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REVIEW

Clinical update

The human coronary collateral circulation: development and clinical importance

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Coronary collaterals are an alternative source of blood supply to myocardium jeopardized by ischaemia. In comparison with other species, the human coronary collateral circulation is very well developed. Among individuals without coronary artery disease (CAD), there are preformed collateral arteries preventing myocardial ischaemia during a brief vascular occlusion in 20–25%. Determinants of such anastomoses are low heart rate and the absence of systemic arterial hypertension. In patients with CAD, collateral arteries preventing myocardial ischaemia during a brief occlusion are present in every third individual. Collateral flow sufficient to prevent myocardial ischaemia during coronary occlusion amounts to one-fifth to one-fourth the normal flow through the open vessel. Myocardial infarct size, the most important prognostic determinant after such an event, is the product of coronary artery occlusion time, area at risk for infarction, and the inverse of collateral supply. Well-developed coronary collateral arteries in patients with CAD mitigate myocardial infarcts and improve survival. Approximately one-fifth of 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. It should aim at growth of large conductive collateral arteries (arteriogenesis). Potential arteriogenic approaches include the treatment with granulocyte colony-stimulating factor, physical exercise training, and external counterpulsation.

Keywords Coronary circulation • Collateral circulation • Anastomosis • Angiogenesis • Arteriogenesis • Vasculogenesis

Introduction

If the human coronary artery tree were a system void of inter-arterial anastomoses as stated in 1881 by Cohnheim on the basis of canine studies,[1] permanent total upstream occlusion of an epicardial branch would invariably result in entirely necrotic downstream myocardium. However, data from less historical work have indicated the absence of myocardial infarction in every other patient with chronic total coronary artery occlusion,[2] thus providing evidence for the functional existence of coronary anastomoses in the presence of coronary artery disease (CAD). However, in the absence of CAD, it was not before the patho-anatomic investigations by William Fulton that the existence of preformed human coronary collaterals was proved beyond doubt (*Figure 1*).[3] Function as opposed to structure of the coronary collateral network can be defined physiologically or in the sense of prognostic relevance: Do structural anastomoses carry detectable flow during temporary or permanent upstream native vessel occlusion? Is permanent coronary occlusion related to normal or abnormal ventricular function? Are well-functioning coronary collaterals related to improved clinical outcome?

The aim of the present article is to provide an overview of the development and clinical importance including therapeutic inducibility of the human coronary collateral circulation both in structural and functional terms.

For the present article, we searched PubMed, BIOS, and ISI Web of Science until February 2013. In addition, abstract lists and conference proceedings from the 2006 to 2012 scientific meetings of the American College of Cardiology, the European Society of Cardiology, the Symposium on Transcatheter Cardiovascular Therapeutics of the American Heart Association, and the World Congress of Cardiology were searched. We also considered published review articles, editorials, and internet-based sources of information (www.tctmd.com, www.theheart.org, www.europcronline.com, www.cardiosource.com, and www.crtonline.com) to assess potential information on studies of interest. Reference lists of selected articles were reviewed for other potentially relevant citations. The search syntax for the database Medline included the terms 'coronary circulation', 'collateral circulation', 'anastomosis', 'angiogenesis', 'arteriogenesis', 'vasculogenesis', 'survival', 'prognosis', and 'mortality'.

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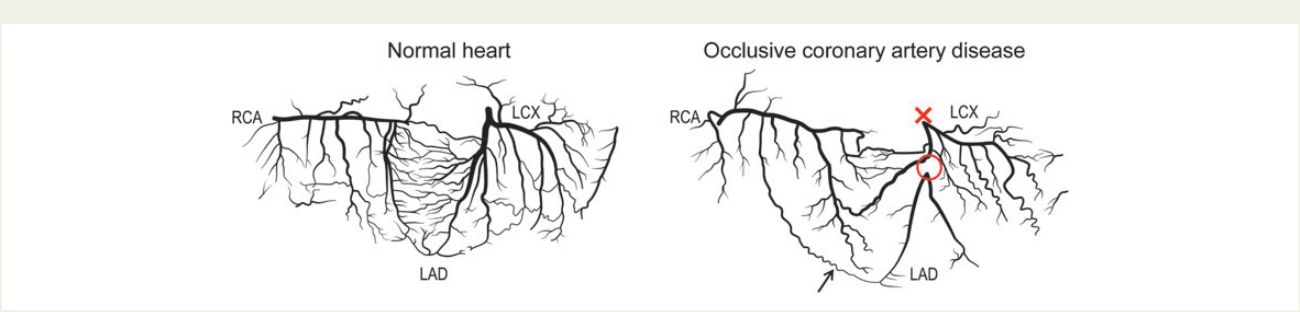

Figure 1 Post-mortem coronary arteriograms in 'unrolled' hearts from an individual without cardiac disease (left) and a patient with coronary artery disease (CAD) and two occlusions of the left main and the left-anterior descending coronary artery (red symbols). In the case with normal heart, numerous anastomoses between the LAD and the right coronary (RCA) territory via the interventricular septum are visible. In the presence of occlusive CAD, a few enlarged collateral arteries between the left and the right coronary artery are discernible; one of them distal to the LAD occlusion is a branch collateral artery between the RCA with proximal origin and distal orifice in the LAD (→). LCX, left circumflex coronary artery.

