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Stimulation of collateral artery growth: travelling further down the road to clinical application

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ABSTRACT

Collateral artery growth is a potent natural defence mechanism to prevent death and myocardial infarction in occlusive artery disease. Given the high prevalence of arterial obstructive disease, a therapeutic compound stimulating collateral vessel growth could have a major impact on morbidity and mortality world wide. Although experimental studies on the stimulation of arteriogenesis have been promising, not a single drug has been proved to be applicable in clinical practice, either because of lack of efficacy or because of undesired side effects. This review summarises current knowledge on the mechanisms of collateral artery growth and examines problems that arise from the clinical implementation of pro-arteriogenic treatments to date. Future directions in the translation from bench to bedside and potential new approaches to the stimulation of vascular growth are discussed.

An important factor that determines outcome of an acute coronary event or progressive luminal narrowing of an artery is the ability of the human body to develop a collateral circulation,¹ a process termed arteriogenesis. Well-developed coronary collateral arteries are associated with reduced long-term cardiac mortality.²

Sufficiently developed collateral arteries that prevent signs of myocardial ischaemia during brief vascular occlusion are present in about one-third of patients with coronary artery disease and in about one-fifth of patients without coronary artery disease.²

Therapeutic stimulation of arteriogenesis presents an appealing concept in the search for alternative treatment options applicable to patients with arterial obstructive disease. It is estimated that classical treatment modalities such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting are not suitable for one out of five patients with coronary artery disease (CAD),³ rendering promotion of collateral artery growth a potential therapeutic approach for this group of patients. However, despite very promising experimental data, the extrapolation to clinical application is still awaited.

MECHANISMS OF ARTERIOGENESIS

The term arteriogenesis refers to the transformation of pre-existing collateral arterioles into functional collateral arteries.⁴ The presence of pre-existing collateral anastomoses in the coronary circulation was demonstrated for the first time by Fulton.⁵ In a recent study, Wustmann *et al* elegantly demonstrated that in subjects without CAD, functional coronary collateral arteries to

prevent ischaemia during balloon occlusion were recruitable in 20–25%, substantiating the presence of pre-existing coronary collateral anastomoses.⁶ In the case of arterial obstruction, an increased fluid shear stress in a pre-existing arteriole is followed by endothelial activation, attraction of mononuclear cells and secretion of cytokines and growth factors. Finally, a new conductance artery is developed. Figure 1 depicts the mechanisms of arteriogenesis.

Ischaemia is not a condition *sine qua non* for arteriogenesis

Ischaemia results in outgrowth of capillary networks—that is, angiogenesis. However, for the initiation of arteriogenesis, hypoxia is not required. Arteriogenesis takes place in a non-hypoxic environment distant from the ischaemic area. Animal studies show that when the femoral artery is occluded in rabbits only the lower leg becomes transiently ischaemic followed by angiogenesis in that area, while arteriogenesis occurs at the level of occlusion (thigh) where there is no rise in ischaemic markers like adenosine diphosphate, adenosine monophosphate or lactate.⁷ Very recent experimental studies in zebra fish embryos have provided additional evidence that arteriogenesis occurs without ischaemia, as the zebra fish gains sufficient oxygen through diffusion to prevent ischaemia.⁸

Shear stress activates the endothelium

Blood vessels enlarge when chronically exposed to high flow; furthermore, they regress when not constantly perfused and their walls become thicker with high pressures. In the case of an occluded artery a steep pressure gradient develops over the pre-existing arteriolar anastomoses which increases blood flow and fluid shear stress in these connections. Blood vessels react to a change in shear stress with growth and remodelling. The changing mechanical forces after arterial occlusion act on endothelial cells and lead to remodelling of their cytoskeleton, as well as altered gene expression. The signal path from an increase of shear stress to an altered gene expression involves structures within the endothelial membrane like integrins, tyrosine kinase receptors and ion channels.⁹ In recent years, the glycocalyx, a network of proteoglycans, glycoproteins and glycosaminoglycans which lines the luminal wall of all blood vessels, has also been shown to act as a shear stress sensor.¹⁰

Shear stress-induced changes in gene expression eventually lead to an upregulation of adhesion molecules, such as intercellular adhesion molecules (ICAM-1 and ICAM-2) on the endothelial surface.

