# THE HUMAN CORONARY COLLATERAL CIRCULATION

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Cardiovascular diseases, in particular coronary artery disease (CAD), are the leading cause of death in industrialised countries. Established options for revascularisation include angioplasty and surgical bypass, both of which are not suitable in 20–30% of patients in whom the extent of coronary atherosclerosis is especially severe. An alternative treatment strategy for revascularisation is therefore warranted both to control symptoms as well as to alter the course of advanced CAD. An ideal candidate to fill in this gap is therapeutic promotion of coronary collateral growth—that is, the induction of natural bypasses. In order to reach this goal, a comprehensive understanding of the human coronary collateral circulation with regard to its relevance, accurate assessment, the pathogenetic and pathophysiological aspects, and the different therapeutic options is mandatory.

## RELEVANCE OF THE CORONARY COLLATERAL CIRCULATION

The coronary collateral circulation has been recognised for a long time as an alternative source of blood supply to a myocardial area jeopardised by ischaemia. More than 200 years ago, Heberden described a patient who had been nearly cured of his angina pectoris by sawing wood each day,[w1] a phenomenon called "warm up" or "first effort angina" which was traditionally ascribed to coronary vasodilation with opening of collateral vessels to support the ischaemic myocardium. Alternatively, and more recently, "walk through angina" has been interpreted as a biochemical (that is, ischaemic preconditioning) rather than a biophysical (that is, collateral recruitment) event leading to heightened tolerance against myocardial ischaemia. Both mechanisms probably contribute to the described phenomenon, which is easily obtainable by careful history taking of the patient.[1] Aside from the controversies just alluded to, there have been numerous investigations demonstrating a protective role of well versus poorly grown collateral arteries (fig 1) showing smaller infarcts,[w2] less ventricular aneurysm formation, improved ventricular function,[w2] fewer future cardiovascular events,[2] and improved survival.[3]

However, the functional relevance of coronary collateral vessels in humans had also been a matter of debate for many years.[w3] Much of this controversy was likely the result of inadequate means for gauging human coronary collaterals and the investigation of populations too small to be representative for all the patients with CAD. The latter is well illustrated by the fact that among patients with haemodynamically significant atherosclerotic lesions, only about a third have functionally sufficient coronary collaterals which are able to prevent signs of myocardial ischaemia during brief vascular occlusions (fig 2[4]). In the absence of stenoses, it has been traditionally assumed that coronary arteries are functional end arteries.[w4] Using direct and quantitative intracoronary collateral measurements (see below), it has, however, been documented very recently that the notion of the human coronary circulation being built without preformed functioning anastomoses between vascular territories is a myth rather than reality; in the absence of obstructive CAD or even in entirely normal hearts, there has been collateral flow to a briefly occluded coronary artery sufficient to prevent ECG signs of myocardial ischemia in 20–25% of the population studied (fig 2).[5]

## ASSESSMENT

### Natural coronary occlusion model (chronic total occlusion model)

In the situation of a spontaneously occurring coronary artery occlusion without myocardial infarction, a well developed collateral circulation must be the reason for the salvaged cardiac muscle. A pathophysiological alternative to this scenario is indicated by the following equation describing infarct size (IS), and it consists of an exceedingly small ischaemic myocardial area at risk (AR)[w5]: $IS = $ coronary occlusion time $\times AR \times$ collateral supply$^{-1}$

The entire filling of a chronically occluded, collateral receiving (that is, ipsilateral) coronary artery from a collateral supplying (that is, contralateral) vessel (fig 1) illustrates that AR is closely and inversely dependent on collateral flow, to the extent that the AR of a certain vessel may

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disappear in the presence of well grown collaterals. The validity of the concept described in the above equation has been recently confirmed in the clinical setting by documenting that coronary occlusion time no longer plays a role as a predictor for IS in the presence of a collateral relative to normal flow (collateral flow index; see below) $\geqslant$ 25%.[6] Thus, to detect normal ventricular wall motion in the presence of a proximal or mid chronic occlusion represents a way of qualifying ''good'' collateral flow. The major disadvantage of this qualitative method for collateral assessment is that it requires coronary angiography to detect vascular occlusion. Having established the diagnosis of an entirely blocked coronary artery, various myocardial perfusion tracers (different radioactive tracers, echocontrast media) are in principle appropriate to measure the gold standard of collateral function (that is, absolute perfusion in ml/min/g of tissue) non-invasively by positron emission tomography or Doppler echocardiography.[w6 w7]

