Important risk factors for cardiovascular disease (CVD) have been identified, but they fail to explain why some patients with atherosclerosis become symptomatic and have recurrent symptoms, disease, and others do not. Apart from the extent of coronary atherosclerosis (among other factors), the sensitivity of organs to episodes of ischemia is probably of importance. An organ may be less sensitive to episodes of ischemia if supplied with sufficient blood flow by well-developed collateral vessels. Unfortunately, some organs or even some individuals do not appear to have well-developed collateral vessels, if developed at all. At present, it is not clear why there are differences between individuals in their capability of developing a sufficient collateral circulation. The potential of individuals to develop coronary collateral circulation has so far been largely neglected but may play a major role in determining myocardial vulnerability.

In the present article, we propose why coronary collaterals are important, and why this individual potential to develop collaterals should be considered an additional indicator of cardiac vulnerability. Also, we review determinants that play a role in collateral coronary blood supply.

**Coronary Collateral Circulation: Current Knowledge**

Coronary collaterals, or “natural bypasses,” are anastomotic connections without an intervening capillary bed between portions of the same coronary artery and between different coronary arteries (Figure 1). Collateral circulation potentially offers an important alternative source of blood supply when the original vessel fails to provide sufficient blood. Timely enlargement of collaterals may even avoid transmural ischemia if supplied with sufficient blood flow by well-developed collateral vessels. In hearts with typical findings of coronary disease at autopsy, the number of large-caliber coronary collaterals is increased, notably in cases with a history of slowly evolved coronary obstruction. Avascular areas were found in acute myocardial infarcts. Baroldi et al suggested that functional coronary collateral circulation results from hypertrophic evolution of vessels, present in normal hearts. Indeed, in 1964, Fulton et al showed that the larger the history of angina, the larger the number of large-caliber coronary collaterals at postmortem examination. When lumen diameter measurements were translated into capacity for blood flow, the functional important of a few large channels was overwhelming compared with a large number of small channels. Since then, much research has been performed with the goal of understanding the mechanisms of collateral vessel growth: vasculogenesis, angiogenesis, and arteriogenesis.

Vasculogenesis refers to the initial events in vascular growth, in which endothelial cell precursors (angioblasts) migrate to discrete locations, differentiate in situ, and assemble into solid endothelial cords, later forming a plexus with endocardial tubes. The term angiogenesis was formerly used to describe the formation of new capillaries by sprouting out from preexisting postcapillary venules. Currently, angiogenesis is considered the subsequent growth, expansion, and remodeling of these primitive vessels into a complex, mature vascular network. Finally, arteriogenesis refers to the transformation of preexisting (collateral) arterioles into functional (muscular) collateral arteries, as a thick muscular coat is added, concomitant with acquisition of viscoelastic and vasomotor properties.

**Risk Factors, Trigger Factors, and Myocardial Vulnerability**

**Risk Factors of CVD**

Much is known about the pathogenesis of atherosclerosis and about risk factors for the initiation and progression of the disorder. Factors strongly associated with CVD, include (among others) age, male gender, smoking, elevated serum cholesterol, disturbed carbohydrate metabolism, and elevated blood pressure. This knowledge is, however, insufficient to adequately predict the initiation and progression of CVD and...
the occurrence of (new) ischemic symptoms. Secondary prevention aims at detection and treatment of these risk factors, in order to slow down the progression of the atherosclerotic process and prevent further morbidity and mortality. Yet most patients with symptomatic CVD have similar levels of traditional risk factors, and all have atherosclerosis to a greater or lesser degree.17

Probably, apart from the extent of coronary atherosclerosis, the sensitivity of organs to episodes of ischemia is of importance. Therefore, other factors may play a role as well: notably, the presence of a collateral circulation. An organ may be less sensitive to episodes of ischemia if it is supplied with sufficient blood flow by well-developed collateral vessels. Coronary collaterals thus may protect the heart and prevent ischemic cardiac events.

