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Enhanced External Counterpulsation in the Management of Patients with Cardiovascular Disease

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Summary: Studies over the past several decades support the hypothesis that enhanced external counterpulsation (EECP) can provide long-term benefits in patients with angina secondary to chronic coronary disease. Numerous non-sham controlled trials have recently been substantiated by a multicenter, randomized trial. Although the mechanism by which this mechanical treatment effects an alteration in cellular processes within the myocardium remains unclear, recent scientific investigations suggest that shear stress induced by chronic exposure to EECP might result in the release of a variety of growth factors and the subsequent stimulation of angiogenesis in the coronary beds. Ongoing clinical trials in patients with significant left ventricular dysfunction, an international registry, and additional clinical trials may help to elucidate further the role of this novel and unique therapy in our clinical armamentarium.

Key words: enhanced external counterpulsation, angina, shear stress

Introduction

Cardiovascular hemodynamics are regulated by a complex relationship between myocardial contractility and the load against which the heart must work. In the normal heart, this relationship is always in balance and the heart is able to adjust rapidly to changes in both contractility and load that occur during times of stress or changes in vascular volume and tone. However, with the onset of disease, the ability of the heart to maintain these homeostatic balance is often compromised, making therapeutic interventions more difficult. For example, in patients with ischemic heart disease, the myocardium benefits from a decrease in peripheral vascular resistance since contractility is increased and energy expenditures are lowered. However, this decrease in afterload diminishes diastolic pressure and in so doing decreases diastolic flow through the already narrowed coronary vasculature. For nearly half a century, investigators have tried to develop techniques that could lower cardiac afterload while at the same time increasing diastolic coronary flow in patients with acute and/or chronic coronary syndromes. This discussion will review the development of enhanced external counterpulsation (EECP), a potentially novel technology for accomplishing these complex goals.

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Historical Perspective

The concept of counterpulsation was introduced in the U.S. in 1953 when Kantrowitz first proposed that elevations of aortic diastolic pressure could improve coronary blood flow and could benefit patients with coronary insufficiency.[1] Although subsequent studies suggested that counterpulsation would indeed benefit some patients with coronary insufficiency, the development of the necessary technology proved challenging.[2] A group of devices that increased coronary blood flow, including flow assist devices and venoarterial bypass systems, proved effective in providing increased coronary blood flow but were unable to reduce the tension time index or work load of the heart.[3,4] More recently, external cardiac massage, internal cardiac massage, venoarterial bypass, implantable auxiliary ventricles, intra-aortic balloon pumps, and cardiopulmonary bypass have all demonstrated hemodynamic benefits; however, their usefulness in clinical practice has been limited because of their inherent invasiveness.[5–8]

In the mid 1960s, several groups began to explore a noninvasive method for producing the salutary physiologic effects of counterpulsation.[9–12] Initial equipment consisted of a hy-