Development of the human coronary collateral circulation

Vasculogenesis occurs during the embryological development of the circulatory system and is defined as the *de novo* formation of blood vessels from endothelial precursor cells, which migrate and differentiate in response to local signals. In full-term neonates, the prevalence of coronary anastomoses as obtained in patho-anatomic studies has been consistently high.[4,5] These structural coronary collaterals found in 80% of the newborns may be interpreted as remnants of the retiform, early stages of arterial development, i.e. of vasculogenesis in embryonic life. In comparison, Zoll *et al.*[6] found structural intercoronary anastomoses in 46% of 1050 post-mortem hearts from adult patients, whereby the prevalence ranged from 9% in normal hearts to 95% in the presence of chronic total coronary occlusion (63% in CAD patients with marked arterial narrowing). Using a much more refined stereo-arteriographic, i.e. vascular overlay detecting technique with bismuth-oxychloride-gelatine radiographic contrast medium containing uniform particles sized 0.5–2.0 μm, Fulton[3] found 'numerous anastomoses in all normal hearts' as well as in those with heart disease (*Figure 1*). Fulton demonstrated a calibre increase of the anastomoses from 10–200 μm in the absence of CAD to 100–800 μm in the presence of CAD. This growth in structural vascular size goes along with a decreasing number of collateral arteries during CAD development, i.e. a process called pruning (*Figure 1*). Pathophysiologically and in the sense of the Hagen Poiseuille law, pruning may be interpreted as a way of effectively reducing vascular resistance to collateral flow, because a large caliber increase of a few vessels is more efficient for bulk flow augmentation than a small increase in size of numerous vessels. More recently, pre-formed arteriolar collaterals indistinguishable from normal arterioles have been found to have a size of about 50 μm in diameter and to consist of one to two layers of smooth muscle cells.[7] The process of arteriogenesis leads to the positive remodelling of an arteriole into an artery up to 12 times its original size.[7] First *in vivo functional* coronary collateral measurements during coronary bypass surgery and percutaneous coronary intervention (PCI) have been performed only during the 1970s.[8] The existence of *in vivo* functional coronary collaterals in the absence of CAD has not been proved before 2003 in a sizeable population.[9] Wustmann *et al.*[9] showed in 100 patients that collateral function in a briefly occluded, normal coronary artery amounted on average to ~18% of the flow through the non-obstructed vessel (collateral flow index, CFI; *Figure 2*). Every fourth individual in this population did not suffer from angina pectoris and every fifth patient did not reveal signs of myocardial ischaemia as obtained by intracoronary ECG during the 1-min coronary balloon occlusion. In comparison to other species including guinea pig, dog, cat, rat, ferret, baboon, rabbit, and pig, humans possess the most advanced coronary collateral function behind the guinea pig, the coronary artery supply of the latter is entirely replaced by collateral flow in case of a native coronary occlusion (*Figure 3*).[10] The following independent determinants of a well functioning, preformed human coronary collateral circulation in the absence of CAD have been described: low heart rate (not related to beta-blockers) and absence of arterial hypertension.[11]

Similar to the above described structural anastomotic calibre increase in the presence of CAD,[3] a shift to a more advanced coronary collateral function has been found in response to CAD development (*Figure 4*).[12] There has been evidence from experimental studies that ageing negatively affects collateral remodelling via impaired endothelial nitric oxide synthase pathways and by increased oxidative stress in coronary arterioles.[13] Notwithstanding, collateral arterioles and arteries do not seem to be prone to atherosclerosis.

Clinical importance of the human coronary collateral circulation

The rightward shift of collateral function to higher CFI values with the development of haemodynamically relevant atherosclerotic lesions is further exemplified by the fact that patients with chronic total coronary occlusion have a higher CFI in the occluded vascular area when compared with patients without chronic occlusion: 0.365 ± 0.190 vs. 0180 ± 0.105 ($P < 0.0001$).[12] Thus, collateral function is a direct indicator of CAD severity, which itself negatively influences clinical outcome. Theoretically, the human coronary collateral function

