 These applications without sufficient scientific and clinical evidence of safety and effectiveness may be too widespread. Even though there were case reports showing EECP was effective in treating these diseases, there was a lack of high quality data on safety and effectiveness as well as dosage (how many hours and how often should EECP be used?). This practice may have pushed EECP therapy in China too far, causing a loss of confidence in its use. The other side of the coin is the restrictive use in the United States and the rest of the world. EECP is used only for patients with refractory disabling angina not readily amenable to invasive revascularization intervention in spite of optimal medical therapy. This restrictive use is due to the Centers for Medicare and Medicaid Services (CMS) and many insurance companies in the United States covering EECP therapy only for patients who have been diagnosed with refractory angina. Consequently EECP has not been accepted widely because of this restrictive coverage.

Equipment and regulatory requirements

Even though the Food and Drug Administration (FDA) in the United States has cleared EECP for use in stable and unstable angina pectoris, AMI, cardiogenic shock and congestive heart failure, there is really no standards issued on the performance requirements of the equipment used for the administration of EECP. The same situation exists in the rest of the world including China. This variability in equipments produced by various manufacturers has led to a lack of quality control with poorly designed ECP equipments that may not delivered optimal EECP, compromising the safety and effectiveness of EECP treatment.

Cost effectiveness

The main cause leading the decline of the number of EECP systems currently being used routinely in China to less than 10% of that at the peak of its popularity is probably due to the reimbursement rate which is only ¥25-¥80 RMB ($4-$12 USD) per hour, substantially far below the cost of providing such treatment. The reimbursement rate in the United States is an average of $140 - $180 US dollars per hour. But the restriction imposed on coverage only for refractory angina patients has made EECP therapy as a treatment to troublesome to give, requiring cardiologists to constantly struggle to find patients satisfying the coverage requirements.

The Future

There are only two randomized controlled clinical trials reported in the literature, one on angina (MUST-EECP) and one on heart failure (PEECH).36, 38 Almost all the papers published in the English language are related to refractory angina and heart failure, therefore it is important to launch more randomized controlled trials to examine the safety, effectiveness and treatment protocol (dosage - frequency and hours) of EECP therapy in the treatment of other cardiovascular disease such as cerebrovascular disease including stroke, chronic kidney disease including effects of patients on dialysis and in the prevention of progression of cardiovascular disease in patients with endothelial dysfunction, a predictor of future cardiovascular events.

The cost of health care in all countries is escalating at a very fast rate. It is important for government to invest in research and encourage reasonable coverage in therapies that can save health care cost. EECP has been shown to reduce hospitalization of heart failure patients from an average of 3.6 hospital visits/year before EECP to 0.5 hospital visit/year post EECP, a reduction of 3 hospital visits/year.44 The average cost of each hospital visit is $5,456 US dollars, the cost of average EECP treatment is $3,640, resulting an annual saving of $10,000 per heart failure patient. There are 5.7 million heart failure patients in the US, assuming half of them require the same hospitalization rate as our study, saving 28 billion dollars.
In another study, the average hospitalization rate for 1,015 refractory angina patients with 95% in CCS functional class III and IV was 1.85 patient/year. Post-EECP hospitalization rate was 0.63/patient/year, giving a hospitalization rate reduction of 0.22/patient/year. The average hospitalization and physician charge in the US was $17,995, and the average EECP treatment cost was $4,880, yielding an annual cost savings/patient of $17,025. Estimates of total savings were calculated by the product of cost savings/patient and the low and high estimates of the prevalence of refractory angina (low: 422,000 patients; high: 1,273,000 patients). This calculation translated the total annual hospitalization cost savings as a potential 7,185 million to 21,673 million dollars. Therefore it is important for government and insurance companies to fund studies examining the cost saving in the use of EECP to prevent the progression of cardiovascular disease.

In conclusion, the evolution of external counterpulsation therapy from temporary circulatory assist device for AMI patients to a therapeutic device in the treatment of coronary heart disease, and with recent findings on the mechanisms of action, EECP may be effective in the prevention of cardiovascular disease progression and reduction of health care cost.

**Reference**