Trigger Factors
By 1986, Oliver18 had introduced a scheme summarizing the most important determinants for the occurrence of cardiovascular events in the presence of atherosclerosis: coronary atherosclerosis, trigger factors, and myocardial vulnerability (Figure 2).18 The presence of atherosclerosis or a vulnerable myocardium in itself does not have to result in the occurrence of symptomatic events. At this point, trigger factors may play an important role. Trigger factors are factors that promote rapid occlusion of arterial vessels already compromised by atherosclerosis, thus “triggering” sudden reductions of coronary flow and ischemia.18 Although particularly clear for coronary heart disease, this is likely to apply to the occurrence of ischemic events in other vascular beds as well, such as the brain. The concept of trigger factors is of vital importance in understanding the final phase of atherosclerotic CVD, when it shifts from asymptomatic to symptomatic disease—a phase in which thrombosis is central.14 Plaque rupture with superimposed thrombosis is the main cause of acute coronary syndromes, including unstable angina, MI, and sudden cardiac death.19 Many mechanical and biological factors are involved in determining plaque stability and in the process leading to plaque rupture, including (among others) plaque architecture (thickness of fibrous cap, location of lipid core), mechanical forces (shear stress, repetitive deformation), extracellular matrix biology (synthesis and degradation), and inflammation.20 Recently, Moons et al19 showed that tissue factor, a potent initiator of the coagulation cascade, may play a key role in determining plaque thrombogenicity.

In addition to thrombogenic factors, other candidates may act as trigger factors, although they may eventually affect thrombogenesis as well, such as sympathetic nervous system activity, vasoactive hormones, smoking, and psychosocial stress.14,21

Figure 1. Left anterior oblique view of the right coronary arteriogram. The left circumflex coronary artery (LCX) is proximally occluded and fills completely by means of collateral circulation from the right coronary artery (RCA). Image courtesy of the Department of Cardiology at the Heronimus Bosch Hospital, Den Bosch, the Netherlands.

Figure 2. Risk factors, trigger factors and myocardial vulnerability in atherosclerosis and coronary heart disease (scheme modified after Oliver18 and Grobbee14).
Myocardial Vulnerability

Equally important is the concept of myocardial sensitivity to episodes of ischemia due to reduced coronary flow. The ischemic episode has to exceed a specific threshold value in duration or severity, in order to produce clinical events such as sudden MI or even sudden cardiac death. This threshold value depends on the sensitivity of the myocardium to ischemia, which is determined by (among other factors) its level of protection—for example, by the presence of a collateral circulation.

At present, there are few methods to simply measure the sensitivity of the myocardium to ischemia due to sudden partial or complete reduction of blood supply. Important factors that have been shown to negatively affect myocardial vulnerability include left ventricular hypertrophy (LVH), diastolic heart failure, and previous MI. These conditions are frequently present in older individuals. The presence of LVH predisposes to ischemia via several mechanisms. There is an inadequate coronary growth relative to muscle mass, resulting in a decreased capillary density. The increased wall thickness increases the epicardial–endocardial distance, resulting in greater transmural loss of subendocardial perfusion pressure and lower subendocardial perfusion pressure. Coronary remodelling occurs with increased medial thickness and perivascular fibrosis. This results in an altered coronary vascular resting tone and a limited ability to increase myocardial perfusion and coronary flow, and a rise in oxygen demand in response to stress. A vicious cycle is created, in which LVH predisposes to ischemia, the ischemia causes an exaggerated impairment of relaxation in the heart with LVH, and this in turn worsens the severity of the subendocardial ischemia.

Other factors that affect myocardial vulnerability include smoking, chronic renal insufficiency, diabetes mellitus, systemic hypertension, restrictive cardiomyopathy (most often amyloidosis), aortic valve stenosis, and hypertrophic cardiomyopathy.