### Artificial coronary occlusion model (angioplasty model)

At present, invasive cardiac examination is a prerequisite for reliable qualitative or quantitative assessment of coronary collaterals. In the natural occlusion model, it is needed to confirm total vascular obstruction, and in the artificial occlusion model, it is essential for briefly blocking the vessel using an angioplasty balloon catheter. In addition, systematically consistent and *exclusive* collateral characterisation (fig 3) requires the permanent or temporary occlusion of the epicardial collateral receiving artery, yielding the so called recruitable—as opposed to spontaneously visible—collateral flow. Employing the angioplasty model, there are several qualitative and quantitative methods subsequently described which can be used to characterise the collateral circulation.

### Angina pectoris and intracoronary ECG during vessel occlusion

The simplest but rather imprecise way to qualify collateral vessels is to ask the patient about the presence of angina pectoris shortly before the end of arterial balloon occlusion.
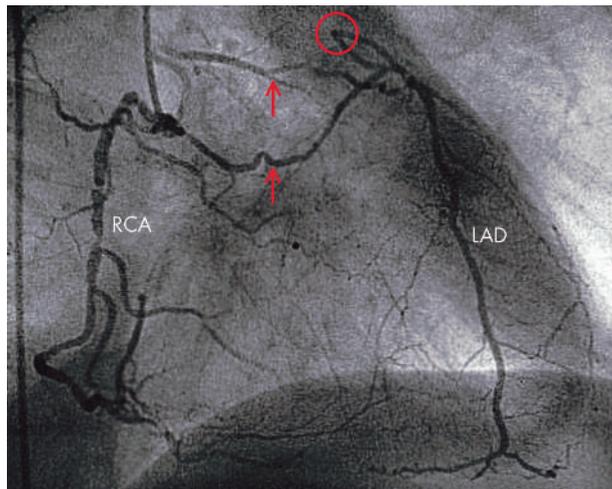


**Figure 1** Coronary angiogram with injection of radiographic contrast medium into the right coronary artery (RCA) and complete filling of the proximally occluded (red circle) left anterior descending coronary artery (LAD) via collateral channels (arrows).

The predictive value of absent or present chest pain for collaterals sufficient or insufficient, respectively, to prevent ischaemia as detected by intracoronary ECG (fig 4) is rather low.[7] The use of an intracoronary ECG lead obtained via the angioplasty guidewire for collateral assessment provides a good representation of the pertinent myocardial area. Intracoronary ECG ST segment changes of $> 0.1$ mV constitute the definition of collaterals insufficient to prevent ischaemia in the respective myocardial territory.[7]

### Angiographic methods

The coronary angiographic method for collateral qualification most widely used is similar but not identical to the one first described by Rentrop and colleagues.[8] The latter provides a score from 0–3 for recruitable collateral vessels upon occlusion of the ipsilateral artery, the former an identical score for spontaneously visible collaterals without artificial vascular occlusion. The score describes epicardial coronary artery filling with radiographic contrast dye via collaterals as follows: 0 = no filling; 1 = small side branches filled; 2 = major side branches of the main vessel filled; 3 = main vessel entirely filled. The fact that in clinical routine, just spontaneously visible collaterals are scored further impairs the method's sensitivity which is quite blunt already. Recruitable collateral vessel grading in the absence of chronic coronary occlusion, however, requires the insertion of two coronary catheters—that is, one for balloon occlusion of the collateral receiving vessel and the second for injection of contrast dye into the collateral supplying artery. An alternative, semi-quantitative angiographic method consists of determining the number of heart beats during coronary occlusion needed to wash out the angiographic medium injected into the ipsilateral artery immediately before balloon occlusion (that is, washout collaterometry[9]). The contrast dye caught distal to the occlusive balloon can only be washed out by collateral flow. A washout time of $\leqslant 11$ heart beats accurately predicts collaterals sufficient to prevent ischaemia during a brief coronary occlusion.

