

Angiogenic therapy: is it still viable?

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Abstract

Coronary collateral vessels are an alternative source of blood supply to myocardium jeopardized by ischemia. Well-developed coronary collateral arteries in patients with coronary artery disease (CAD) mitigate myocardial infarcts and improve survival. Coronary collateral flow can be assessed only during vascular occlusion of the collateral-receiving artery. The reference for coronary collateral assessment is the measurement of the intracoronary occlusive pressure-derived collateral flow index (CFI) expressing collateral flow as a fraction of flow during vessel patency. Approximately one out of five patients with CAD cannot be revascularized by percutaneous coronary intervention or coronary artery bypass grafting. Therapeutic promotion of collateral growth is a valuable treatment strategy in those patients. Promotion of collateral growth should aim at inducing the development of large conductive collateral arteries (ie, arteriogenesis) rather than the sprouting of capillary-like vessels (ie, angiogenesis). Collateral function expressed as CFI, and thus arteriogenesis, is effectively promoted by the activation of monocytes/macrophages by means of granulocyte colony-stimulating factor or of augmenting coronary arterial shear force.

Keywords: Angiogenesis; arteriogenesis; collateral circulation; coronary circulation

■ Heart Metab. (2013) 58:20–24

Introduction

Cardiovascular diseases are the leading cause of death in industrialized countries. In Europe, annual mortality from all causes in the general population amounts to approximately one per 100 inhabitants, one person out of 200 dies from cardiovascular disease, and one out of 300 experiences CAD and its consequences. Established options for revascularization in CAD include angioplasty and surgical bypass, both of which are not suitable in approximately one out of five patients in whom the extent of coronary atherosclerosis is especially severe. In such patients, an alternative treatment strategy to revascularization is warranted both to control symptoms as well as to alter the course of advanced CAD. An ideal candidate to fill this therapeutic gap is the promotion of coronary collateral growth, ie, the induction of natural bypasses.

In this context, the question given in this paper's title on the viability of angiogenic therapy is vital. This review aims to outline the reasons for its lack of efficacy in the clinical setting, and to provide evidence for the usefulness of a conceptually more sound and thriving strategy for collateral structural promotion, that is, arteriogenesis.

Relevance of the coronary collateral circulation

The coronary collateral circulation has been recognized for a long time as an alternative source of blood supply to an ischemic myocardial area. More than 200 years ago, Heberden [1] described

a patient who had been nearly cured of his angina pectoris by sawing wood each day, a phenomenon called warm-up or first effort angina, which was traditionally ascribed to coronary vasodilation with opening of collateral vessels. There have been numerous investigations demonstrating a protective role of well, versus poorly, developed collateral arteries resulting in smaller myocardial infarcts [2], less ventricular aneurysm formation, improved ventricular function [2], fewer future cardiovascular events [3] and improved survival [4]. However, the functional relevance of coronary collateral vessels in humans has also been a matter of debate for many years [5]. Much of this controversy was probably due to inadequate means for gauging human coronary collateral function and to the investigation of populations too small to be representative of all the patients with CAD. In the absence of stenoses, it has been traditionally assumed that coronary arteries are functional end-arteries. Using direct and quantitative intracoronary collateral measurements (Fig. 1), it has, however, been documented that the notion of the human coronary circulation being built without preformed functioning anastomoses between vascular territories is a myth rather than reality. In the absence of obstructive CAD or even in entirely normal hearts, there is collateral flow to a briefly occluded coronary artery sufficient to prevent ECG signs of myocardial ischemia in one fifth to one fourth of the population studied [6]. In the context of therapeutically promoting the function of collaterals, the existence of such pre-formed anastomoses is crucial.

Therapeutic promotion

Therapeutic angiogenesis/arteriogenesis are strategies for revascularizing ischemic myocardial tissue by the formation/remodeling of “natural bypasses”, ie, collateral vessels. Understanding the basic steps and regulatory mechanisms of angio and arteriogenesis as opposed to vasculogenesis is important for designing such strategies.

Vasculogenesis

The initial steps for the formation of the vascular system during embryonic life involve the differentiation of mesodermal cells into angioblasts that give rise to endothelial cells forming the first primitive blood vessels [7].

