Coronary Collateral Growth and Its Therapeutic Application to Coronary Artery Disease

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There is a tremendous body of data concerning the coronary collateral circulation in both experimental animals and humans. The functional importance of a well-developed coronary collateral circulation has now been documented. The paradigm regarding the principal stimulus for coronary collateral growth has shifted from myocardial ischemia to increased shear stress at the site of pre-existing collateral arteries. Numerous experimental and clinical studies have contributed to elucidation of the mechanisms of coronary collateral growth. Stimulation of coronary collateral growth is an alternative therapeutic approach to patients with intractable angina pectoris who are not indicated for percutaneous coronary intervention and/or coronary artery bypass grafting. Pharmacological and mechanical modulations accelerating coronary collateral growth have been challenged. Because it is conceivable that a well-developed coronary collateral circulation attenuates myocardial ischemia upon exercise, further research addressing coronary collateral growth is needed in both experimental models of myocardial ischemia and human coronary artery disease.  (Circ J 2010; 74: 1283–1289)

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For a long time, the functional role of the coronary collateral circulation as a blood-conveying channel has been disputed. Because a well-developed coronary collateral circulation is usually associated with severe coronary stenosis, some investigators assumed that the existence of collateral circulation is a marker of coronary artery disease (CAD). Over the past 3 decades, accumulating evidence has documented that pre-existing well-developed coronary collateral circulation at the onset of acute myocardial infarction plays an important functional role in preserving left ventricular function, reducing infarct size, preventing left ventricular aneurysm formation and survival. Thus, a significant functional role of coronary collateral circulation is now well appreciated. In the past decades, we and others have emphasized the importance of arteriogenesis of the collateral vessels for enhanced coronary collateral circulation, compared with angiogenesis of the capillaries in areas perfused by occluded or critically stenosed coronary arteries. On the other hand, there has been considerable controversy concerning the stimulus for coronary collateral growth. It is now clear that long-standing high-grade coronary stenosis is mainly responsible for collateral vessel growth. Severe coronary narrowing results in myocardial ischemia and a pressure gradient between the providing and receiving coronary arteries across the collateral network. New establishment of a pressure gradient leads to recruitment of collateral blood flow and increased shear stress at the site of pre-existing collateral vessels. Thus, severe coronary narrowing is inevitably accompanied by 2 potential stimuli for the development of collateral circulation, namely, myocardial ischemia and shear stress.

One of the hot topics of coronary collateral growth is the role of bone-marrow-derived stem or endothelial progenitor cells in arteriogenesis. It is still controversial whether these cells contribute to collateral growth by supplying cytokines and proteases related to arteriogenesis or by building up the collateral vessel as a result of the incorporation of these cells into vessel walls. Thus, this review constitutes a summary of the historical background and current knowledge of coronary collateral growth in reference to the therapeutic potential for treating CAD.

Stimulus of Coronary Collateral Growth

Animal Models
For a long time, there was no general idea concerning the principal stimulus for coronary collateral growth. In 1967, Schaper proposed a new concept concerning the importance of mechanical factors on collateral growth. He emphasized the crucial role of increased tangential (radial) shear stress at small pre-existing collateral arteries, which results from increased intravascular pressure and arteriolar dilatation. In contrast, Scheel et al considered that myocardial ischemia is important for coronary collateral growth on the basis of observation of an elegant canine experimental model. In a model using an excised canine heart, conductance of coronary and collateral circulation can be separately and
plays a vital role in the development of collateral circulation.