Review

Figure 1 Mechanisms of arteriogenesis. (A) Without significant stenosis, there is no significant pressure gradient over pre-existing collateral anastomoses, which are small and barely carry blood. (B) Development of a significant arterial obstruction leads to a drop in pressure and oxygen saturation distal in the vascular bed (purple-blue colour), while proximal pressure and oxygen saturation proximal remain normal (red colour). The pressure gradient over the collateral circulation increases fluid shear stress in these arterioles. (C) Close-up on the cellular level. The endothelium senses increased fluid shear stress via its cytoskeleton, transmembrane proteins (integrins, ion channels) and the glycocalyx. In an activated state, the endothelium expresses adhesion molecules (ICAM-1), to which circulating monocytes bind via their Mac-1 receptor. Monocytes transmigrate into perivascular tissue, differentiate to macrophages and secrete growth factors and cytokines that attract further monocytes and stimulate proliferation of smooth muscle cells and endothelial cells. (D) Adequately developed collateral arteries restore distal perfusion and provide sufficiently oxygenated blood to distal tissues. bFGF, basic fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; MCP, monocyte chemoattractant protein; MMPs, matrix metalloproteinases; TGFβ, transforming growth factor β.

A study in mice by Scholz and Schaper speculates that collateral arteries continue to remodel after the increase of shear stress is no longer present, indicating only an initiating role for shear stress in arteriogenesis.¹¹ On the other hand, collateral vessels regress after shear stress ceases. During this process, called “pruning”, most collateral anastomoses degenerate, while a small number of large collateral arteries continue to grow in size.¹² Enhancing the magnitude of fluid shear stress over the pre-existent collateral vasculature in an animal model by implementation of an arteriovenous shunt leads to a restoration of flow even exceeding the levels of flow of the native circulatory system.¹³

A recent study showed that collateral flow was undiminished in patients 24 h after opening of a chronic total occlusion (CTO) of a coronary artery,¹⁴ whereas another investigation described a rapid re-recruitment of collateral-dependent perfusion directly after PCI of the original artery.¹⁵ In a large study comprising more than 100 patients with CTO, collateral function declined by 23% directly after PCI and by another 23% after 5 months. Collateral arteries were not readily recruitable after acute re-occlusion, but had the potential to recover in cases of chronic re-occlusion.¹⁶

Role of circulating cells

Monocytes were first recognised as important players in arteriogenesis by Schaper *et al* in 1976.⁴ After activation of the endothelium by shear stress, monocytes are recruited to the site of collateral artery growth. Details of monocyte recruitment, adhesion to the endothelial surface molecule ICAM-1 via their receptor Mac-1 and transmigration to the perivascular tissue have been reviewed in detail elsewhere.¹⁷

Experimental research in recent years has further elucidated monocyte function and emphasised its importance in arteriogenesis. Once in the perivascular region, monocytes become macrophages and create an inflammatory environment. The glycoprotein tumour necrosis factor α (TNFα) is one of the inflammatory factors secreted by macrophages.¹⁸ TNFα knock-out mice show delayed arteriogenesis, and the inhibition of TNFα signalling using the TNFα antagonists infliximab and etanercept also resulted in attenuated arteriogenesis.¹⁹ Anti-inflammatory treatment with aspirin attenuated arteriogenesis in a rabbit model.²⁰

The glycoprotein CD44 is of importance for the interaction of transmigration monocytes with the extravascular matrix. It is functionally involved in arteriogenesis in mice and was