Angiogenesis

New vessels can subsequently develop from the pre-existing plexus by sprouting and intussusception. This formation of new vessels has been called angiogenesis [8]. In addition to endothelial cells, pericytes (for capillaries) and smooth muscle cells (for larger vessels) are necessary for the maturation of these newly growing vessels [8]. Angiogenesis and arteriogenesis are not restricted to the growing organism. Tissue repair and regeneration, eg, wound healing and the cyclic changes of the female reproductive system, are manifestations of angiogenesis. New capillaries form around zones of tissue ischemia, as occurs in myocardial infarction and stroke. In the context of ischemia with hypoxia, growth factors such as hypoxia-inducible factor 1 α and inflammatory mediators are

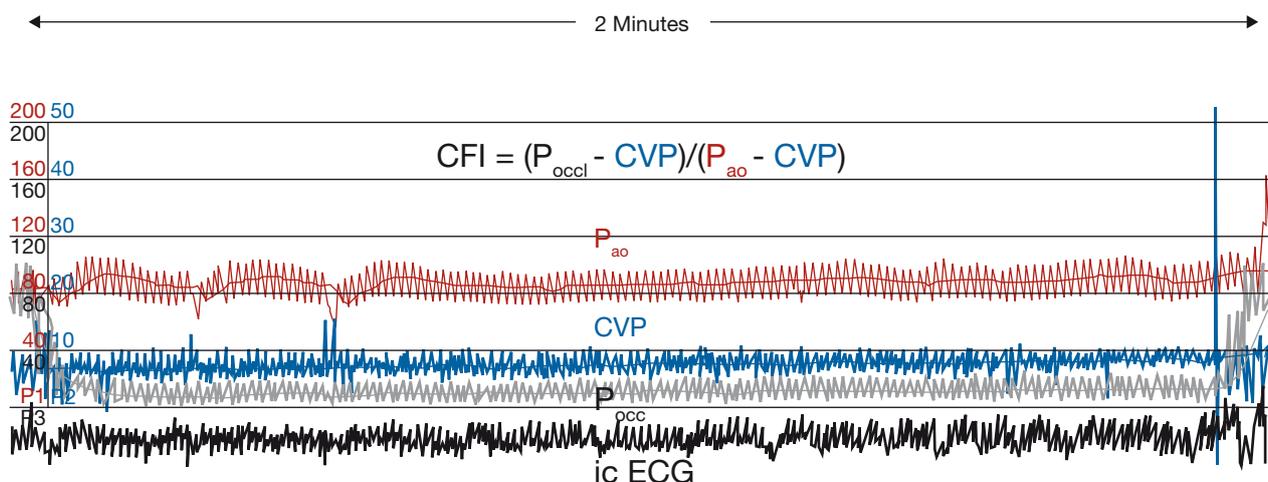


Fig. 1 Invasive measurement of coronary collateral flow index (CFI) by simultaneous recording of mean and phasic aortic pressure (P_{ao}), distal coronary occlusive pressure (P_{occl}) and central venous pressure (CVP). In addition, an intracoronary (ic) ECG is obtained during the 2-minute coronary occlusion.

released locally, leading to vasodilation, enhanced vascular permeability and the accumulation of monocytes and macrophages, which in turn secrete more growth factors and inflammatory mediators [9] (Fig. 2). These inflammatory cells release metalloproteinases that dissolve the surrounding matrix and the basal membrane of the preformed vessel. Hypoxia sensitizes the local endothelial cells to the chemotactic and proliferative effects of various growth factors by upregulating their receptors. Endothelial cells detach from their neighbors, migrate, proliferate and subsequently form a new vessel with a lumen. Pericytes and smooth muscle cells are also involved in this process.

Arteriogenesis

Invasive cardiologists have long been aware of the occurrence of large epicardial branch or septal collateral vessels after total or subtotal occlusion of a major coronary artery. These usually become visible within 2 weeks following an occlusion, and they arise from preformed collaterals. The remodeling process involved in this structural recruitment of already existing collateral vessels has been termed arteriogenesis [9, 10]. Large bridging collaterals are physically much more effective in salvaging ischemic myocardium than small peri-ischemia, ie, "angiogenic" capillaries. The complete obstruction of a coronary artery leads to a fall in post-stenotic pressure and to a redistribution of

blood to pre-existing, anastomotic arterioles originating from the nonischemic vascular region. The resulting longitudinal shear forces lead to an increased expression of certain endothelial chemokines, adhesion molecules and growth factors (Fig. 2). Within days, circulating monocytes attach to the endothelium of the bridging collateral vessels causing a local inflammatory reaction [9]. Matrix dissolution occurs and the vessels undergo a growth process with active proliferation of their endothelial and smooth muscle cells.