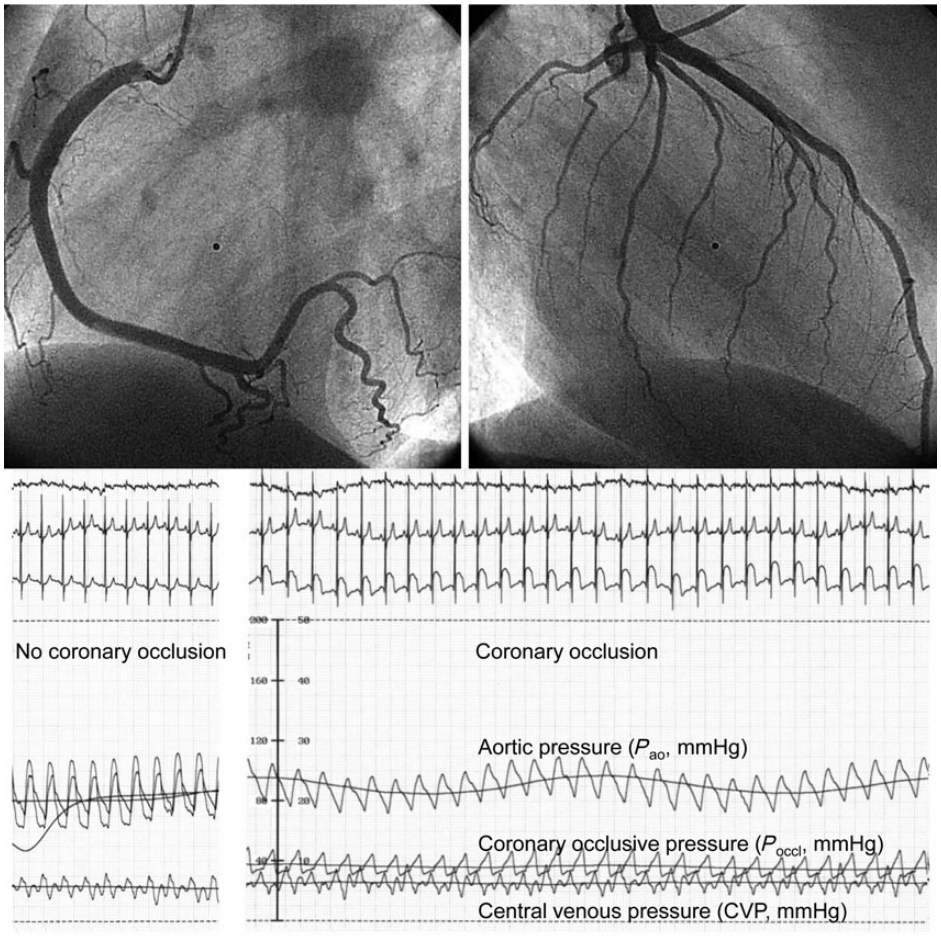

Figure 2 Normal coronary angiogram with collateral flow index (CFI) measurement in the left-anterior descending artery (lower panel). The following pressures are simultaneously recorded before (left side) and during (right side) coronary artery balloon occlusion: mean and phasic aortic, distal coronary (before and during occlusion), and central venous pressure. CFI = $(P_{occl} - CVP)/(P_{ao} - CVP)$, amounting to ~0.35 in this case.

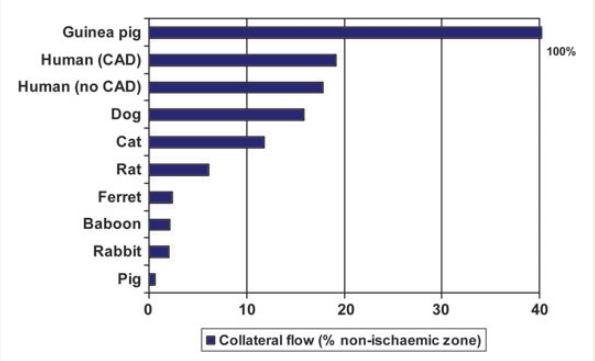

Figure 3 Inter-species differences in coronary collateral relative to normal flow in the non-occluded vessel.

can, thus, be a marker of poor outcome in CAD, while having a causal relation to favourable outcome in the context of its salvaging effect on myocardium jeopardized by flow limiting stenoses. In the *individual* patient, the myocardial salvaging effect of coronary collaterals is well known to every interventional cardiologist. Such a case is illustrated on *Figure 5*: A 55-year-old woman who was admitted for invasive cardiac examination for atypical, non-exercise-induced chest pain revealed chronic total occlusion of the proximal left-anterior descending (LAD) artery with entirely normal left-ventricular (LV) systolic function. The occluded LAD was entirely filled by a branch collateral artery extending via the LV apex and by several septal collateral arteries (*Figure 5*). In this case, the well-developed coronary collateral circulation served both as an indicator for the severity of the LAD lesion and as the cause for the preservation of the anterior wall systolic LV function. Following revascularization with stenting of the LAD occlusion, an instantaneous fall of LAD filling with contrast from the contralateral right coronary artery could be observed (*Figure 5*). Functionally, the collateral circulation has been observed also to decrease 24 h after of a chronic total occlusion revascularization, and this loss in collateral function has been documented to continue 6 months after the intervention.[14]

Figure 6 ('patient A', left side) depicts the pressure-derived CFI measurement of the above described patient with simultaneous

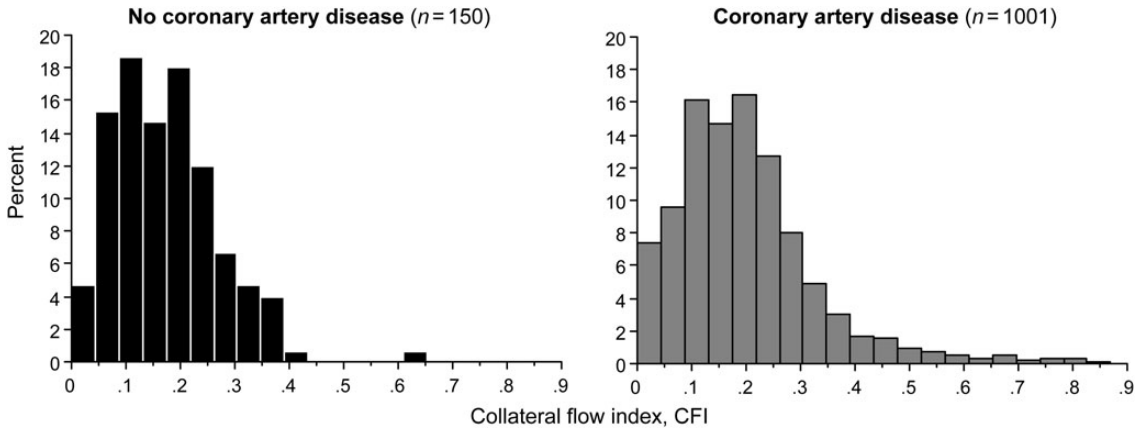

Figure 4 Frequency distribution of collateral flow index in patients without and in those with coronary artery disease.