In 1981, Franklin et al developed a new canine model for coronary collateral development, namely, repetitive, brief coronary occlusions. At that time, the reason why collateral development increased after the establishment of a pressure gradient across the collateral network was not clear. In a canine model, arteriogenesis is found in a remote region rather than myocardial ischemia as a stimulus for collateral development. In a rabbit hindlimb ischemia model, arteriogenesis is found in a remote region far from the ischemic lower hindlimb, where myocardial ischemia is mild, if present at all. More recently, Schaper’s group demonstrated directly the importance of fluid shear stress for collateral development. A rabbit hindlimb ischemia model showed that arteriogenesis is found in a remote region far from the ischemic lower hindlimb, where myocardial ischemia is much milder than that in the subendocardial layer. Furthermore, a rabbit hindlimb ischemia model showed that arteriogenesis was found in a remote region far from the ischemic lower hindlimb, where myocardial ischemia is mild, if present at all. More recently, Schaper’s group demonstrated directly the importance of fluid shear stress for collateral development. A rabbit hindlimb ischemia model showed that arteriogenesis is found in a remote region far from the ischemic lower hindlimb, where myocardial ischemia is much milder than that in the subendocardial layer. Furthermore, a rabbit hindlimb ischemia model showed that arteriogenesis was found in a remote region far from the ischemic lower hindlimb, where myocardial ischemia is mild, if present at all. More recently, Schaper’s group demonstrated directly the importance of fluid shear stress for collateral development.

In an elegant study by Symons et al, an ameroid constric tor was used for collateral development in a pig model. Although myocardial ischemia was attenuated with β-blocker administration, the speed and extent of collateral development were similar to those of non-treated control pigs. These findings also indicate the significance of fluid shear stress rather than myocardial ischemia as a stimulus for collateral growth. In the canine heart, pre-existing collateral vessels are located in the subepicardial layer, where the extent of myocardial ischemia is much milder than that in the subendocardial layer.

Clinical Studies

The presence of total occlusion of the coronary artery to be perfused by the collateral circulation is a prerequisite for the precise assessment of the extent of coronary collateral circulation. Collateral circulation disappears immediately after the loss of a pressure gradient across the collateral network resulting from reperfusion of the collateral-receiving coronary artery. The aforementioned desirable situation for collateral assessment is obtained from a totally occluded infarct-related coronary artery or balloon-inflated coronary artery during percutaneous coronary angioplasty.

In 1987, we found that the presence of long-standing pre-infarction angina indicative of myocardial ischemia was important for collateral growth in 37 patients undergoing coronary angiography within 6 h of the onset of first acute myocardial infarction (AMI). Collateral channels were visualized in 9 of the 18 patients with pre-infarction angina, but were visible in only 2 of 19 patients without angina. Because high-grade coronary artery narrowing causes not only anginal pain (myocardial ischemia), but also a pressure gradient between collateral- providing and -receiving coronary arteries, it is likely that the shear stress at pre-existing collaterals is augmented. At that time, the reason why collateral circulation was present in 2 of 19 patients without angina, namely, severe coronary stenosis, remained unclear. This is now explained, at least in part, by the fact that native functionally sufficient collateral vessels do exist in approximately 20–25% of subjects with angiographically normal coronary artery. Thus, our observation did not necessarily on the basis of observation that 15–60 s repeated coronary occlusions failed to develop a functionally significant collateral circulation. This misunderstanding of the original data may be explained by several factors. First, at that time, myocardial ischemia was generally considered to be a predominant factor for coronary collateral development. Second, it was overlooked that a briefer period of coronary occlusion has neither myocardial ischemia nor increased shear stress as a molding force of arteriogenesis, and it takes longer to augment collateral flow after the establishment of a pressure gradient across the collateral network. Finally, although the presence of myocardial ischemia is well acknowledged by several parameters, it is difficult to display the presence of increased shear stress because of a lack of methods for its direct measurement.

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separate these 2 factors of collateral stimulation. Thereafter, we evaluated the determinants of coronary collateral development in 248 patients undergoing coronary angiography within 12 h of the onset of first AMI using multivariate analysis. This analysis consisting of a larger cohort of patients revealed again that a history of long-standing pre-infarction angina is the only significant predictor of collateral growth. Thus, it was concluded that a history of pre-infarction angina is a clinical marker for the presence of well-developed collaterals.

Rentrop et al demonstrated during elective coronary angiography that the prevalence of angiographically demonstrable collateral circulation increased as the lesion of the collateral-receiving coronary artery increased beyond 70% diameter narrowing. Intracoronary flow velocity and/or pressure measurements during routine coronary occlusion provided a quantitative method for assessing coronary collateral circulation in humans. Pohl et al nicely demonstrated a positive correlation between the extent of coronary stenosis and collateral flow index in 450 patients with CAD.