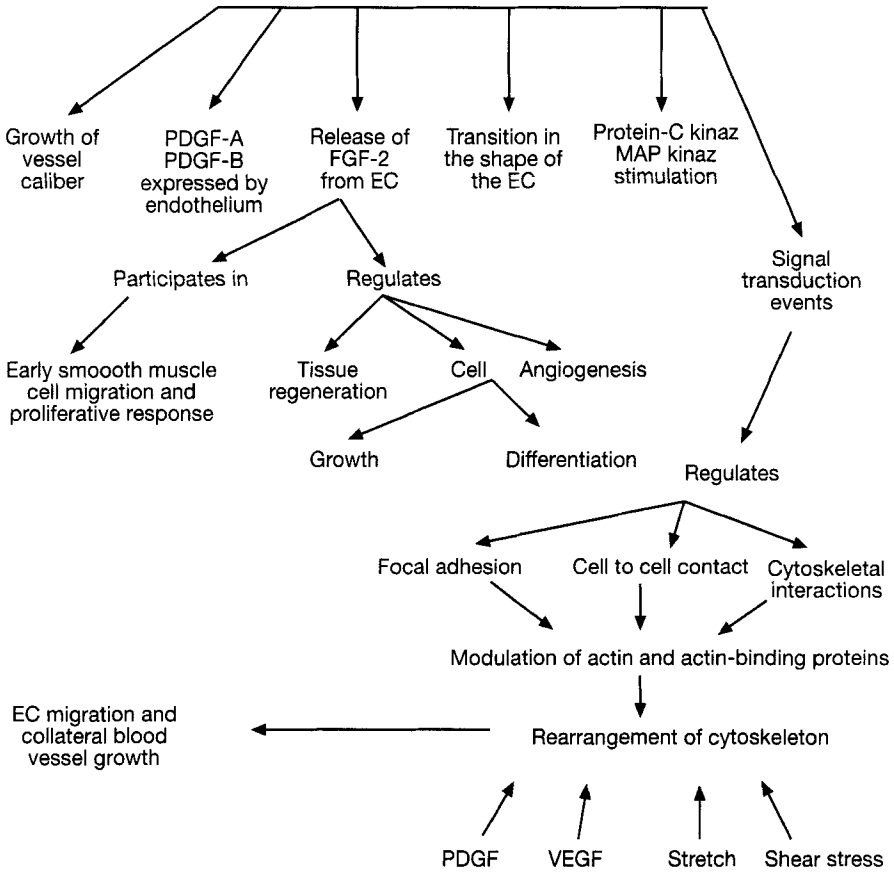

FIG. 1 Biological process affected by shear stress. PDGF = platelet-derived growth factor, FGF = fibroblast growth factor, EC = endothelial cell, VEGF = vascular endothelial growth factor.

draulically driven unit with a pair of water-filled bladders that could be wrapped around the lower legs and thighs of the patient.[13] However, the external pressure could only be applied to a limited amount of tissue mass thereby producing suboptimal diastolic augmentation of coronary flow.[14] However, in 1975, Zheng *et al.* began the development of an air-driven EECP system consisting of three sets of balloons wrapped around the lower legs, thighs, and upper thighs of the patient (Fig. 1). Air pressure was applied sequentially from the lower legs to the thigh and upper thigh resulting in "milking" of oxygenated blood from the lower extremities toward the heart with greater efficiency.[15] It has been demonstrated that the sequential inclusion of the upper thigh provided a critical advantage to EECP, effecting a 44% increase in diastolic augmentation compared with studies using only the lower extremity cuffs.[14, 15] Subsequent modifications of the EECP prototype with microprocessors allowed for precise cuff inflation and deflation and gating with the electrocardiogram. The lower cuffs were inflated at the start of diastole as represented by the beginning of the T wave, while simultaneous deflation of all three chambers was triggered just prior to systole at the onset of the P wave. The retrograde flow provided by EECP increased both the volume and pressure of diastolic flow such that diastolic to systolic ratios exceeded 1.2.[16]

Enhanced External Counterpulsation in Cardiogenic Shock

Cohen *et al.* compared the effects of EECP with intra-aortic balloon pumping (IABP) in normal experimental animals and in those with cardiogenic shock.[16] Although diastolic augmentation of the central aortic pressure pulse was achieved uniformly with both methods, EECP increased cardiac output to a greater degree. It effected a 25% increase in cardiac output in normal baboons and a 17% increase in baboons with cardiogenic shock. By contrast, IABP increased cardiac output by only 4% in normal animals and by 9% in animals with cardiogenic shock. Unfortunately, the role of EECP in patients with cardiogenic shock appears far less clear.[17] In two relatively small studies, IABP was far more effective than EECP in decreasing myocardial oxygen consumption although both techniques improved diastolic augmentation and cardiac index. However, EECP did not appear to have any beneficial effects on survival, whereas at least some of the patients receiving IABP demonstrated a reversal of the shock state.[18] Although the results were discouraging, both studies were performed without negative external pressure. The release of diastolic positive pressure or the application of negative pressure during cardiac systole might decrease the peripheral resis-

tance. Indeed, the use of EECP in the positive-negative mode was associated with a survival rate of 45% in patients with cardiogenic shock.[19, 20] However, this study utilized historical controls, and therefore the potential benefits of EECP in cardiogenic shock remain undefined.