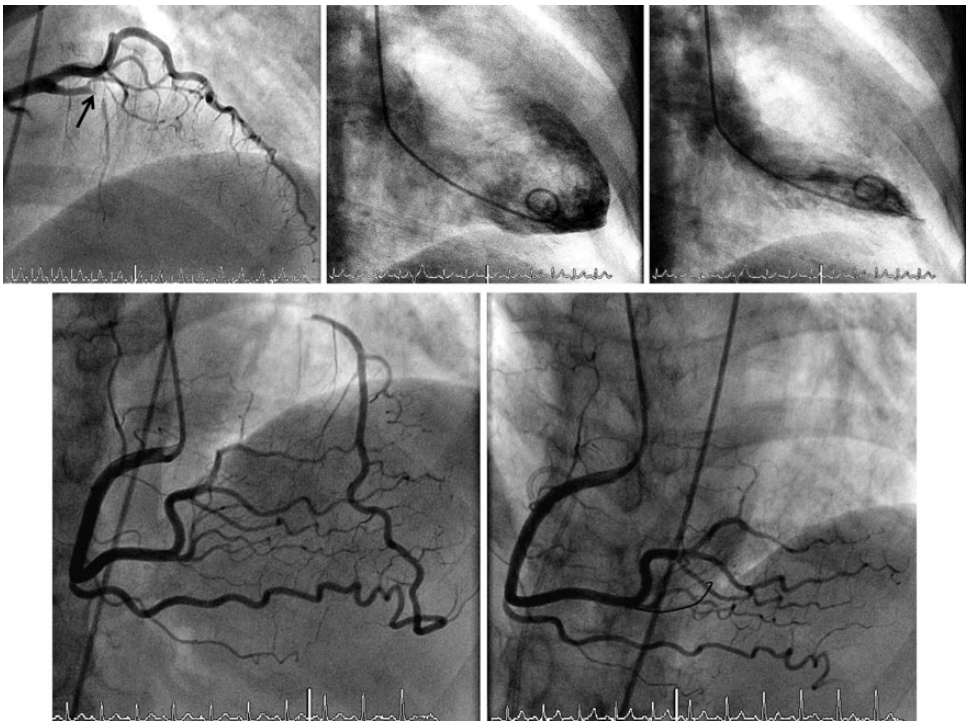

Figure 5 Chronic total occlusion of the proximal left-anterior descending coronary artery (arrow; LAD) with a normal left-ventricular angiogram (upper panels). Contrast injection into the right coronary artery of the same patient shows complete retrograde filling of the LAD via a branch collateral artery up to the proximal occlusion site (lower left panel). The filling disappears after percutaneous coronary intervention of the chronic LAD occlusion (lower right panel).

recordings of aortic, distal coronary occlusive, and central venous pressure as well as an intracoronary ECG obtained from the coronary pressure guidewire. Collateral relative to normal antegrade flow in this patient was equal to 0.76, and no ECG changes indicative of ischaemia were visible during coronary occlusion (*Figure 6*, left side). In comparison, another patient with a CFI of 0.19 (*Figure 6*, 'patient B', right side) revealed marked ST-segment elevation on intracoronary ECG during vs. before coronary balloon occlusion. The intracoronary ECG at a threshold of ST-segment elevation of >0.1 mV is widely accepted as a sensitive tool for the detection of myocardial ischaemia.[15] Accordingly, there is a second method for collateral assessment during coronary balloon occlusion, which is entirely independent of the CFI measurement, and which provides direct qualitative (>0.1 mV present or absent) or quantitative (continuous