Growth factor candidates

A variety of physiological molecules has been identified that appear to promote angio and arteriogenesis. Most act by stimulating the migration and proliferation of endothelial cells and/or smooth muscle cells, like the family of fibroblast growth factors (FGF) and vascular endothelial growth factors (VEGF). Both cause vasodilation by stimulating the release of nitric oxide. It is, therefore, important in animal and clinical studies to differentiate between improved perfusion caused by mere vasodilation and true collateral growth. Other growth factor candidates include placental growth factor, angiopoietin 1, transforming growth factor β , platelet-derived growth factor and about half a dozen other cytokines, proteases and proteins [11,12]. Arteriogenesis has been shown to be induced by activated macrophages [13], by lipopolysaccharide [9], monocyte chemoattractant protein 1 [10], tumor necrosis factor α , FGF and also via granulocyte macrophage colony-stimulating factor (recombinant human GM-CSF; Molgramostim) [14].

Clinical studies

Angiogenesis may be induced by various promoters, such as VEGF and FGF, angiogenic agents most often used in current clinical studies [15, 16]. Although animal studies have established the principle that collateral function improves after delivering angiogenic growth factors [17], and although the first uncontrolled clinical studies have demonstrated the safety and feasibility of VEGF and basic FGF [18], efficacy data on angiogenic therapy have been scarce. The largest controlled clinical trials using VEGF165 (Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis; VIVA [19]) and FGF2 (Fibroblast Growth Factor Initiating Revascularization Trial; FIRST [20]) in 178 and in 337 patients with CAD, respectively, have not shown an effect on the study endpoints treadmill

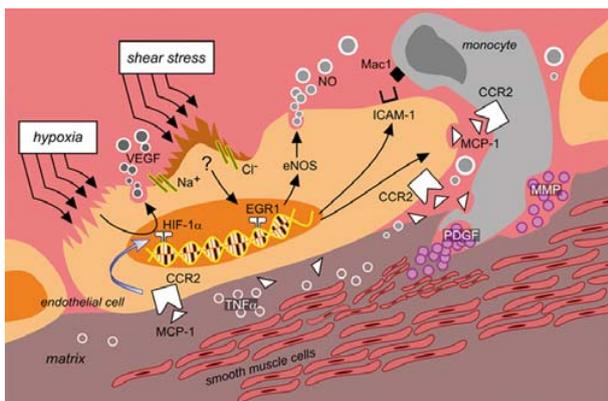


Fig. 2 Cartoon illustrating the hypothesized molecular pathways involved in human collateral growth. Reproduced from Seiler [12], with permission. CCR2, CC-motif chemokine receptor; EGR1, early growth response 1; eNOS, endothelial nitric oxide synthase; HIF-1 α , hypoxia-inducible factor 1 α ; ICAM-1, intercellular adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; TNF α , tumor necrosis factor α ; VEGF, vascular endothelial growth factor.

exercise time, angina pectoris at 60 and 120 days (VIVA) and, respectively, exercise tolerance test duration at 90-day follow-up and changes in the magnitude of myocardial ischemia by Tc99m single photon emission computed tomography. Negative results of angiogenic growth factors in promoting coronary collaterals have probably been due to the use of endpoints for their assessment that have been too blunt to discern subtle changes in collateral function. At this phase of clinical angiogenic therapy, during which screening for the most effective growth factor among more than a dozen candidates has not even properly begun, selection of the best agents ought to be based on accurate and direct invasive measurements of coronary collateral flow. Equally important, angiogenic factors may have been employed that induce the formation of small, high resistance capillaries (angiogenesis) rather than the large interconnecting arterioles (arteriogenesis) that are required for the salvage of myocardium in the presence of occlusive CAD. In two randomized placebo-controlled clinical trials, GM-CSF has been shown to be effective with regard to sequentially and invasively obtained collateral flow in patients with CAD [21, 22]. However, GM-CSF appears to be related to atherosclerotic plaque rupture and can, therefore, not be regarded as safe in the treatment of patients with CAD [22]. Granulocyte colony-stimulating factor has recently been shown to be effective in the promotion of collateral function in a controlled randomized trial among 52 patients undergoing baseline and follow-up collateral flow index (CFI) measurements (Fig. 3) [23].

Arteriogenesis is related to enhanced tangential shear forces at the vessel wall in response to increased flow through pre-existing collateral connections (Fig. 2). Therefore and aside from the biochemical stimulation of monocytes/macrophages, physical exercise would be a therapeutic option for inducing arteriogenesis, because cardiac output and thus coronary flow is elevated along the arterial branches of the coronary circulation during exercise. So far, a prospective investigation in humans on the effect of exercise regarding collateral growth has employed an insensitive instrument for collateral assessment, ie, angiographic imaging of spontaneously visible collateral vessels, and has had negative results [24]. Data from our own laboratory suggest that even in the absence of CAD, collateral flow as assessed by intracoronary pressure-derived mea-