Enhanced External Counterpulsation in Acute Myocardial Infarction

In 1972, Mueller *et al.* first studied the potential benefits of EECP in a group of patients with uncomplicated myocardial infarction. Enhanced external counterpulsation was associated with an increase in diastolic pressures and an increase in coronary blood flow.[21] Subsequently, Parmley *et al.* demonstrated that the combined use of nitroprusside and EECP provided benefits over and above those of either agent alone. The addition of EECP to nitroprusside reversed the decrease in the diastolic arterial pressure that was produced by nitroprusside-induced vasodilatation and augmented the cardiac index.[22] Unfortunately, a series of subsequent studies, albeit small, were unable to demonstrate conclusively that EECP could salvage myocardium and/or improve survival.[23] Indeed, Triulzi *et al.* attempted to map the ischemic area in a group of patients with uncomplicated myocardial infarctions using precordial ST-segment mapping.[24] They found a reduction in the size of the ischemic area during EECP; however, this reduction was not observed 2 h after stopping treatment. Furthermore, in a group of 131 patients with acute myocardial infarctions, statistically significant improvements could not be seen in patients undergoing EECP. Although Zheng *et al.* were able to demonstrate improved ventricular function in patients with acute myocardial infarctions, this end point is of little importance in the present era because aggressive strategies for revascularization improve function and long-term outcomes.[25]

External Counterpulsation in the Treatment of Angina

Over the past decade, there has been an increasing number of patients with anginal symptoms, largely unresponsive to medical therapy, who are not candidates for either surgical or percutaneous revascularization procedures. These include but are not limited to patients with previous coronary bypass revascularization, patients with coronary lesions that are not amenable to percutaneous catheter-based procedures, and patients who have had restenosis of native vessels or in-stent restenosis. It is this group of patients who appear to benefit the most from EECP. As seen in Table I, a large number of studies has suggested the efficacy of EECP in the therapy of patients with chronic stable angina.[15, 26–29] Although the majority of these studies have been small and most have not included sham-treated controls, the results have been highly consistent. Indeed, the first sham-controlled study, reported by Clapp *et al.* in 1972, demonstrated improvement in functional classification, nitrate usage, and double product.[30] Subsequent studies have demonstrated the efficacy of EECP by measuring improvements in exercise tolerance, reduction in anginal symptoms, improvements in objective measures of ischemia as measured by thallium scintigraphy, and a 5-year survival comparable with patients undergoing coronary artery bypass grafting or percutaneous revascularization.[31, 32] It is important to note that in virtually all of these clinical studies EECP was safe and without major adverse effects when used in patients free of varicosities, peripheral vascular disease, lower extremity venous stasis, and pulmonary embolism.

TABLE I Review of studies in the treatment of angina

First author/ (Ref.)	Patient number	Treatment number	Angina relief	Improvement in thallium test	Exercise tolerance
Zheng (15)	200	16	97%	NA	NA
Karim (26)	38	36	86%	86%	78%
Lawson (27)	27	35	NA	78%	NA
Lawson (28)	18	36	89%	78%	94%
Banas (29)	21	5	81%	NA	81%

Abbreviation: NA = nonassessed.