### Intracoronary pressure or Doppler sensor measurements

Today, pressure or Doppler sensor-tipped angioplasty guidewires are available which are almost equivalent to regular guidewires in their handling properties. The theoretical basis for the use of intracoronary pressure or blood flow velocity measurements to determine collateral flow relates to the fact that perfusion pressure ($>$ central venous ''back'' pressure) or velocity signals obtained distal to an occluded stenosis originate from collaterals (fig 3). The measurement of aortic and intracoronary pressure or velocity provides the basic variables for the calculation of a pressure derived or velocity derived collateral flow index (CFI),[7] both of which express the amount of flow via collaterals to the vascular region of interest as a fraction of the flow via the normally patent vessel. Pressure derived CFI is determined by simultaneous measurement of mean aortic ($P_{ao}$), mean distal coronary occlusive ($P_{occl}$), and central venous pressure (CVP) (fig 4): CFI = $(P_{occl} - CVP)/(P_{ao} - CVP)$. Velocity derived CFI is measured by obtaining distal occlusive coronary flow velocity ($V_{occl}$) and coronary flow velocity during vessel patency ($V_{\emptyset occl}$) taken at the same location and following occlusion induced reactive hyperaemia: CFI = $V_{occl}/V_{\emptyset occl}$. CFI measurements have been documented to be very accurate with regard to ECG derived dichotomous collateral assessment,
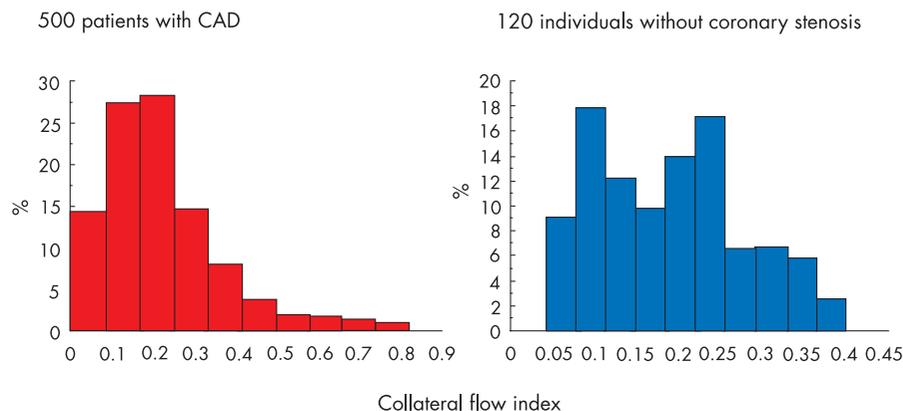
**Figure 2** Frequency distribution (per cent of the entire population, vertical axis) of collateral flow obtained during coronary artery balloon occlusion relative to normal flow during vessel patency (collateral flow index, horizontal axis). The left panel shows the distribution in 500 patients with haemodynamically relevant coronary artery stenoses. In the right panel, the distribution in 120 individuals without coronary stenoses is depicted.

with regard to each other, but also to quantitative $^{99m}$Tc-sestamibi imaging during balloon occlusion.[7 10] Pressure and Doppler derived intracoronary collateral measurements are regarded as the reference method for clinical assessment of coronary collateral flow.

## PATHOGENESIS

Clinical or ''environmental'' factors consistently described as influencing the development of coronary collaterals in humans are the severity of coronary artery stenoses,[4 8 11] and the duration of myocardial ischaemic symptoms.[11] Conversely, there has been discordant information about the influence of metabolic disorders on collateral development such as diabetes mellitus.[w8–10] In our experience encompassing 437 non-diabetic and 89 diabetic patients who underwent intracoronary collateral flow measurements, CFI (see above) is practically identical: mean (SD) 0.215 (0.146) and 0.209 (0.128), respectively (p = 0.71). A possible relevance of cholesterol metabolism on the expansion of the collateral circulation has been indicated only experimentally.[w11] The presence of systemic hypertension has also been suggested to promote well grown collaterals. Previous studies on the pathogenesis of collateral vessels in humans have often lacked sufficient patient numbers and/or quantitative means for collateral assessment. Although coronary stenosis severity is *the* independent predictor for collateral development in humans, CFI may vary for a given stenosis of, for example, 95% diameter narrowing between 0.0 and 0.70.[4] Conversely, in the absence of a coronary artery stenotic lesion, CFI ranges between 0.05−0.4.[5] Therefore, aside from the ''environmental'' factors just described, the influence of a certain genetic background or the temporarily varying up/down regulation of genes on the formation of well conductive collateral arteries even before the start of CAD must be very relevant, but so far only rarely investigated.[w12]

## FUNCTIONAL ASPECTS

Functional, haemodynamic or biophysical aspects of well grown collateral arteries relate to the fact that they constitute a network within the coronary circulation (fig 3). Such connections between adjacent vascular territories together with spatially varying vascular resistances to blood flow[w13] are the basis for pathophysiological aspects of collaterals rarely considered, such as the redistribution of blood during vasodilation away from a region in need (that is, coronary steal[12]), the decrease in collateral flow to a certain vascular region following recanalisation of a chronically occluded coronary artery,[w14] and the enhanced risk of coronary restenosis following percutaneous coronary intervention in the presence of high and competitive collateral flow to this area.[w15] The latter situation is similar to that of competitive flow between a barely stenotic coronary artery and a bypass graft to this vessel which was unnecessarily implanted; usually, the lifespan of such a bypass is very much abridged.