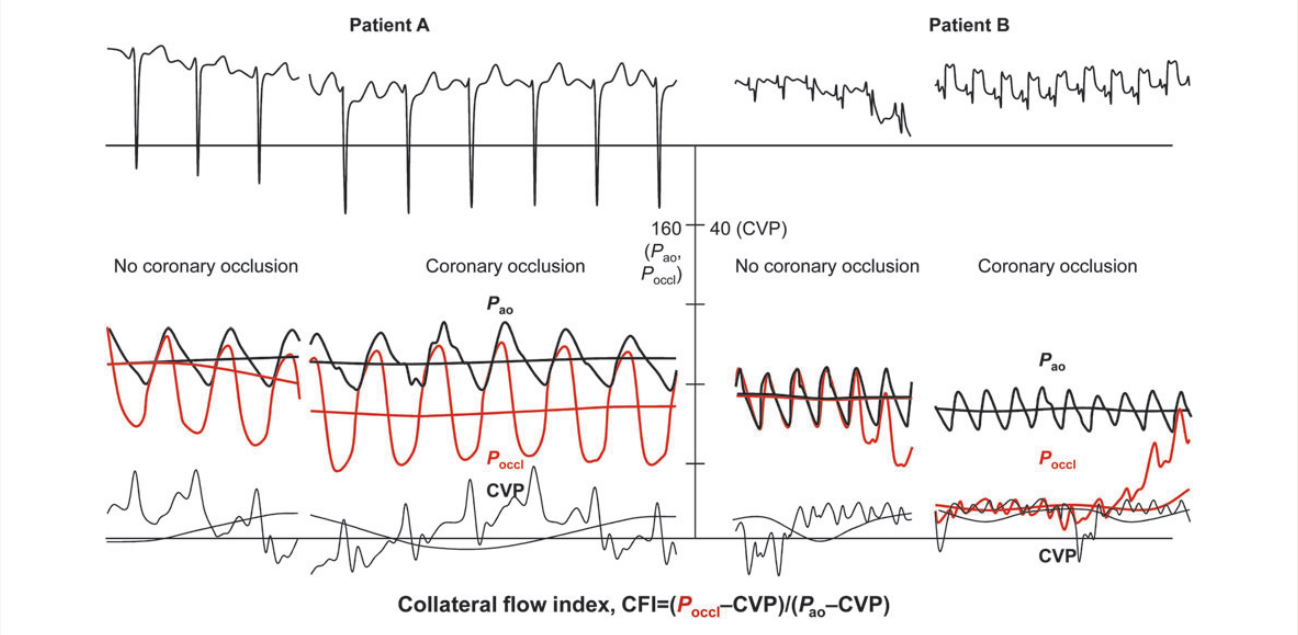

Figure 6 Left panel (same patient as in *Figure 5*, 'patient A'): Simultaneous recording of mean and phasic aortic (P_{ao}, thick line), coronary occlusive (P_{occl}, red line), and central venous (CVP, thin black line) pressure for the calculation of collateral flow index, CFI. During coronary balloon occlusion, no intracoronary ECG signs of myocardial ischaemia are visible. In comparison (right panel), 'patient B' shows a much lower P_{occl} and marked intracoronary ECG ST-segment elevation during coronary occlusion (right side of the panel).

value of ECG ST elevation or depression) information on whether collateral function is insufficient or sufficient to prevent ischaemia. Additionally, the presence or absence of angina pectoris during a systematic 1-min coronary balloon occlusions can be employed for dichotomous grading of insufficient or sufficient collateral function.[12] A strong inverse relation between CFI and the intracoronary occlusive ECG ST-segment shift (elevation or depression) as quantified in mV has been described.[11] A sufficient CFI $\geq$ 0.217 can be accurately detected using an ST-segment shift $\leq$0.1 mV on intracoronary ECG.[11] More importantly, absence of ECG ST-segment shift during brief coronary occlusion in patients with chronic CAD conveys a decreased long-term mortality.[11]

From canine studies[16] and from clinical investigations in the setting of acute myocardial infarction,[17] it has been well known that the degree of epicardial ECG ST-segment elevation is related to infarct size, and that infarct size is a prognosticator for outcome, respectively. A subsequent, large-scale investigation in patients with acute myocardial infarction has confirmed the ECG ST-segment elevation as a surrogate marker for outcome.[18] ECG ST-segment elevation itself is directly influenced by the duration of coronary occlusion, by the ischaemic area at risk, by the absence of preconditioning episodes of myocardial ischaemia preceding the infarct, by the lack of collateral supply to the ischaemic area, and by the level of myocardial oxygen consumption during coronary occlusion.[19] The ischaemic area at risk and its collateral supply are intimately and inversely related as illustrated by *Figure 5*, i.e. it may become negligible in case of extended contralateral collaterals. Also, the time of coronary occlusion may become irrelevant with sufficient collateral supply to prevent myocardial ischaemia.

In the above context, the question arises on the *collective* prognostic relevance of a well-developed coronary collateral circulation. Despite the fact that the coronary collateral circulation has long been recognized as an alternative source of blood supply to a myocardial area jeopardized by ischaemia, its prognostic relevance for the population of patients with CAD has been controversial until recently. The debate was in part related to different populations examined (acute vs. chronic CAD, varying severity of CAD), to the term 'prognosis', and to methodological issues such as the statistical power of the investigation relative to the occurrence of study endpoints, the duration of follow-up and the instrument employed to measure collateral supply. For example, two recent studies have documented a reduction in non-fatal cardiovascular events among patients with vs. those without angiographic coronary collaterals in chronic stable CAD.[20,21] Conversely, data from the same group have indicated an unfavourable prognosis in the presence of well-developed collaterals among patients with more severe chronic CAD.[22]

Acute coronary artery syndrome and clinical events in relation to collaterals: pre-primary percutaneous coronary intervention data

In a study by Waldecker *et al.*,[23] angiographic collaterals to myocardium distal to an acutely occluded coronary artery were detected in 334 of 626 patients (69%) during the acute infarct phase, whereby the prevalence was shown to increase to 75% between 3 and 6 h following symptom onset, and the absence of collaterals was related to the early occurrence of cardiogenic shock in patients

with inferior myocardial infarction. Earlier investigations have observed collateral vessels at the onset of acute myocardial infarction less frequently, i.e. in about 40% of patients.[24] Schwartz *et al.*[24] reported an analysis of the coronary collateral circulation in a series of 116 post-infarction angiograms from patients with persistent total occlusion of their infarct artery. Of 42 patients studied within 6 h of infarction, about half of them had angiographic evidence of coronary collateral development when compared with over 90% studied 1 day to 2 weeks after infarction.[24] Residual blood flow carried by collaterals at the time of acute myocardial infarction implies reduced infarct size and improved residual LV ejection fraction.[25] However, the question of whether the collateral circulation improves clinical prognosis after acute myocardial infarction has not been frequently investigated and the answer seems to be still controversial. Considering the numerous variables influencing the relevance of collateral supply in acute coronary syndrome, such as the time window of study inclusion after symptom onset, the mode of revascularization (none, thrombolysis, PCI), the differentiation of preformed or subsequently grown collaterals, the mode of collateral assessment, the debate is not unexpected.