Several important caveats regarding the use of EECP have come from this large number of clinical studies: (1) Improvement appeared to be related to the location and severity of coronary disease;[30] (2) relapse in symptoms was rare in patients with a positive response even after long-term follow-up;[31, 32] (3) patients with prior surgical revascularization appeared to have a higher incidence of improvement than did patients who had not been previously bypassed;[33] (4) EECP appeared most effective in patients in whom at least one patent conduit, either graft or native coronary, provided coronary flow to ischemic areas of myocardium;[34, 35] (5) favorable effects on anginal symptoms in patients with significant left ventricular dysfunction could be associated with improvements in both ejection fraction and myocardial perfusion;[36] and (6) positive effects were most evident in patients in whom diastolic augmentation was satisfactory.[29, 30] It is interesting that EECP was also associated with improvement in depression scores, a finding that was in marked contrast with the commonly negative psychosocial sequel of revascularization procedures.[37] Finally, although several early studies did not show benefits of EECP on left ventricular oxygen consumption, lactate metabolism or coronary sinus blood flow, these studies were limited by the fact that EECP was only provided for four sessions.[38, 39] As will be discussed below, it would appear that the now commonly used algorithm of 35 consecutive 1-h sessions is required for effective therapy.

Although a substantial number of clinical trials supported the usefulness of EECP in the therapy of patients with chronic angina, these studies were viewed as being largely anecdotal because of their relatively small size and lack of a sham control. Therefore, for the more definitive assessment of the efficacy of EECP in the therapy of patients with unremediable angina, a trial was designed to assess the effects of EECP in a randomized and sham-controlled study. Outpatients ($n = 139$) with documented symptomatic coronary artery disease and

positive exercise treadmill tests were enrolled in this study. Of these, 71 patients were randomized to EECP treatment while 66 were randomized to a sham group. Patients underwent 35 h of either active counterpulsation or inactive counterpulsation (sham). Outcome measures were exercise duration and time to > 1 mm ST-segment depression, average daily anginal attack count, and nitroglycerin (NTG) usage. Time to >1 mm ST-segment depression increased significantly in active compared with inactive counterpulsation. In addition, patients receiving active counterpulsation experienced a decrease in the incidence of angina episodes compared with patients receiving therapy with inactive counterpulsation. Furthermore, NTG usage decreased in the active-counterpulsation group. Thus investigators concluded that EECP could reduce angina and extend the time to ischemia on exercise treadmill tests in patients with symptomatic CAD.[40]

Hemodynamic Effects of Enhanced External Counterpulsation

The benefits of balloon counterpulsation have been well described, and the hemodynamic effects that it imparts in acute coronary syndromes, as an adjunct to angioplasty and in patients with congestive heart failure, are well recognized. Because invasive monitoring accompanies balloon counterpulsation, the immediate effects of augmented diastolic pressure, increased cardiac output, and afterload reduction can be documented. By contrast, the hemodynamic effects of EECP cannot be readily measured by traditional hemodynamic monitoring. The presence of the EECP balloons around the limbgirdle precludes invasive monitoring via the femoral artery or veins, and the increased venous return to the heart raises concern about the safety of venous balloon-tipped catheters in the pulmonary artery. Thus, investigators have relied on plethysmography to record the hemodynamic effects of EECP. Recently, we studied the effects of EECP on arterial flow velocity by studying flow in internal mammary arteries using transthoracic Doppler echocardiography. A patent internal mammary artery has flow characteristics similar to those of coronary arteries and therefore allows us an opportunity to study the effects of counterpulsation (either by IABP or EECP) on arterial flow noninvasively. These studies suggested that both IABP and EECP provided a comparable increase in coronary flow. In contrast to IABP, EECP can provide a chronic increase in coronary flow and, by virtue of this increased flow, an appreciable increase in coronary shear stress.[41]

Possible Mechanisms Accounting for the Beneficial Effects of Enhanced External Counterpulsation

