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·研究报告· ·Review·

The Past, Present and Future of External Counterpulsation

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Abstract: Enhanced external counterpulsation(EECP) was developed in our laboratory and applied in clinical setting since 1976. Before the year of 1990, the mechanism of this treatment was supposed to promoting collateral circulation by increasing diastolic pressure during counterpulsation. According to a series of investigations, we discovered and confirmed that the flow shear stress were increased obviously during EECP, regulating a series of reaction of shear stress responsive elements, inducing vascular endothelial cell (VEC) repair mechanism, improving VEC function, all of which contribute to the inhibition of development of atherosclerosis. A new generation of EECP device was designed based on the advances above and aimed at promoting the aterial flow shear stress more effectively in turn to protect vascular endothelium.

Key words: collateral circulation; EECP; atherosclerosis; vascular endothelial cells

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体外反搏的过去现在与将来

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摘 要:体外反搏技术于 1976 年首先在我院创立。上世纪 90 年代之前,体外反搏作用机制主要定位在提高动脉舒张压,促进侧枝循环建立,进而改善器官组织的缺血状态。近年来经过大量的基础研究和临床观察证实,体外反搏在增加器官组织血流灌注的同时,还通过促进动脉血流加速,提高血流切应力,从而具有保护血管内膜,促进损伤血管内皮细胞的结构与功能修复,从而抑制动脉粥样硬化的发生与进展。这些作用被认为与体外反搏促进了血管内皮相关基因的表达与调控有关。基于上述基础理论的最新研究成果,我们研制成功了更有效地提高血流切应力,更适宜于保护血管内膜功能的新一代体外反搏装置。

关键词:侧枝循环; 增强型体外反搏; 动脉粥样硬化; 血管内皮细胞

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In the year of 1972, our hospital, the First Affiliated Hospital of SUN Yat-sen University, organized an Assisted Circulation Team. The first project to start with was the intra-aortic balloon pumping (IABP). After three years of intensive research, design, development and testing, an IABP device went into clinical trial in 1975. During the course of research and animal experiments, we discovered an important finding. We measured the coronary peripheral pressure (CPP) by inserting a

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plastic tube toward the distal end of the descending artery. CPP is an indication of the force promoting the coronary collateral circulation. We found that: the higher the diastolic augmentation, the greater the coronary peripheral pressure. That means augmenting the diastolic pressure will increase coronary collateral circulation. This effect could be clearly seen by selective coronary angiography after autopsy. Based on this finding, we truly believed that the counterpulsation could be a good method for promoting coronary collaterals and salvaging the ischemic myocardium. However, IABP is an invasive method, understandably rejected by most patients at that time. We decided to find a non-invasive method to implement the counterpulsation.

One of the first non-invasive counterpulsation devices was developed in Harvard University during early 1960's. And it became a product in the year of 1970's, named "Cardiassist". They used a hydraulic driving system, in which the pressures were applied only on the legs and thighs simultaneously (non-sequential). The diastolic augmentation could only reach the level of systolic pressure, and the systolic pressure could not be reduced.

Based on the knowledge we learnt from IABP and the lessons from the first set ECP in 1970's, we developed a four-limb sequential external counterpulsation (SECP) device in 1975, and started to use it in a clinical setting in 1976 [1,2]. This was the first generation of our ECP device. In the years to come, we have made more improvements along the way. The first one was the addition of upper-thigh balloon. In our research and experiments on dogs, we found that the lower-leg muscles of dogs were too thin; we had to apply pressures on not only their thighs, but also the biggest muscles-their upper-thighs. Coincidentally, we observed a significant improvement in diastolic augmentation. This encouraged us to develop an upper-thigh balloon for human being. Subsequent clinical trials had confirmed that the diastolic augmentation from "SECP with added upper-thigh balloon" was in fact 45.8% higher than that from SECP alone. In 1983 we renamed the term "SECP with added upper-thigh balloon" to "Enhanced External Counterpulsation" (EECP), and EECP was used in all of our publications since then[3,4]. Nowadays, EECP has been served as a worldwide standard term indicating Enhanced External Counterpulsation and introduced into ACC/AHA Guidelines for the management of chronic stable angina[5,6]. In fact, most ECP devices in the world today are pneumatic systems in which pressures were applied to the legs, thighs and upper-thighs in a sequential manner.