All these findings indicate that high-grade coronary artery narrowing is responsible for collateral growth. However, in the clinical setting, it seems impossible to discriminate myocardial ischemia from increased shear stress as a stimulus for collateral development, because severe coronary stenosis simultaneously leads to myocardial ischemia and a pressure gradient across the collateral network. Myocardial ischemia induces angiogenesis, namely, the proliferation, migration, and tube formation of capillaries in the center of ischemic regions; meanwhile, increased shear stress at the site of pre-existing collateral vessels induces arteriogenesis, namely, increased size of pre-existing collateral arterioles with proliferation of vascular smooth muscle cells.

Mechanisms of coronary arteriogenesis have been well investigated and signal cascades initiated by increased fluid shear stress at the site of pre-existent collateral vessels have been elucidated in animal models. However, it had not been clarified whether cytokines and angiogenic growth factors act similarly in humans. We collected pericardial fluid from patients with CAD and demonstrated that increased pericardial fluid levels of basic fibroblast growth factor and decreased levels of endostatin in patients with angiographically documented CAD. Recently, it has been demonstrated, using directly collected collateral blood, that plasma levels of pro-angiogenic growth factors and cytokines, such as basic fibroblast growth factor, transforming growth factor-β, and monocyte chemoattractant protein-1 (MCP-1), are increased in patients with less matured collateral circulation; meanwhile, these levels are decreased in those with more developed collateral circulation. These findings suggest that these substances largely contribute to ongoing arteriogenesis.

**Therapeutic Approaches to Arteriogenesis**

Despite recent advances in medical treatment and revascularization procedures, a large number of patients with severe CAD remain symptomatic. Stimulation of arteriogenesis is an attractive alternative therapeutic approach. Mechanical modulation augmenting shear stress at the site of pre-existing collateral vessels is a promising candidate for inducing arteriogenesis. Potentiation of angiogenic growth factors with heparin and stimulation of monocyte function through cytokine application are also therapeutic approaches to arteriogenesis.

Schaper et al proposed a working hypothesis concerning arteriogenesis. At first, a pressure gradient between the collateral network provokes collateral blood flow, with resultant increased shear stress at the site of pre-existent collateral vessels. Endothelium activated by shear stress produces and releases MCP-1 and adhesion molecules. Accumulated monocytes/macrophages produce a variety of angiogenic growth factors and proteases. These bioactive substances contribute to coronary collateral growth, together with tissue degradation. On the basis of the aforementioned conceptual framework of arteriogenesis, a number of pharmacological treatments have been attempted to enhance arteriogenesis. So-called angiogenic therapy is divided into 2 types. Some investigators selectively infused various angiogenic growth factors and progenitor cells into the area perfused by the recanalized coronary artery. Those studies failed to separately evaluate arteriogenesis and angiogenesis in the ischemic area. Others attempted to potentiate arteriogenesis to the ischemic area exclusively supplied with collateral circulation. To elucidate the favorable effects of therapeutic approaches to coronary collateral growth, this review focuses on the collateral-targeted studies.

**Exercise**

Although it is well appreciated that a long-term exercise regimen is effective for coronary collateral development in patients with CAD, the precise mechanisms involved remain unclear. In animal experiments, exercise-induced collateral development was not shown in normal dogs without coronary stenosis. After constricting a coronary artery, exercise stress was effective for the induction of functionally significant collateral circulation. Thus, severe stenosis in a collateral-receiving artery is indispensable for the establishment of a pressure gradient across the collateral network, which is a necessary condition for collateral flow. The exercise stress provokes not only myocardial ischemia but also an increase in collateral flow by 2 mechanisms. Resistance vessels in the territory perfused by the collateral-receiving artery maximally dilate to provide maximal flow to the potentially ischemic area to meet myocardial metabolic requirements during exercise. Increased blood pressure (perfusion pressure) caused by exercise stress also augments collateral blood flow in the presence of maximally dilated collateral and collateral-receiving coronary vessels. Thus, exercise stress induces arteriogenesis, as well as ischemia-induced angiogenesis; the former is more important in terms of collateral circulation than the latter.