Table 1 Cytokines shown to stimulate arteriogenesis in experimental models

Factor	Mechanism of action	Experimental validation
MCP-1	Chemoattractant for monocytes via CCR-2 receptor. Acts as mediator of TGFβ1- and bFGF-induced growth	Increases arteriogenesis in rabbit hindlimb model ³⁰ and in large ³¹ and disease models (Watanabe rabbits, ApoE—mice) ^{32, 33}
GM-CSF	Mobilises progenitor cells from bone marrow, ³⁴ protects monocytes from apoptosis ³⁵	Pro-arteriogenic capacity shown in rabbit hindlimb, pig hindlimb ³⁶ and rat cerebra ³⁷ model
G-CSF	Mobilises progenitor cells from bone marrow ³⁴	Shown to stimulate arteriogenesis in a mouse model
TGFβ1	Chemoattractant for monocytes, induces monocyte cytokine expression, ³⁸ induces cardiac ankyrin repeat protein ³⁹	Stimulates arteriogenesis in rabbit model, ⁴⁰ also with stent-based intra-arterial delivery ⁴¹
FGF-2	Upregulates MCP-1. ⁴² Acts as NO-dependent vasodilator. ⁴³ Proliferative effects on endothelial and smooth muscle cells ⁴⁴	Stimulates arteriogenesis in rat hindlimb model ⁴⁵
FGF-4	Proliferative effect on endothelial and smooth muscle cells	Stimulates arteriogenesis in rabbit hindlimb model ⁴⁶
VEGF	Increased integrin expression and monocyte transmigration. ⁴⁷ Attracts progenitor cells ⁴⁸	Stimulates arteriogenesis in large animal model ⁴⁷
PIGF	Acts on VEGF receptor-1, activates monocytes ⁴⁹	Stimulates arteriogenesis in mouse hindlimb model ⁴⁹
PDGF	Upregulation of the PDGF receptor by FGF-2 ⁵⁰	Stimulates arteriogenesis in combination with FGF-2 in rat and rabbit hindlimb model ⁵⁰
TNFα	Creates an inflammatory environment	Stimulates arteriogenesis via p55 receptor. ⁵¹ TNFα antagonists infliximab and etanercept inhibit arteriogenesis ¹⁹
Angiopoietin	Increases endothelial and arteriolar proliferation ⁵²	Well-documented positive influence on angiogenesis and, potentially, arteriogenesis ⁵³
LPS	Activates monocytes ¹⁸	Enhances arteriogenesis ¹⁸

bFGF, basic fibroblast growth factor; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; PDGF, platelet-derived growth factor; PIGF, placental growth factor; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

furthermore shown to be differentially regulated in monocytes from patients with sufficiently and insufficiently developed coronary collateral arteries.²¹ The essential role of monocytes for arteriogenesis could also be demonstrated in a murine model of monocyte deficiency.²²

The role of the other leucocyte subpopulations in collateral artery growth is still under debate. In a rabbit hind limb model of arteriogenesis, lymphocyte- or granulocyte-attracting chemokines could not enhance collateral artery growth.²³ In contrast, blood flow recovery after induction of ischaemia was clearly hampered in CD4 knockout mice, indicating a significant role of T lymphocytes in this process.²⁴ CD8+ T lymphocytes are also thought to contribute to arteriogenesis, attracting CD4+ mononuclear cells to sites of collateral artery growth.²⁵ Mast cells may also play a role in arteriogenesis, since they are detected in the wall of growing collateral arteries, but their precise role is not clear.²⁶

Similar to other regenerative processes such as angiogenesis or myocardial regeneration, a role in collateral artery growth has been attributed to stem cells. The paracrine function of pluripotent progenitor cells in arteriogenesis has been discussed by Heil and Schaper.¹⁷ Mechanistically, it could be shown that activation of the SDF-1/CXCR-4 axis results in recruitment of progenitor cells and leads to enhanced collateral artery growth.²⁷

Smooth muscle cell proliferation

Proliferation of smooth muscle cells constitutes the most important process in arteriogenesis.²⁸ Although only a few extra endothelial cells are needed in the formation of a new conductance artery, several layers of smooth muscle cells have to be created in a larger vessel. In arteriogenesis, smooth muscle cells are modified from a differentiated, contractile phenotype to an immature synthetic phenotype.²⁶ Smooth muscle cells proliferate, secrete extracellular matrix components and digest

the internal elastic lamina. Matrix metalloproteinases-2 and 9 facilitate outward remodelling of pre-existing arterioles and positively influence invasive and proliferative capacities of circulating cells.²⁹ After numerous cell divisions endothelial and smooth muscle cells change back into their original phenotype.