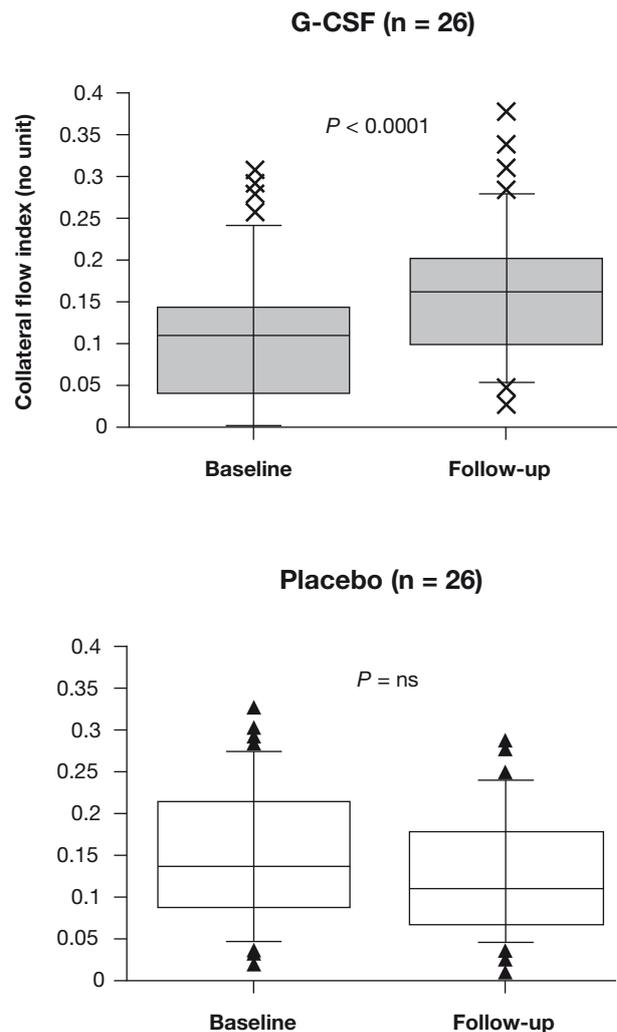


Fig. 3 Collateral flow index (vertical axis; box plot with median, 25% and 75% confidence intervals) obtained in stenotic as well as normal coronary arteries of patients before and after treatment (horizontal axis) with granulocyte colony-stimulating factor (G-CSF) (left panel) or placebo (right panel).

surements is augmented substantially in response to endurance exercise training [25]. Also, a study in CAD patients participating in a 3-month rehabilitation programme has shown improved collateral function in comparison to a sedentary control group [26].

An alternative mechanism to physical exercise of applying augmented vascular shear forces is based on external counterpulsation (ECP), which is synchronized to the ECG and executed during diastole. Encouragingly, the first controlled trial in a group of CAD patients undergoing a 30-hour programme of high-pressure ECP (300 mm Hg) and in a group undergoing sham ECP at 80 mm Hg inflation pressure has recently revealed an unexpectedly high increase in CFI between baseline and follow-up at 4 weeks (Fig. 4) [27].

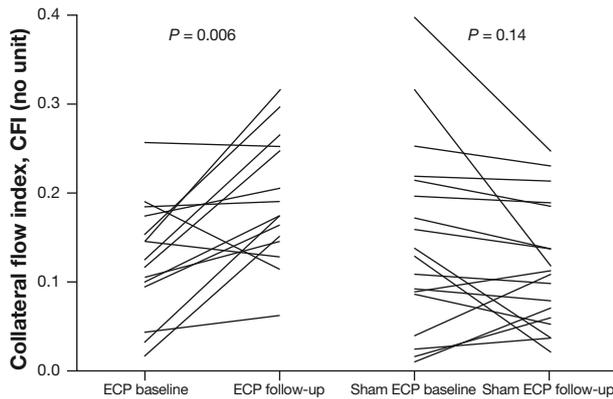


Fig. 4 Individual changes of collateral flow index (CFI; vertical axis) from baseline to follow-up measurement in response to external counterpulsation (ECP; left) and to sham ECP (right).

Conclusions

Therapeutic promotion of collateral growth is a valuable treatment strategy for patients with CAD. The promotion of collateral growth should aim at inducing the development of large conductive collateral arteries (ie, arteriogenesis) rather than the sprouting of capillary-like vessels (ie, angiogenesis). Collateral function is effectively promoted via the activation of monocytes/macrophages by means of granulocyte colony-stimulating factor or of augmenting coronary arterial shear force. •

Acknowledgments This study was supported by grants from the Swiss National Science Foundation for Research, grant no. 32003B_141030/1 and the Swiss Heart Foundation.

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