Acute coronary artery syndrome and clinical events in relation to collaterals: primary percutaneous coronary intervention data

Investigations on the prognostic effect of collaterals in patients with successful primary PCI within the 6 h window of symptom onset are methodologically advantageous over the above described pre-PCI studies, because their populations are much more homogeneous and thus, better comparable. In a study including 238 patients with acute myocardial infarction due to mid- or proximal LAD occlusion, Pérez-Castellano *et al.*[26] found a significantly higher in-hospital mortality among patients without when compared with those with collaterals on the angiogram obtained during primary PCI. The study by Pérez-Castellano *et al.*[26] focused on collaterals present during the 6 h time window after symptom onset, and thus, examined the relevance of preformed collaterals.[26] The study by Antoniucci *et al.*[27] is comparable to that by Pérez-Castellano *et al.*,[26] since both studied the outcome in patients with acute myocardial infarction undergoing primary PCI within 6 h from symptom onset, and the rate of angiographic collaterals in both was similar, i.e. 23%, respectively, 36%. However, Antoniucci *et al.*'s[27] work included a much larger study population of 1164 patients who presented with acute infarct of any territory, and the follow-up of clinical events was registered until 6 months after initial revascularization. At 6 months, 11 out of 264 patients in the group with visible collaterals (4%) and 80 out of 900 patients without collaterals (9%) had died (*Figure 7*).[27] Steg *et al.*[28] documented in 2173 patients with subacute myocardial infarction that the angiographic presence of coronary collaterals was associated with lower cumulative 60-month event rates of death ($P = 0.009$), class III and IV heart failure ($P = 0.0001$), or either ($P = 0.0002$), but had no association with the risk of reinfarction. However, by multivariate analysis, collateral flow was neither an independent predictor of death nor of the primary trial endpoint (composite of death, reinfarction, or class IV heart failure). In recent meta-analysis on the topic,[29] the risk ratio to die from any cause for high vs. low or absent collateralization in patients with subacute myocardial infarction was 0.53 (95% confidence interval 0.15–1.92; $P = 0.335$), and for patients with acute myocardial infarction, it was 0.63 (95% confidence interval 0.29–1.39; $P = 0.257$).

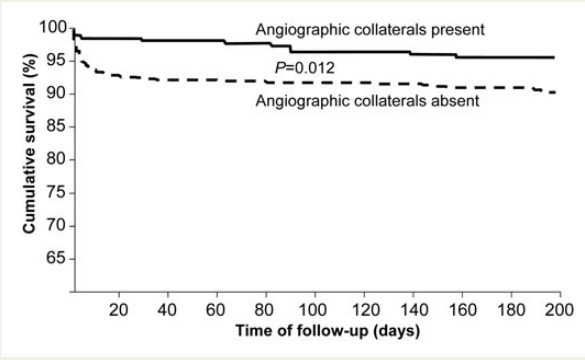

Figure 7 Cumulative survival related to all-cause mortality in patients with and without angiographically visible collateral vessels during percutaneous coronary intervention in the context of acute myocardial infarction.

Chronic coronary artery disease and clinical events in relation to collaterals

Regarding the practical dilemma of the collateral circulation being both a marker of CAD severity and a predictor of future cardiac events, the setting of acute or chronic CAD does not make a difference. Thus in both situations, an investigation focusing on the prognostic relevance of collaterals should correct for their role as indicators for CAD severity. While in acute CAD, the collateral circulation as an indicator for CAD is corrected for by primary PCI, thus rendering the study population homogeneous with regard to the variable stenosis severity, a similar effect can be reached in chronic CAD by focusing exclusively on total coronary occlusions. However, strictly speaking, chronic total occlusion with downstream *infarcted* myocardium ought to be excluded from such an analysis.

Angiographic evidence of collaterals and outcome

The majority of studies on the prognostic relevance of collaterals in chronic CAD has used angiographic assessment for characterizing the degree of collateral perfusion. It was not before 2004 that the topic regained heightened interest using the tool of angiographic collateral qualification in relation to their prognostic relevance.[20] In 281 patients randomized to off-pump or on-pump coronary artery bypass grafting, Nathoe *et al.*[20] found angiographic collaterals to be present in close to 50%. Cumulative rates of event-free survival at 1 year were 87% in patients with and 69% in those without collaterals after off-pump bypass surgery ($P = 0.01$), and the respective figures were 66 and 63%, respectively ($P = 0.79$), following on-pump surgery.[20] The protective effect of collaterals in the off-pump group appeared to be conveyed by fewer peri-operative myocardial infarcts than in the on-pump group. In an attempt to untangle the relevance of the collateral circulation as a marker of CAD severity from that as a prognostic determinant, Koerselman *et al.*[22] performed a case–control study in 244 patients admitted for elective PCI.