1 EECP in China- From Bench to Bedside

From year 1978 to 1988, the popularity of EECP therapy has increased tremendously in mainland China[7]. There were about 4 000 machines spread all over the country during that period mainly due to the following reasons: ①EECP therapy is really an effective, non-invasive and safe treatment for the most patients in China. It is also very cost effective and simple to use. All these make it rather easy for general population in our country to be accepted. ②In addition to coronary heart disease (CHD), a number of ischemic diseases of other organs had been treated successfully by EECP treatments as well. These include cerebral thrombosis, transient cerebral ischemia (TIA), embolism of central retinal artery, ischemic optical neuropathy, central serous chorio-retinitis, traumatic optic nerve atrophy, idiopathic deafness, etc. As we all know, until now, there are no satisfactory therapies available for these diseases and it is encouraging to find relief of these diseases from EECP treatments. ③Prior to 1986, China did not have patent laws or a patent administration system. There were more than 10 manufacturers copying or imitating our EECP device and sold them over the country. As good as it did to the popularity and visibility of EECP; it also presented a huge problem for quality control and caused a lot of confusions and misconceptions. The capability of design and manufacturing, quality control and services of these manufacturers were so poor, 80% of these machines could not last for more than 3 to 4 years.

Despite the wide acceptance of EECP in China, there are a number of issues and challenges. The biggest one that hinders the development of EECP in this country is the financial problem that EECP providers face. During the past 25 years the living expenses has risen about 15 times. The prices for the existing medicines and therapies including EECP treatments in public hospitals, however, were restrained. For example, patients who were treated with EECP therapy were only allowed to be charged for $50 RMB per hour (that is only four times higher than that of 1970 's). That equals to $6 USD/h. This incredible price drives nobody can keep providing EECP services without incurring a deficit. How can the 4 000 centers survive on that?! We can do it for the sake of a good treatment for our patients, for the conscience of a doctor, for the development of medical sciences, but it is very hard to sustain. Therefore, today, as far as I know may be less than 10% of the 4 000 machines still exist in medical center or hospitals in China.

During the years from 1995 to 2000, to evaluate the effectiveness and safety of EECP treatment for patients with CHD, a multi-center study including five teaching hospitals in Beijing, Shanghai and Guangzhou was organized by the central government of China. This is a prospective, randomized trial, in which all 473 patients had been confirmed CHD by either coronary angiography or having prior history of acute myocardial infarction (AMI) 3 months before. Compared with conventional medical management only, EECP combined with conventional medical management could be better in improving myocardial ischemia, decreasing nitroglycerin consumption, promoting coronary collateral formation and improving 12-months survival in the patients with stable angina post myocardial infarction or silent ischemia.

One of the areas we have been focused on was the effect of EECP on morphological and functional changes of the vascular endothelium. Since 1994 we had calculated the shear stress by measuring the flow rate on the carotid artery of dogs [8-13]. It has been observed that the mean shear stress during EECP procedure is typically 54.5% higher than that of the base line. The increase in peak value of shear stress during counterpulsation is 87.5%. These levels after the increase are still within the normal physiological range (around 50 dyne/cm^2). During the past ten years, we have evaluated a series of vaso-active substances (NO, ET-1, PGI2, TXA2, cAMP, cGMP, Ang-II, etc) from numerous patients, pre- and post-EECP, most of which showed positive correlations to EECP procedures even though it is not conclusive[14-23].