Although the exact mechanism by which EECP improves symptoms in patients with chronic angina remains undefined, recent studies suggest that EECP might increase the development of collateral circulation with subsequent improvement in myocardial perfusion. Zheng *et al.* studied the effects of IABP in dogs with chronic ischemia secondary to coronary ligation. Intra-aortic balloon pulsation induced an increase in the mean peripheral pressure of the coronary artery that was proportional to the diastolic augmentation, an increase that could be explained by an increase in the collateral circulation. Indeed, postmortem angiography of the coronary arteries of these dogs demonstrated collateral development in dogs whose diastolic augmentation (DA) was in the range of 120 to 146 mmHg but was not increased in dogs whose DA was in the range of 103 to 110 mmHg—levels that were near systolic pressure.[42]

The hypothesis that EECP could improve symptoms by increasing the development of collaterals in the coronary circulation is supported by a variety of basic science investigations that strongly suggest that shear stress in the coronary circulation is a potent activator of pathways involved in angiogenesis. Liebow *et al.* noted that blood flow and/or flow-oriented stress affected the growth of vessel caliber.[43] In developing chick embryos, the pathways of the fastest blood velocity became the main arteries while those with slower velocity atrophied. Indeed, vascular sheer stress is maintained at an optimal level by an autoregulatory mechanism consisting of acute changes in constriction or dilatation and chronic changes in vessel caliber.[44,45] The essential autoregulatory mechanisms appear to be mediated at the level of the endothelium.[46] Recent investigations demonstrate that, in response to shear stress, the endothelium expresses platelet-derived growth factor A and B (PDGF), a mitogen for smooth muscle cell, and a vasoconstrictor that mediates vascular remodeling through smooth muscle cell and connective tissue growth.[47,48] Shear stress also effects a transition in the shape of the endothelial cell from a polygonal to an elongated shape with the long axis of the cell parallel to the direction of flow.[49] However, the strongest link between shear stress and angiogenesis comes from the recent demonstration that mechanical strain tightly controls fibroblast growth factor-2 (FGF-2) release from both vascular smooth muscle and endothelial cells.[50–53] Fibroblast growth factor-2 regulates a variety of cell responses including growth, differentiation, tissue regeneration, and angiogenesis and participates in the early smooth muscle cell migratory and proliferative responses that are important in both angiogenesis and the response to arterial injury.[54] Shear stress also stimulates protein kinase C and MAP kinase activities in endothelial cells, signal-transduction events that may be important in regulating focal adhesions, cell-to-cell contacts, cytoskeletal interactions with plasma membrane, and nuclear membrane structures.[55] Modulation of these signal transduction pathways might also be important in modulation of actin and actin-binding proteins which could lead to rearrangement of the cytoskeleton.[56]

A primary step in the development of vessel growth is the migration of endothelial and smooth muscle cells. This migration is facilitated by the actin cytoskeleton. Changes in the actin cytoskeleton can be induced by many stimuli including growth factors such as PDGF, VEGF, and mechanical stimuli such as stretch and shear stress. These stimuli appear to be mediated by tyrosine kinase-dependent pathways within the

endothelium. Once activated, the tyrosine kinase receptor phosphoylates a group of submembraous proteins in the endothelial cell which induce changes in the actin cytoskeleton that are necessary for endothelial cell migration and hence for collateral blood vessel growth. Thus, the increased velocity of flow provided by EECP may provide a level shear stress that can act as a mechanical stimulus to direct alterations in the actin cytoskeleton or effect changes through the expression of growth factors. This hypothesis is supported by the finding that patients responding to chronic therapy with EECP had a significant increase in circulating VEGF, another closely related vascular growth factor;[57] however, further evaluation of the relationship between EECP and the initiation of vascular growth and remodeling is required.

Conclusion

Recent data suggest that EECP may provide a novel adjunctive therapy for patients with stable angina secondary to coronary artery disease. Although the mechanism responsible for the beneficial effects of EECP remain undefined, recent evidence from basic science investigations suggests salutary effects of EECP-induced sheer stress on the coronary vasculature. It is hoped that ongoing studies will expand our understanding of the mechanism responsible for effects of EECP as well as for defining additional patient populations that might benefit from this technology.

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