Regarding the vasomotor response of collateral arteries, experimental studies have shown that physical exercise induces a more than twofold perfusion increase in collateral dependent myocardium via β adrenergic and nitric oxide mechanisms.[w16] In up to 50% of patients with chronic total coronary artery occlusions, there may be no infarcted myocardium within the vascular territory supplied by the blocked vessel. It is unknown how many such patients remain completely asymptomatic, and therefore must have a normal *collateral* coronary flow reserve–that is, the capacity to augment flow in response to increased myocardial demand. However, some of the patients with chronic total occlusions without myocardial infarction suffer from chest pain on
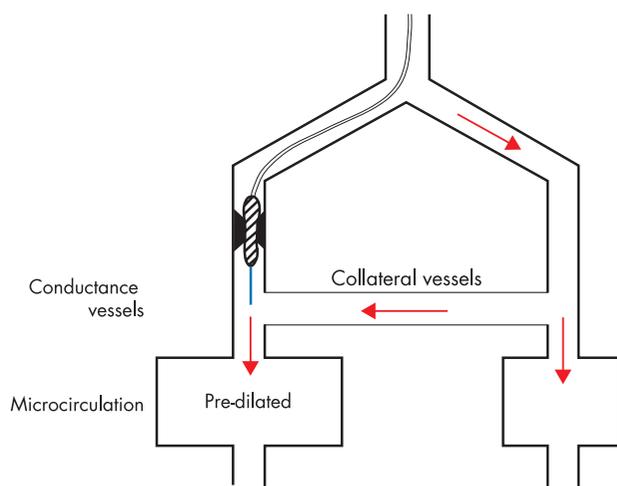


**Figure 3** Diagram illustrating the principle of collateral assessment during coronary artery balloon occlusion using an angioplasty sensor guidewire (blue line). This pressure or Doppler guidewire is positioned distal to the occluded site. Pressure signals (except for venous back pressure) or flow velocity signals detected during vascular occlusion originate from collateral vessels supplying the blocked vascular region.
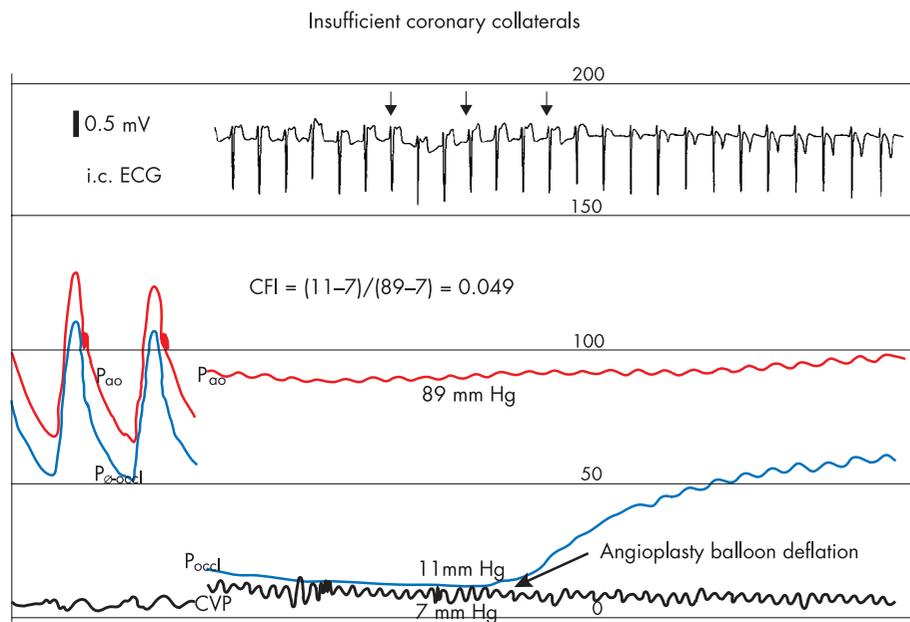
**Figure 4** Simultaneous recordings of an intracoronary (i.c.) ECG lead (top), phasic (left side) and mean (right side) aortic ($P_{ao}$, mm Hg), coronary occlusive ($P_{occl}$, mm Hg), and central venous pressures (CVP, mm Hg). $P_{ao}$ is gauged via a 6 French coronary artery guiding catheter, $P_{occl}$ via a pressure guidewire positioned distal of a stenosis to be dilated, and CVP via a right atrial catheter. To the right of the phasic pressure tracings obtained during coronary artery patency, mean pressures are recorded during and after angioplasty balloon deflation. During inflation, there are pronounced ECG ST segment elevations (arrows) indicating collateral vessels insufficient to prevent myocardial ischaemia. Collateral flow index (CFI) is calculated as follows: $CFI = (P_{occl} - CVP)/(P_{ao} - CVP)$.