STIMULATION OF ARTERIOGENESIS BY EXOGENOUSLY APPLIED FACTORS

Extensive research has been performed searching for compounds to stimulate collateral artery growth. In experimental models several growth factors influencing monocyte function or endothelial or smooth muscle cell proliferation have demonstrated the feasibility of exogenous stimulation of collateral artery growth. Table 1 summarises the best described pro-arteriogenic factors as derived from experimental models.

Because of the large body of positive data from experimental studies on the stimulation of collateral artery growth, clinical studies were initiated at an early stage. While the first small, non-randomised trials supported the experimental findings, subsequently performed larger randomised trials did not show beneficial effects.

The first trials on the stimulation of vascular growth focused on capillary sprouting (angiogenesis). Because they have been reviewed extensively elsewhere⁵⁴ they are not discussed in detail here. The VIVA trial for CAD⁵⁵ and the RAVE trial for peripheral arterial disease,⁵⁶ both investigating the therapeutic potential of vascular endothelial growth factor, had negative results. Similarly, the AGENT and the FIRST trial for CAD,^{57, 58} as well as the TRAFFIC trial for peripheral arterial disease,⁵⁸ showed that application of basic fibroblast growth factor did not result in the expected significant stimulation of angiogenesis in a clinical setting.

Table 2 Clinical trials for the stimulation of arteriogenesis

Clinical trial	Disease studied	Substance/route of administration	Results
TRAFFIC ⁵⁸	PAD	FGF-2 IA	Increase in peak walking time at 90 days, double dose no better than single dose
START ⁶⁰	PAD	GM-CSF SC	No effect on maximal walking distance after 14 or 90 days
Grossman <i>et al</i> ⁶¹	PAD	DEL-1 plasmid IM	No change in exercise capacity at 30, 90 and 180 days
Seiler <i>et al</i> ⁶⁹	CAD	GM-CSF IC and SC	Increase in coronary collateralisation assessed by CFI
Belardinelli <i>et al</i> ⁶²	CAD	Dipyridamole PO	Treatment improved coronary collateralisation, especially when combined with exercise
AGENT ⁶³	CAD	Adenoviral FGF-2 IC	Non-significant increase in exercise time at 4 weeks
FIRST ⁵⁷	CAD	FGF-2 IC	No significant difference compared with placebo
Zbinden <i>et al</i> ⁶⁴	CAD	GM-CSF SC	Increase in CFI, prematurely terminated because two patients developed acute coronary syndrome

CAD, coronary artery disease; CFI, collateral flow index; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IA, intra-arterially; IC, intracoronary; IM, intramuscularly; PAD, peripheral arterial disease; PO, by mouth; SC, subcutaneously.

The first clinical study focusing specifically on arteriogenesis studied the potential of granulocyte-macrophage colony-stimulating factor (GM-CSF) to improve collateral flow in the coronary circulation. Seiler *et al* showed an increase in the collateral flow index in 11 patients as compared with placebo.⁵⁹ The effect of GM-CSF administration on collateral artery growth in the peripheral circulation was assessed in the START trial. No difference in the increase in maximal walking distance was seen between the placebo and GM-CSF groups after 14 or 90 days.⁶⁰ Table 2 summarises the clinical trials for the stimulation of arteriogenesis. Note that studies explicitly focusing on angiogenesis (capillary sprouting) are not listed as they have been reviewed extensively elsewhere.⁵⁴

Although the exact role of stem cells in arteriogenesis has still not been completely unravelled, their multitude of possible beneficial effects led to early clinical investigations. A correlation between coronary collateralisation and the number of circulating progenitor cells could be demonstrated.¹⁴ Recently published trials using progenitor cells derived from bone marrow in myocardial infarction to improve left ventricular function show divergent results.^{65–67} The exact mechanism behind the effect of these cells remains unclear, but data on improvement of peripheral resistance in the infarct artery after cell treatment suggest an effect on vascular growth.⁶⁸

