The coronary collateral circulation revisited

N. Hakimzadeh • J. J. Piek

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The coronary collateral circulation constitutes a vascular network that forms bridges between adjacent arteries. In response to obstructive coronary artery disease (CAD) due to atherosclerotic plaque progression, these bridging vessels enlarge by a complex interplay of physical forces along with molecular and cellular players. This process of vascular enlargement is known as *arteriogenesis*. The progression of vessel stenosis exerts a pressure gradient on the downstream vasculature, leading to increased shear stress. Collateral vessel growth and maturation is then dominated by monocyte infiltration. Expansion of these bridging vessels into large calibre collateral arteries allows blood flow to bypass the site of obstruction, thereby maintaining perfusion to the surrounding tissue. Many clinical studies have implicated a functional significance of collateral arteries in relation to preserving left ventricular function, reducing infarct size and lowering future adverse cardiac events.

The present meta-analysis by Akin et al. was performed to evaluate the significance of collateral vessels with respect to death and re-infarction in the present era of primary percutaneous coronary interventions (PCI) [1].

This analysis considered nine studies with a total of 6791 patients. In these studies, collateral vessel grading was based on angiographic assessment, with the exception of the study by Meier 2007. Although coronary angiography can be used to determine the functional capacity of collateral vessels to preserve left ventricular function in cases of chronic total occlusion

(CTO), it is limited by its resolution and poor accuracy. The coronary angioplasty study of Rentrop et al. showed that detection of collateral vessels is dependent on the relative pressure gradient exerted upon the collateral network [2]. Based on this study it was determined that many clinical studies classifying collateral vessels by coronary angiography were incorrect.

During baseline conditions, collateral vessels are largely undetected. Their presence only becomes evident during total occlusion of the recipient artery by natural or artificial means, such as CTO or balloon occlusion. These collateral vessels have been coined as ‘recruitable’ and in cases of non-CTO conditions, the introduction of an arterial catheter for contrast injection is required for their visualisation during balloon coronary artery occlusion. Spontaneously visible collateral vessels represent only a small fraction of the entire collateral vascular network, as angiography is limited to the assessment of vessels >100 µm in diameter. Thus, collateral vessel assessment using coronary angiography alone leaves a large portion of these bridging anastomoses unexplored. Schwartz et al. showed in angiographic examination of thrombolytic therapy in patients with acute myocardial infarction that collateral vessels are initially undetected and become evident between 10 and 14 days after chronic coronary occlusion [3]. Therefore, the most relevant information regarding the collateral circulation is obtained in angiographic studies that are performed during the acute cardiac event by visualisation of the donor artery at the time that the recipient artery is occluded [4].

This was the case in 4 of 9 studies that were included in the meta-analysis, while one study (Meier 2007) used pressure-derived collateral flow index (CFI_p) to assess collateral flow. The results of these 5 studies show a uniform positive effect of the presence of collateral vessels with respect to the endpoints of death and re-infarction following primary percutaneous coronary intervention (PCI). These findings are in line with previous clinical studies that were performed in the pre-primary PCI era emphasising the functional significance of coronary collateral vessels. However,

N. Hakimzadeh
Department of Biomedical Engineering & Physics,
Academic Medical Center, Room L0-114, Meibergdreef 9,
1105 AZ Amsterdam, the Netherlands

J. J. Piek (✉)
AMC Heart Center, Academic Medical Center,
University of Amsterdam, Room B2-250, P.O. Box 22660,
1100 DD Amsterdam, the Netherlands
e-mail: j.j.piek@amc.uva.nl

the major clinical challenge remains to stimulate the process of arteriogenesis for symptomatic improvement or to alter the natural course of coronary artery disease.

Identification of wall shear stress and monocyte recruitment as key modulators of collateral vessel growth led to the discovery of pro-arteriogenic compounds in experimental studies. Among the compounds explored for modulating monocyte homing and survival, monocyte chemoattractant protein 1 (MCP1) and colony stimulating factors (CSFs) were the most extensively tested. Experimental studies showing atheroprotectancy of MCP1 in hyperlipidaemic mice prevented any clinical testing of MCP1 for collateral vessel growth. Nonetheless, clinical trials initiated to test the therapeutic efficacy of CSFs also led to disappointing outcomes, whereby negligible therapeutic outcome was outweighed by alarming atheropotent side effects.

Overlap between arteriogenesis and atherogenesis has introduced a benefit vs. risk phenomenon. Both processes are governed by fluid shear stress changes and inflammatory pathways, thus deeming any pro-arteriogenic compounds that stimulate and sustain inflammatory cytokine, or monocyte homing and infiltration, as having potentially atherogenic side effects. Although, negative consequences exist for many therapeutic agents, the dangers of enhanced plaque progression and lack of therapeutic outcome in clinical trials made it imperative to change the conventional thinking surrounding arteriogenesis research.

While Akin et al. conclude in this meta-analysis that atherosclerotic risk factors were not associated with well-developed collateral vessels, it has been shown in animal studies that mice highly susceptible to atherosclerosis are also good collateral vessel formers and vice versa. Genetic heterogeneity resulting in phenotypic differences in the collateral network in mice has also been seen in patients with insufficient vs. sufficient collateral vessels, emphasising that genetic predispositions contribute to collateral vessel growth. Several clinical trials were initiated to elucidate such genetic heterogeneity in CAD patients by transcriptional profiling of peripheral blood monocytes. In these trials patients with good and bad collateral circulation were distinguished according to CFI_p measurements. Based on these studies, patients with insufficient collateral vascular network were shown to have elevated activation of inhibitory pathways as well as less responsive monocytes. These inhibitory pathways were identified based on increased interferon- β and galectin-2 mRNA expression in peripheral blood monocytes [5, 6]. In addition, a distinct genetic polymorphism was associated with patients with insufficient collateral vessels [6]. These recent studies emphasise the relevance of a reversed bench-to-bedside approach for identifying novel targets for therapeutic arteriogenesis.

The change in conventional thinking surrounding arteriogenesis research is the method of augmenting therapeutic collateral vessel growth and methods to monitor such

progression. Previous studies focused on identifying compounds that stimulate and enhance monocyte/macrophage function. Nonetheless, based on the identification of genetic predispositions characterised by inhibitory pathways in patients with poor collateral vessels, it may be more beneficial to block such inhibitory pathways as they hinder arteriogenesis. It is hoped that this will directly result in collateral vessel growth stimulation. New developments in microRNA research have potentially opened new avenues for modulating gene activity, as miRNA modulate gene expression by means of translational suppression or degradation of respective mRNA targets.

Finally, new avenues for collateral vessel growth also require sufficient means of collateral vessel detection. As described, angiographic methods alone are insufficient and provide an inaccurate representation of the collateral network. Invasive measurements such as CFI_p are the gold standard in quantifying functional capacity of collateral vessels. Nonetheless, new methods for non-invasive diagnostic imaging techniques are emerging for identification of collateral vessels in CTO patients [4]. Recent advancements have introduced hybrid diagnostic imaging modalities and molecular imaging, resulting in improved sensitivity and spatial resolution.

By exploiting multiple techniques with the use of agents that target the innate factors impeding collateral vessel development in CAD patients, therapeutic arteriogenesis may one day be realised. Although the discussion on functional significance and therapeutic potential of a well-developed collateral network is revisited from time to time, uniform means of collateral vessel detection and quantification are imperative and equally important as the methods of promoting arteriogenesis.

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