Angiographic collaterals were absent in 153 and present in 91 patients, and the results indicated that in chronic CAD, the presence of angiographic collaterals may indicate an adverse outcome, in particular, if present to a limited extent.[22] The authors of that study proposed that the fate of a patient is determined by the balance between CAD severity and the presence and extent of the coronary collateral circulation. The same research group studied the relation between angiographic collaterals and cardiac death or myocardial infarction at 1 year after coronary revascularization in 561 patients who were enrolled in a randomized study that compared stent implantation with bypass grafting.[21] Collaterals were present in 176 patients (31%). The adjusted odds ratio of cardiac death or infarction was 0.18 (95% confidence interval 0.04–0.78) in the presence of collaterals, and the cumulative survival free of death or infarction was 1.1% with and 5.3% without collaterals ($P = 0.01$).[21] Considering the very low absolute numbers of cardiac death and myocardial infarction of 3, respectively, 4, and of 26, respectively, 21 in both studies by Koerselman *et al.*[22] and by Nathoe *et al.*,[21] the opposing conclusions are difficult to appreciate. In comparison to these underpowered investigations, the one by Abbott *et al.*[30] compared the baseline characteristics and cumulative 1-year event rates of 6183 consecutive patients undergoing PCI by target vessel collateral status. Collateral status was defined angiographically as follows: absent ($n = 5051$), treated artery *supplied* collaterals ($n = 239$), and treated artery *received* collaterals ($n = 893$). As a major limitation of this study, the discrimination between the absence of angiographic collaterals to the artery of interest and collaterals taking off that vessel (i.e. supplying another artery) lacks any clear definition, and has to be regarded as very difficult especially in the context of registry data. Compared with the no-collaterals group, the one with PCI of a collateral receiving artery had lower adjusted death/myocardial infarction rates (relative risk of 0.72, 95% CI 0.54–0.96, $P = 0.02$) and repeat revascularization rates (relative risk 0.73, 95% CI 0.59–0.91, $P = 0.005$).[30] Cumulative 1-year mortality was 4.7% in the group without and 4.1% in the group with collaterals to the vessel undergoing PCI ($P = 0.70$). Due to the unusual angiographic collateral definition, the important all-cause mortality data are difficult to interpret. Recently, Regieli *et al.*[31] retrospectively analysed data from a lipid lowering trial involving 879 male participants undergoing coronary angiography and being followed for 24 months. The rate of collaterals spontaneously visible on angiography was assessed. Event-free survival after 2 years was 84% in patients without collaterals and 92% in patients with collaterals ($P = 0.0020$; events: cardiac death, myocardial infarction, repeat PCI, coronary artery bypass grafting). Despite the fact that the absolute numbers of death and myocardial infarction were low and similar to the abovementioned figures (eight deaths, 19 infarcts),[31] the authors concluded that the 'protective effect is independent of disease burden, and remains present in patients with extensive CAD'.

Quantitative collateral assessment and outcome

The analysis of a database on quantitative invasive collateral assessment has provided clinical and haemodynamic data of 845 individuals (age, 62 ± 11 years), 106 patients without CAD and 739 patients with chronic stable CAD, who underwent a total of 1053 quantitative, coronary pressure-derived collateral measurements between March 1996 and April 2006.[32] All patients have been prospectively included in the CFI database containing information on recruitable collateral flow parameters obtained during a 1 min coronary balloon occlusion. Collateral flow index was calculated as described earlier (*Figures 2* and *6*). In this study by Meier *et al.*,[32] patients were divided into groups with poorly (CFI < 0.25) or well-functioning collateral vessels (CFI ≥ 0.25). Follow-up information on the occurrence of all-cause mortality and major adverse cardiac events after study inclusion was collected. Cumulative 10-year survival rates free of all-cause and cardiac deaths were 71 and 88%, respectively, in patients with low CFI and 89 and 97% in the group with high CFI ($P = 0.0395$, $P = 0.0109$) (*Figure 8*). Using Cox proportional hazards analysis, the following variables independently predicted elevated cardiac mortality: age, low CFI (as continuous variable), current smoking.[32] In the above-mentioned meta-analysis,[29] the risk ratio to die from any cause for high vs. low or absent collateralization in patients with stable CAD was 0.59 (95% confidence interval 0.39–0.89), $P = 0.012$.

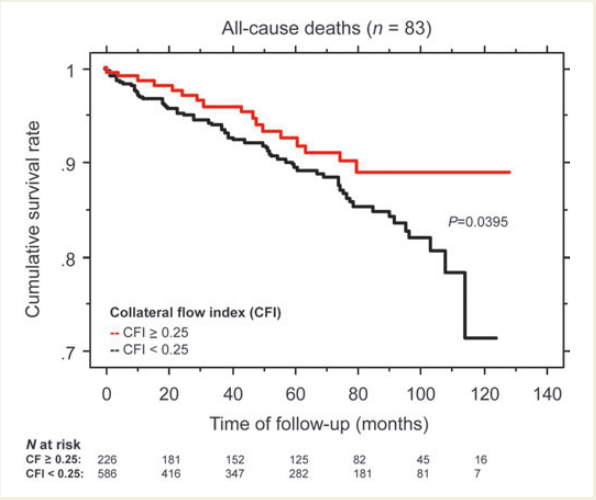

Figure 8 Cumulative survival related to all-cause mortality in patients with chronic coronary artery disease and collateral function sufficient (collateral flow index, CFI ≥ 0.25, red line) or insufficient (CFI < 0.25, black line) to prevent myocardial ischaemia during a brief vascular occlusion.