Determinants of Coronary Collateral Circulation

Myocardial Ischemia

Recurrent and severe myocardial ischemia is assumed to stimulate the development of coronary collateral circulation. Takeshita et al suggested that coronary collaterals develop in response to intermittent myocardial ischemia and that these collaterals are preserved even if they are closed at rest, in order to offer immediately function on acute coronary artery occlusion, after reperfusion. Indeed, Herlitz et al showed that patients with chronic angina pectoris (AP) before an acute MI had smaller infarcts compared with patients with AP of short duration before an acute MI. They had, however, a higher 1-year mortality rate and a higher risk of reinfarction. This probably reflects more extensive coronary artery disease (CAD) in these patients, with a higher risk of death. Besides, the fact that the patients with chronic AP had smaller infarcts might leave them with a larger area at risk, and thus they would be more likely to develop a reinfarction. Myocardial ischemia, per se, can be a sufficient stimulus to induce coronary collateral development, possibly through biochemical signals, including release of angiogenic growth factors. Exposure to low oxygen levels, both in vitro and in vivo, induce accumulation of vascular endothelial growth factor (VEGF) mRNA. Many other genes directly or indirectly involved in angiogenesis are also upregulated in response to hypoxia—among others, the VEGF receptors and transforming growth factor (TGF)-β. A transcriptional complex, composed of hypoxia inducible factors, serves to augment expression of several of the genes involved in angiogenesis and cell survival. However, the growth of collateral arteries through arteriogenesis is not dependent on ischemia. Collateral arteries develop in nonhypoxic tissue. Whereas angiogenesis is induced by hypoxia, arteriogenesis is induced by an increase in shear stress. The chemokines and growth factors involved in both processes also differ. Factors inducing angiogenesis (among others, TGF-α, VEGF, and basic fibroblast growth factor [b-FGF]) induce proliferation of endothelial cells, whereas factors stimulating arteriogenesis (among others, TGF-β, granulocyte-macrophage colony-stimulating factor [GM-CSF], and b-FGF) also induce proliferation of smooth muscle cells.

Pressure Gradient and Shear Stresses

The process of arteriogenesis is mediated mechanically through an increase in shear stresses. For example, in the event of a hemodynamically relevant stenosis of a main feeding artery, a pressure gradient is created and collateral arteries are recruited. Because of the decrease in arterial pressure distal to the stenosis, blood flow is redistributed through the preexistent arterioles that now connect a high-pressure with a low-pressure area. This results in an increased flow velocity and therefore increased shear stress in the preexistent collateral arteries, which leads to a marked activation of the endothelium, upregulation of cell adhesion molecules, and increased adherence of monocytes, which transform into macrophages. Subsequently, several morphological changes and vascular remodeling occur.

Growth Factors

Different growth factors and chemokines are involved in angiogenesis and arteriogenesis. These include VEGF, TGF-α, and acidic fibroblast growth factor (a-FGF) in angiogenesis; and GM-CSF, monocyte chemoattractant protein-1 (MCP-1), and TGF-β in arteriogenesis. Some growth factors play a role in both processes: for example, b-FGF and PDGF (platelet-derived growth factor). In ischemic tissue, enhanced expression of several angiogenic factors and their receptors has been demonstrated. Conversely, impaired collateral circulation in diabetes, hyperlipidemia, and aging has been associated with reduced expression of angiogenic factors. Several studies have reported increased levels of circulating angiogenic factors in patients with ischemic heart disease, stroke, or limb ischemia, probably in response to tissue ischemia and injury. Finally, Sasayama et al observed that mast cells are associated with neovascularization by increasing endothelial cell migration as the earliest event in the formation of a capillary sprout. They even proposed to treat ischemic heart disease with drugs (heparin) to promote...
the development of coronary collateral circulation. Since then, this concept of therapeutic angiogenesis and arteriogenesis has attracted much attention.11 Interesting results have recently been published on therapeutic angiogenesis in peripheral artery disease by enhancing collateral development through administration of angiogenic growth factors.27,28 In ischemic heart disease, early studies, using recombinant proteins, or genes encoding for vascular growth factors, showed encouraging results with clinical improvement, and suggested slightly improved myocardial perfusion in the treated area. However, subsequent trials failed to demonstrate a treatment effect.11,12