**Enhanced External Counterpulsation (EECP)**

The basic principle of EECP is diastolic augmentation of arterial pressure, lowering of systolic pressure, together with increasing venous return, which are noninvasively achieved by sequential inflation and rapid deflation of compressive cuffs wrapped around the lower extremities, synchronized to the cardiac cycle using an ECG. EECP theoretically ameliorates myocardial oxygen balance as a result of decreased myocardial oxygen demand and increased coronary and collateral blood flow. Arora et al demonstrated in a prospective, well-controlled, randomized, multicenter clinical trial that EECP effectively and safely improves exercise tolerance and anginal symptoms in patients with chronic stable angina. It is tempting to speculate on the mechanisms by which EECP stimulates arteriogenesis. Diastolic augmentation of arterial pressure results in increased coronary collateral blood flow because of its diastolic predominant flow pattern.
Whole-body periodic acceleration

Intravascular radial shear stress ↑

MCP-1 ↑
GM-CSF ↑

Angiogenic growth factors ↑

Arteriogenesis ↑

Myocardial functional improvement

Figure 2. Proposed mechanisms for myocardial functional improvement with whole-body periodic acceleration in angina patients with old myocardial infarction. Whole-body periodic acceleration augments intravascular pulsatile shear stress of pre-existent coronary collateral vessels, and activates production and release of monocyte chemotactic protein-1 (MCP-1) and granulocyte monocyte-colony stimulating factor (GM-CSF) at the site of pre-existent collateral vessels. Accumulated and activated monocytes produce various angiographic growth factors with enhanced arteriogenesis (collateral vessel growth). Increased collateral flow improves resting left ventricular function and increased collateral flow reserve alleviates stress-induced myocardial ischemia. On the other hand, increased shear stress upregulates endothelial nitric oxide synthetase (eNOS). Released nitric oxide (NO) suppresses NF-κβ activity with reduced production of inflammatory cytokines, and attenuates oxidative stress. These changes act favorably on myocardial performance.

Exercise

Myocardial ischemia ↑
Intravascular shear stress ↑

VEGF + Heparin
bFGF + Heparin

Angiogenesis ↑
Arteriogenesis ↑

Coronary collateral circulation ↑

Figure 3. Proposed mechanisms for coronary collateral development with heparin–exercise treatment. Strenuous exercise provokes myocardial ischemia and augments shear stress of pre-existent coronary collateral vessels resulting from enhanced collateral blood flow. Heparin potentiates the function of vascular endothelial growth factor (VEGF) released from the ischemic myocardial tissue, and induces angiogenesis. Heparin also potentiates the function of basic fibroblast growth factor (bFGF) released at the site of pre-existent collateral vessels, and leads to arteriogenesis. Finally, coronary collateral flow reserve is substantially improved.
enhanced collateral flow results in increased laminar and radial shear stresses at the site of pre-existing collateral vessels. Finally, the increased shear stress activates the endothelial cells to release angiogenic growth factors and chemokines. As a stimulator of arteriogenesis, differences between exercise and EECP should be addressed, because exercise augments myocardial oxygen demand resulting from increased heart rate and systolic blood pressure, and inevitably results in myocardial ischemia in the presence of limited coronary and collateral flow reserves. In contrast, EECP increases collateral blood flow in the milieu of unchanged or decreased myocardial oxygen demand. Thus, EECP is more favorable than exercise, because patients are free from the anginal pain and arrhythmia induced by myocardial ischemia.