Therapeutic promotion of the human coronary collateral circulation

In the context of a relevant prognostic effect of the coronary collateral circulation among patients with CAD, the crucial question is whether it is therapeutically promotable. Angiogenesis and arteriogenesis as opposed to vasculogenesis are possible therapeutic strategies for inducing the growth of new blood vessels.

Angiogenesis

New vessels can subsequently develop from the pre-existing plexus by sprouting and intussusception. This formation of new vessels has been called angiogenesis.[33] In addition to endothelial cells, pericytes and smooth muscle cells are necessary for the maturation of these

newly growing vessels.[33] During angiogenesis, new capillaries form around zones of tissue ischaemia, as it occurs in myocardial infarction and stroke. With ischaemia, growth factors such as hypoxia-inducible factor 1α and inflammatory mediators are released locally leading to vasodilation, enhanced vascular permeability, and accumulation of monocytes and macrophages which in turn secrete more growth factors and inflammatory mediators.[34] 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 up-regulating their receptors. Endothelial cells detach from their neighbours, migrate, proliferate, and subsequently form a new vessel with a lumen. Pericytes and smooth muscle cells are also involved in this process.

Although animal studies have established the principle that collateral function improves after delivering angiogenic growth factors,[35] and although first uncontrolled clinical studies have demonstrated safety and feasibility of vascular endothelial growth factor and basic fibroblast growth factor,[36] efficacy of angiogenic therapy has not been shown so far.

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 several weeks following an occlusion, and they arise from preformed collaterals. The remodelling process involved in this structural recruitment of already existing collateral vessels has been termed arteriogenesis.[34,37] Large bridging collaterals are physically much more effective in salvaging ischaemic myocardium than small peri-ischaemia 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 non-ischaemic vascular region. The resulting longitudinal shear forces lead to an increased expression of certain endothelial chemokines, adhesion molecules, and growth factors. Within days, circulating monocytes attach to the endothelium of the bridging collateral vessels causing a local inflammatory reaction.[34] Matrix dissolution occurs and the vessels undergo a growth process with active proliferation of their endothelial and smooth muscle cells.

Arteriogenesis has been shown to be induced by activated macrophages,[38] by lipopolysaccharide,[34] monocyte chemotactic protein-1,[37] tumour necrosis factor-alpha, FGF, and also via granulocyte-macrophage colony-stimulating factor (recombinant human GM-CSF).[39] In two small randomized placebo-controlled clinical trials, GM-CSF has been shown to be effective with regard to sequentially and invasively obtained collateral function (CFI) in patients with CAD.[40,41] However, GM-CSF appears to be related to atherosclerotic plaque rupture and can, therefore, not be regarded safe in the treatment of patients with CAD.[41] Granulocyte-colony-stimulating factor (G-CSF) has recently been shown in a controlled randomized trial among 52 patients undergoing baseline and follow-up CFI measurements to be effective in the promotion of collateral function.[42]

Arteriogenesis is related to enhanced tangential shear forces at the vessel wall in response to increased flow through pre-existing collateral connections. 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 (*Table 1*). So far, a prospective investigation in humans on the effect of exercise regarding collateral growth has employed an insensitive instrument for collateral assessment, i.e. angiographic imaging of spontaneously visible collateral vessels, and has been negative.[43] Data from our own laboratory suggest that even in the absence of CAD collateral flow as assessed by intracoronary pressure-derived measurements is augmented substantially in response to endurance exercise training.[44] Also, a study in CAD patients participating in a 3-month physical exercise-based cardiac rehabilitation program has shown improved collateral function in comparison to a sedentary control group.[45]

Table 1 Factors that can improve the collateral circulation

Method	Remarks
GM-CSF[40,41]	Granulocyte macrophage colony-stimulating factor, a growth factor. Two small randomized controlled trials (RCT) ($n = 21, n = 12$). Stopped early because of potential plaque destabilization.
G-CSF[42]	Granulocyte colony stimulating factor. One small randomized trial ($n = 52$)
Physical exercise[45]	No randomized data
External counterpulsation[46]	One randomized controlled trial, observational studies

An alternative mechanism to physical exercise of applying augmented vascular shear forces is based on external counterpulsation (ECP), which is triggered to the ECG and executed during diastole. Recently, the first controlled trial in a group of CAD patients undergoing a 30 h program of high-pressure ECP (300 mmHg) and in a group undergoing sham ECP at 80 mmHg inflation pressure has revealed an unexpectedly high increase in CFI between baseline and follow-up at 4 weeks.[46]

Conclusions

In conclusion, the human coronary circulation has an extensive anastomotic network even in the absence of CAD. Such preformed coronary collaterals are able to prevent signs of myocardial ischaemia during a brief coronary occlusion in one-fourth of individuals, and their function is associated with low heart rate and the absence of arterial hypertension. With the development of CAD, the prevalence of collaterals sufficient to prevent ischaemia increases to one-third, and a well-developed coronary collateral function is related to reduced mortality in these patients. Therapeutic promotion of coronary collateral function is, thus, a promising concept, and potential arteriogenic approaches include the treatment with G-CSF, physical exercise training and ECP.

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