Experimental studies have demonstrated that arteriogenesis can be stimulated by augmenting shear stress in pre-existing collateral arterioles. Indeed, in a recent study, Zbinden *et al* could show, in accordance with animal studies, that exercise training augments the development of coronary collateral arteries in patients.⁶⁹

UNRESOLVED PROBLEMS IN THE TRANSLATION FROM BENCH TO BEDSIDE

A number of problems hamper translation of experimental success of pro-arteriogenic compounds into the clinical setting. Given the fact that different mouse strains show differences in pre-existing collateral anastomoses as well as in the rate growth of collateral arteries,⁷⁰ genomic and biological dissimilarities between mice and men can be easily appreciated. Although only a few cell cycles are required to transform a pre-existing arteriole of 20–40 µm into a mature collateral artery of maximally 100 µm in mice, pre-existing arterioles in humans require many more cell cycles and massive degradation of surrounding tissue before a mature collateral artery has developed. Furthermore, controlled experimental conditions allow the “dose–response” of pro-arteriogenic treatment to be studied in detail in animal

models, whereas in humans these effects are less predictable. To minimise the difference between animal experiment and clinical application, larger animal models have been used to mimic clinical conditions.⁶⁶

However, comorbidities like dyslipidaemia or diabetes, which are thought to impede arteriogenesis,⁷¹ are seldom implemented. Conversely, almost all patients in need of a sufficiently developed collateral circulation have these classical risk factors of atherosclerotic disease, which have also been shown to impede arteriogenesis. Single experimental studies that did use disease models to investigate the potential of a pro-arteriogenic treatment had unwanted side effects. In a model investigating arteriogenesis we have shown that local monocyte chemoattractant protein 1 treatment stimulates collateral artery growth in a hypercholesterolaemic animal model but also induces plaque progression.³³ The mechanisms underlying collateral artery growth closely resemble those of atherosclerosis: both are inflammatory processes involving enhanced monocyte adhesion leading to an inherent trade-off of potential pro-arteriogenic effects and pro-atherogenic effects.⁷² Apart from monocyte chemoattractant protein 1, other known pro-arteriogenic factors also worsen atherosclerotic disease.⁷³ Possible destabilisation of atherosclerotic plaques is another concern examined in earlier trials using cytokine treatments in the stimulation of arteriogenesis: treatment of seven patients with GM-CSF to stimulate collateral growth was associated with an acute coronary syndrome in two.⁶⁴ The solution to this problem may lie in the use of pro-arteriogenic, yet anti-inflammatory compounds, the use of pro-arteriogenic factors that do not aggravate atherosclerosis (eg, transforming growth factor β1) or the selective delivery of factors into the collateral circulation (eg, by using a stent-based approach).⁴¹

Another important factor which potentially influences vascular growth is age. Animals used for investigations of vascular growth mostly are healthy and young. In experimental studies in mice and rabbits, a negative effect of age on vascular growth has been suggested.^{74–75} Few patient studies have tried to elucidate potential negative effects of older age on vascular growth. Taking only studies into account that are based on “gold standard” haemodynamic measurements (intracoronary measurements of pressure and flow velocity), no correlation between age and coronary collateralisation was found.⁷⁶ Similarly, subanalyses of the larger trials using vascular endothelial growth factor to stimulate coronary vessel growth could not find an age-dependent response to pro-angiogenic treatment.^{14 55 56} On the other hand, endothelial-mediated

dilatation of coronary arteries, a marker of vascular (endothelial) function, is indeed negatively affected by increasing age,⁷⁷ and similarly, numbers of endothelial progenitor cells were found to be depressed in older patients.⁷⁸ Although both these findings point towards attenuated vascular biological regenerative capacities in older age, physiological studies of angiogenesis or arteriogenesis in older patients have hitherto been inconclusive.⁷⁹

Besides differential effects of cytokine treatment it has to be acknowledged that the experimental model can at best only mimic the clinical situation. Although collateral arteries in humans proliferate upon slow narrowing of a larger conduit vessel, experimental models mostly make use of acute occlusions—for example, in hind limb models of femoral artery ligation. This abrupt arterial occlusion leads to an immediate rapid increase in shear stress in the pre-existing collateral anastomoses, as opposed to a slowly progressing stenosis in patients with stable angina pectoris.