Based on our strong background of EECP basic research and clinical practice, a recent study on porcine models of atherosclerosis ($n=63$) has documented that the therapeutic effects of EECP on cardiovascular diseases lie not only in increasing coronary blood flow and promoting coronary collaterals, but in increasing shear stress of blood flow, regulating a series of reaction of shear-stress-responsive elements, inducing VEC repair mechanisms, improving VEC functioning, all of which contribute to the inhibition of the development of atherosclerosis[24-26]. In our study, we have conducted modern cellular/molecular biological techniques such as in vivo experiments, gene chips, proteomics, and successfully verified the correlation between gene expression of VEC regulated by EECP and EECP treatment duration, in which prolonged EECP treatment duration will result in a decreased inflammation-related and apoptosis-related gene expression. Variation of gene expression spectrum also indicates a time-duplicate effect of EECP on its atherosclerosis-inhibiting profile. Meanwhile, in vivo animal experiments have yielded findings that long-term EECP therapy has potential anti-atherosclerotic impact on VEC via improvement of cell functioning, enhancement of anti-oxidation, down-regulation of mechanosensitive proteins, decreased VEC uptake of LDL, and down-regulation of inflammatory cytokines.

It is also reported that there were 8 different VEC-related proteins exhibiting enhanced expression after EECP. Some of the proteins play certain roles in energy metabolism and apoptosis of cells; the others are closely related to lipid metabolism. It is deducible from these findings that long-term EECP therapy has therapeutical potentials via its impact on VEC which can be summarized as its alteration of VEC gene expression, participation in cellular growth and material/energy metabolism, modification of cellular adhesion and immune/inflammatory reaction, inhibition of VEC apoptosis, and attenuation of intracellular lipid disposition.

2 EECP in United States and the Rest Countries of the World

In 1983, We published two EECP papers in United States, which reported this non-invasive technique for the treatment of CHD and its clinical success in China [1,2]. Then it was reported in detail in a United States medical journal "Cardiovascular News" (Vol.2 No.9 1983). This led to Dr. Soroff visit in China in 1986 and led to initiation of clinical evaluation in patients with disabling angina pectoris at State University of New York at Stony Brook in 1989. Their clinical results shown that: After EECP, all patients experienced substantial improvements in anginal symptoms even when medical and surgical treatments had failed. Well tolerated in all patients, no complications occurred. Significantly reduced frequency and severity of anginal attacks. Resolved reversible ischemic defects (by 99mTc SPECT imaging). Increased exercise tolerance during maximal stress testing. Reduced or eliminated need for antianginal medications. Facilitated a more independent, mobile and active lifestyle. Benefits persisted for at least five years after treatment (event-free survival in 61% of patients, comparable to PTCA and CABG).

In the year of 1995 to 1997, a multi-center study (MUST study) conducted by seven university hospitals in United States, 139 patients with stable angina were enrolled randomizely in active counterpulsation (AC) and inactive counterpulsation (IC) groups for comparison. The results shown that: EECP reduces angina and extends time to exercise-induced ischemia in patients with symptomatic CHD. EECP treatment was relalively well tolerated and free of limiting side effects in most patients [27-30]. Today, more than one thousand EECP devices were used in clinical setting in the United States and other 23 countries in the world.

3 The Future

It has been 30 years since the first external counterpulsation device in China was born. During this period, EECP technology has gone through clinical tests and practices, and not only has it gotten proven track records in treating ischemic diseases of organs, more importantly, its surprising effects of providing systemic anti-atherosclerosis has also been discovered. As we now know, the restoration of endothelial dysfunction is achieved by morphological and functional changes of vascular endothelium that comes with increasing flow shear stress on blood vessel with external counterpulsation procedures[31].

So what do I see in the crystal ball in the years to come?

From a business standpoint, EECP technology is still searching for a right path in China today. It has some short term challenges and obstacles to overcome. But in the long run, EECP technology will become more mature. The new generation of EECP device was designed to aim at promoting the flow shear stress of the blood; it will be highly intelligent; safe and easy to use even for average consumers. They will be quieter, smaller, and more robust and fit right into not only hospital environment where ischemic diseases can be treated, but also smaller clinics, gyms, health clubs and even average households. EECP can have far reaching impacts on preventive medicine and the prolonging of human lives.

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