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exertion, and they have been found, using positron emission tomography, to exert a reduced collateral dependent flow reserve in response to dipyridamole.[13] Interestingly, the same patients also revealed impaired systolic function in the collateral supplied left ventricular region as opposed to individuals with maintained collateral coronary flow reserve featuring normal regional wall motion.

## THERAPEUTIC PROMOTION

An alternative treatment strategy is needed in 20−30% of patients with CAD in whom the extent of coronary atherosclerosis is too severe to allow conventional revascularisation. Therapeutic angiogenesis/arteriogenesis are new strategies for revascularising ischaemic myocardial tissue by formation of "natural bypasses"—that is, collateral vessels. Understanding the many steps and regulatory mechanisms of angio- and arteriogenesis as opposed to vasculogenesis is important for designing such strategies.

### Vasculogenesis

The initial steps in the formation of the vascular system during embryonic life involve the differentiation of meso-dermal cells into angioblasts that give rise to endothelial cells forming the first primitive blood vessels.[14]

### Angiogenesis

New vessels can subsequently develop from the pre-existing plexus by sprouting and intussusception. This formation of new vessels from pre-existing ones has been called angiogenesis.[w17] In addition to endothelial cells, pericytes (for capillaries) and smooth muscle cells (for larger vessels) are necessary for the maturation of these newly growing vessels.[w17] Angiogenesis and arteriogenesis are not restricted to the growing organism. Tissue repair and regeneration (for

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### Abbreviations

**AR:** area at risk for myocardial infarction
**BFGF:** basic fibroblast growth factor
**CAD:** coronary artery disease
**CFI:** collateral flow index (no unit)
**CVP:** central venous pressure (mm Hg)
**GM-CSF:** granulocyte−macrophage colony stimulating factor
**IS:** infarct size
**$P_{ao}$:** mean aortic pressure (mm Hg)
**$P_{occl}$:** mean coronary occlusive or wedge pressure (mm Hg)
**VEGF:** vascular endothelial growth factor
**$V_{occl}$:** intracoronary occlusive blood flow velocity (cm/s)
**$V_{\varnothing occl}$:** intracoronary non-occlusive blood flow velocity (cm/s)

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### Relevance and assessment of coronary collaterals: key points

► Well developed coronary collateral arteries in patients with CAD mitigate myocardial infarcts with less ventricular aneurysm formation and improved ventricular function, reduce future cardiovascular events, and improve survival
► Collateral arteries preventing myocardial ischaemia during brief vascular occlusion are present in a third of patients with CAD
► Among individuals without relevant coronary stenoses, there are preformed collateral arteries preventing myocardial ischaemia in 20–25%
► Collateral flow sufficient to prevent myocardial ischaemia during coronary occlusion amounts to ≥ 25% of the normal flow through the open vessel
► Myocardial infarct size is a product of coronary artery occlusion time, area at risk for infarction, and the inverse of collateral supply
► Coronary collateral flow can be assessed only during vascular occlusion of the collateral receiving artery
► Presently, the gold standard for clinical coronary collateral assessment is the measurement of intracoronary occlusive pressure or velocity derived collateral flow index which expresses collateral flow as a fraction of flow during vessel patency

example, wound healing and the cyclic changes of the female reproductive system) are manifestations of angiogenesis. New capillaries form around zones of tissue ischaemia, as occurs in myocardial infarction and stroke. However, vessel formation and growth is also a part of pathogenic processes like proliferative retinopathies, psoriasis, haemangiomas, tumours, and atherosclerotic plaques.[15] Upon angiogenic stimulation—for example, after tissue injury or ischaemia with hypoxia and hypoglycaemia—growth factors 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.[w18] These inflammatory cells release metalloproteinases that dissolve the surrounding matrix and the basal membrane of the preformed vessel. Hypoxia sensitises the local endothelial cells to the chemotactic and proliferative effects of various growth factors by upregulating 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.