**Collateral Circulation and Prognosis**

Coronary collaterals may help protect the myocardium in patients with CAD. They limit myocardial ischemia during coronary occlusion in patients.39 Fukai et al30 found that well-developed coronary collaterals may minimize the infarct area and predict the presence of viable myocardium in patients with a history of anteroseptal MI. Sabia et al31 demonstrated that the myocardium may remain viable for a prolonged period in patients with a recent acute MI and an occluded infarct-related coronary artery in the presence of collaterals. Myocardial viability appeared to be associated with the presence of coronary collateral blood flow within the infarct bed. In case of an acute MI, the presence of coronary collaterals may extend the period of time available until successful coronary reperfusion.32,33

Collateral circulation can be visualized on coronary angiography.34 The degree of collateral filling on angiography has been related to AP and the extent of previous MI in patients with CAD.29,30 Similarly, the degree of collateral filling could predict the presence of residual viable myocardium in patients with an old MI.30 However, studies in which collateral extent and function are studied as prognostic determinants of vascular outcome are hardly available. Only recently, Antoniucci et al35 published a study on the significance of preintervention angiographic evidence of coronary collateral circulation in patients with acute MI who underwent primary angioplasty or stenting within 6 hours of symptom onset. At 6 months, the mortality rate was lower in patients with coronary collateral circulation compared with patients without collaterals, without clear effects on clinical outcomes.35

However, this study only considers the presence of coronary collaterals in patients with acute MI. Also, the duration of follow-up was rather short. Clearly, cardiovascular end-point studies with long-term follow-up are needed, in which collateral extent and function are studied as prognostic determinants of vascular outcome in patients with significant atherosclerosis.

We postulate that the potential of individuals to develop collaterals should be considered an additional indicator of cardiac vulnerability. The ability to develop collaterals is likely to provide an important response to vascular occlusive disease and to determine in part the severity of ischemic tissue damage.

**Conclusion**

The potential of individuals to develop coronary collateral circulation is often neglected but is of potential major importance in myocardial vulnerability. Well-developed coronary collaterals may help protect the myocardium from infarction during episodes of ischemia and may extend the limited number of valuable “golden hours” from the onset of an acute myocardial infarct to successful coronary reperfusion. Promising results have recently been published on gene therapy in CVD by promoting collateral development through the administration of angiogenic growth factors. Still, cardiovascular end point studies with long-term follow-up, in which collateral extent and function are studied as prognostic determinants of vascular outcome, are needed to determine the position of collaterals in the mechanisms leading to ischemic events in patients with significant atherosclerosis. This may indicate new opportunities for prevention of reevents in patients suffering from CAD or for prevention of events in those with advanced coronary atherosclerosis.

**Acknowledgments**

Funding for this paper was received as part of a program grant from the Netherlands Organisation for Scientific Research–Medical Sciences (NWO-MW; project No. 904-65-095). This funding source had no involvement in the writing of this paper or in the decision to submit it for publication. We thank the Department of Cardiology at the Jeroen Bosch Ziekenhuis, Locatie Groot Ziekenhastu (‘Her- onimus Bosch Hospital”), Den Bosch, the Netherlands) for providing the angiogram depicted in Figure 1.

**References**

15. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and


**KEY WORDS:** angiogenesis • collateral circulation • coronary disease • growth substances • prevention
Coronary Collaterals: An Important and Underexposed Aspect of Coronary Artery Disease
Jeroen Koerselman, Yolanda van der Graaf, Peter P.Th. de Jaegere and Diederick E. Grobbee

Circulation. 2003;107:2507-2511
doi: 10.1161/01.CIR.0000065118.99409.5F

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/19/2507

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/