Whole-Body Periodic Acceleration

Although EECP appears to be effective for arteriogenesis, this treatment is not indicated for everyone. There are a significant number of exclusion criteria: overt congestive heart failure, severe asymptomatic peripheral artery disease, varicosities, deep vein thrombosis, bleeding diathesis or warfarin use, atrial fibrillation or frequent ventricular premature beating that would interfere with EECP triggering, and so on. Moreover, periodic compression of the patient’s lower extremities imposes bruising and discomfort. Whole-body periodic acceleration in the direction of the spinal axis using a horizontal motion platform increases the shear stress of the vascular endothelium as well as EECP. The subject is coupled to a foot board for repetitive head-to-foot movements of a gurney-like motion platform driven by a 2-flywheel motor assembly under the platform at approximately 140 cycles/min with an acceleration rate of approximately 0.25 g (±2.2 m/s²). We demonstrated that whole-body periodic acceleration improves vascular endothelial function in sedentary adults, which is also the case in EECP. The chronic intermittent enhancement of the pulsatile shear stress with periodic acceleration may lead to endothelial nitric oxide release via the activation of endothelial nitric oxide synthase. Recently, we used whole-body periodic acceleration to treat patients with chronic angina pectoris who were not indicated for percutaneous coronary intervention and/or coronary artery bypass grafting under a conceptual framework that the augmented shear stress at the site of pre-existing coronary collateral vessels would induce arteriogenesis. In 10 patients treated with 20 sessions of 45-min whole-body periodic acceleration, myocardial perfusion in the collateral dependent area improved remarkably at rest and during adenosine infusion, indicating a significant development of collateral circulation. Before and after the treatment, a treadmill exercise test with the standard Bruce protocol was repeated. The double product at 0.1 mV ST depression increased by 13%, suggesting an increase in blood supply to the ischemic region. Interestingly, left ventricular end-diastolic volume decreased markedly by 18%, with an increase in the left ventricular ejection fraction from 50% to 55%. Although the number of treated patients is too small to definitely prove the usefulness of the new treatment with periodic acceleration, these results are promising and a future study consisting of a large-scale, randomized, controlled design is necessary. Figure 2 is a schematic diagram of the proposed mechanism for myocardial functional improvement by repeated whole-body periodic acceleration.

Heparin

In 1987, we reported for the first time that heparin pretreatment accelerates collateral development in Franklin’s model on the basis of the observation that protamine, an antagonist of heparin, retards angiogenesis. The details of angiogenic therapy with heparin have been described elsewhere (Figure 3). The basic principle of heparin treatment is potentiation of angiogenic growth factors, which are overexpressed by increased shear stress at the site of pre-existing collateral vessels as a result of exercise, EECP or whole-body periodic acceleration. Although the precise mechanisms by which heparin potentiates arteriogenesis remain to be completely elucidated, heparin administration combined with exercise or EECP has great potential in treating patients with effort angina who are not indicated for conventional reperfusion therapy.

Therapy With Cytokines and Stem Cells for Arteriogenesis

Granulocyte-macrophage colony stimulating factor (GM-CSF) is upregulated in vascular endothelial cells as a result of increased shear stress. Buschmann et al demonstrated that locally delivered GM-CSF promotes collateral artery growth by potentiating the function of monocytes and macrophages. Seiler et al extrapolated these experimental results to clinical situations. Intracoronary or subcutaneous GM-CSF definitely increased the collateral flow index in randomized, double-blind, placebo-controlled studies. However, coronary plaque rupture occurred in 2 of 7 GM-CSF-treated patients. Recently, bone-marrow-derived stem or endothelial progenitor cells have been proposed for recruitment to and incorporation into regions of neovascularization. Ziegelhoeffer et al reported that bone-marrow-derived cells do not incorporate into growing collateral vessels, although the relative contribution of transplanted cells to neovascularization is still controversial. It is now generally appreciated that favorable effects of cell therapy are mainly related to several angiogenic growth factors and cytokines secreted by transplanted cells.

Conclusions

Recent advances in molecular biology and gene technology have largely contributed to the elucidation of the mechanisms responsible for coronary collateral growth. Progress in catheter-based collateral functional analysis has also provided a variety of clinical evidence in this fascinating area. It is desirable that large-scale clinical studies targeted for coronary collateral growth be performed.

References


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