### Arteriogenesis

Cardiologists have long been aware of the occurrence of large and often epicardial collateral vessels after total or subtotal occlusion of a major coronary artery (fig 1). These usually become visible within two weeks following an occlusion, and they arise from preformed arterioles. The remodelling process involved in this recruitment of already existing collateral vessels has been termed arteriogenesis.[16] Large bridging collaterals are likely to be much more effective in salvaging ischaemic myocardium at risk for necrosis than small peri-ischaemic 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 arterioles. The resulting stretch and shear forces may 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.[w18] Matrix dissolution occurs and the vessels undergo a growth process with active proliferation of their endothelial and smooth muscle cells.

### Growth factor candidates

A variety of physiological molecules have been identified that appear to promote angio- and arteriogenesis. Most act by stimulating migration and proliferation of endothelial cells and/or smooth muscle cells, like the family of fibroblast growth factors (FGF) and vascular endothelial growth factors (VEGF). Both cause vasodilation by stimulating the release of nitric oxide. It is therefore important in animal as well as clinical studies to differentiate between improved perfusion caused merely by vasodilation and true collateral growth. Other growth factor candidates include placental growth factor, angiopoietin 1, transforming growth factor β, platelet derived growth factor, and about half a dozen other cytokines, proteases, and proteins.[15] Arteriogenesis has been shown to be induced by activated macrophages,[w19] by lipopolysaccharide,[w18] monocyte chemotactic protein-1,[16] tumour necrosis factor α, FGF, and also via granulocyte–macrophage colony stimulating factor (recombinant human GM-CSF; Molgramostim).[14 17]

### Clinical studies

Angiogenesis may be induced by surgical or catheter based delivery of various promotors, such as VEGF and FGF, angiogenic agents most often used in current clinical studies.[w20 w21] Although animal studies have established the principle that collateral function improves after delivering angiogenic growth factors,[w22] and although the first uncontrolled clinical studies have demonstrated the safety and feasibility of VEGF and basic FGF,[w23] efficacy data of angiogenic therapy have been scarce and controversial. The most recent and largest controlled clinical trials using VEGF165 (VIVA: VEGF in ischemia for vascular angiogenesis[18]) and FGF2 (FIRST: FGF initiating revascularization trial[19]) in 178 and 337 patients with CAD, respectively, have not shown an effect on the study end points—that is, treadmill exercise time, angina pectoris at 60 and 120 days (VIVA), and, respectively, exercise tolerance test duration at 90 day follow up and changes in the magnitude of myocardial ischaemia by Tc99m SPECT.

Controversy over the ability of angiogenic growth factors to promote coronary collaterals is likely due to the use of end points for their assessment which are too blunt to discern subtle changes in collateral flow. At this early phase of clinical angiogenic/arteriogenic therapy during which screening for the most effective growth factor among more than a dozen candidates has not even started properly, selection of the best agents ought to be based on accurate and direct invasive measurements of coronary collateral flow (figs 3 and 4)—that is, the variable hypothesised to be positively influenced by the growth factors. Equally important, angiogenic factors may have been employed which induce the formation of small, high resistance capillaries (angiogenesis) rather than large interconnecting arterioles (arteriogenesis) which are required for the salvage of myocardium in the presence of occlusive CAD. In the first randomised, placebo controlled clinical trial, GM-CSF has been shown to be effective with regard to sequentially and invasively obtained collateral flow among 21 patients with CAD.[20]

Arteriogenesis is related to enhanced shear forces at the vessel wall in response to increased flow through pre-existing collateral connections. Therefore, physical exercise would be an ideal therapeutic option for inducing arteriogenesis, because cardiac output and thus coronary flow is elevated along the arterial branches of the coronary circulation during exercise. So far, the only prospective investigation in humans on the effect of exercise regarding collateral growth has employed an insensitive instrument for collateral assessment—that is, angiographic imaging of spontaneously visible collateral vessels—and has been negative.[w24] Preliminary 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.[w25]

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