Yet another problem making translation of results derived from experimental models into clinical practice difficult is end-point assessment.⁸⁰ Although a continuing discussion on the proper end points to be used when evaluating pro-arteriogenic treatments in animal studies is taking place,⁸¹ the discussed “gold-standard” methods of microsphere perfusion under conditions of maximal vasodilatation are unavailable to the clinician. Often used angiography-based techniques of assessing coronary collateral flow in patients such as the Rentrop score do not accurately assess collateral function.^{82–83} Guidewire-based pressure and flow measurements in the coronary circulation have emerged as the standard in the assessment of coronary collateral artery growth.⁸⁴ Myocardial contrast echocardiography (MCE) is another valuable method of measuring not only epicardial collateral flow but also collateral-dependent tissue perfusion during angioplasty or in CTOs. The combination of MCE and guidewire-based collateral flow index measurements allows the assessment of absolute collateral perfusion in ml/min/g.⁸⁵ MCE-derived arteriolar blood volume determinations, which are used to identify coronary stenoses, are influenced by the degree of collateral flow.⁸⁶ Recently, assessment of MRI-derived hyperaemic delay of contrast arrival has been reported to reliably detect collateral-dependent myocardium.⁸⁷

DISCUSSION AND CONCLUSION

Research on collateral artery growth has been developing for several decades⁴ and underlying mechanisms of arteriogenesis have been thoroughly explored in experimental models. Because the stimulation of vascular growth and proliferation may be of benefit to millions of patients, numerous factors have been investigated for their pro-arteriogenic potential. Many of these factors, mainly cytokines and growth factors, have proved successfully to enhance collateral artery growth in experimental models. Despite this large body of evidence for the feasibility of pharmacological stimulation of arteriogenesis in the experimental setting, none of the large randomised clinical trials could show beneficial effects in patients. There are several explanations for this lack of validation of experimental results in the clinical setting, which have been discussed in detail. Open questions remain about the optimal time at which to start treatment and the need for multiple factors. These questions suggest the benefit of cell treatment in which (progenitor) cells are delivered for the stimulation of vascular growth. All cytokine and also cell treatment approaches, however, create a proinflammatory environment and therefore entail an increased risk of aggravating plaque progression and destabilisation.

Several very strong pro-arteriogenic compounds had to be removed from the list of promising new therapeutic targets because of these safety concerns. Interestingly, on the other hand, antiproliferative treatments, applied locally with drug-eluting stents, were recently shown to have significant negative effects on collateral artery development.⁸⁸

Another explanation for the difficulties in bringing our detailed knowledge on the stimulation of arteriogenesis from bench to bedside is the paucity of information on the molecular mechanisms of collateral artery growth in humans. Because of the heterogeneity in the arteriogenic response upon arterial obstruction,⁷⁶ pilot studies have begun looking for genetic determinants in patient populations.⁸⁹ Bringing differential gene expression data from patients to the experimental level in a reverse bedside-to-bench approach, new factors influencing arteriogenesis have been discovered.⁹⁰

Data on potential negative effects of (coronary) collateral arteries are still ambiguous. While Perara *et al* found that coronary collateralisation is not a predictor of restenosis after PCI,⁹¹ Jensen *et al* recently demonstrated a close correlation between the degree of collateralisation and the frequency of restenosis after stent implantation.⁹²

Future research thus has to focus on mechanisms of collateral artery growth in man to potentially develop new approaches lacking the difficulties of contemporary pro-arteriogenic treatments. A better understanding of human arteriogenesis might lead to the long-desired treatment, which ultimately requires a stimulatory effect on vascular growth while leaving atherosclerosis unaffected.

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