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Factors causing variability in formation of coronary collaterals during coronary artery disease

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Coronary artery disease (CAD) is one of the major causes of death worldwide. CAD is narrowing of coronary arteries that prevents adequate blood supply to the heart muscle and results in acute coronary syndrome which includes unstable angina and myocardial infarction. The only remedy for it is to restore the perfusion through percutaneous intervention and grafting which may sometime cause reperfusion injury and other complications. Coronary collaterals are small inter-arterial connections that act as natural bypass which provide blood flow to the vascular territory, when the artery supplying to it gets obstructed. Acute collateral recruitment can occurs as a remedy for these adverse cardiac events. Various methods of therapies considered for the promotion and sustenance of functional coronary collaterals. The determinants of human coronary collaterals give clear evidence for prognosis in CAD and a new insight for further therapeutic promotion of coronary collaterals. This review mainly focuses on various studies done on coronary collaterals and the effect of various demographic, morphological and cardiovascular risk factors on the formation of coronary collaterals during obstructive CAD. Many studies have proven that various independent variables such as morphology of coronary artery, location of the lesion, duration of the occlusion, coronary dominance, biochemical factors, and cardiac risk factors, such as diabetes, hypertension, also affect collateral formation. The current update review gives a holistic view on coronary collaterals and findings of various authors on the effect of these independent variables on collateral formation. (Folia Morphol 2022; 81, 4: 815–824)

Key words: angiogenesis, arteriogenesis, percutaneous intervention, collateralisation, vascular endothelial growth factors, shear stress, oestrogen receptors

INTRODUCTION

Heart diseases are a major cause of death in India. One fifth of heart disease cases are caused by complete or partial obstruction of the coronary arteries. Cardiovascular disease was a major cause of death worldwide in 2013 [8]. Reperfusion is the only method of restoration of blood flow to the area at risk, but it can cause damage to the tissue — a phenomenon called "reperfusion injury" — and also cause additional episodes of myocardial infarction, stroke and even death in elderly patients [27].

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Coronary collaterals serve as alternative conduits of blood flow during obstructive coronary heart disease [3]. The existence of coronary collaterals during coronary artery disease (CAD) was first documented in 2003 [62]. Coronary collateral circulation is an adaptive mechanism of the heart against ischaemia which aids in maintaining tissue perfusion. Collaterals are inter-arterial connections that maintain the blood flow so that the organ which is supplied by the artery is protected from ischaemia [74].

Based on studies done by Baroldi et al. [7] on angiograms and post mortem specimens it was found that coronary arteries are not end arteries but are interconnected with an arteriolar network that expands during coronary occlusion. Zoll et al. [79] showed in his studies on post mortem specimens that the grades of anastomosis between the coronary arterioles depends on the severity of coronary stenosis and it was found to be 9% in normal heart and 95% in complete stenosis. Habib et al. [25] showed in his studies that in humans the process of coronary collateralisation reduced the severity of myocardial infarction as well as helped maintain the ventricular function. Elsman et al. [19] suggested that there was much difference in the survival rate of the patients with and without collaterals and found that the survival rate is lower in patients without collaterals when compared with subject with well-developed coronary collaterals. Evidence from various studies supported the idea that the presence of coronary collaterals act as a great prognostic indicator during coronary heart disease [63]. It was found that the presence of functional collaterals promotes mortality reduction and reduces myocardial infarct size, which in turn reduces the risk of rupture of papillary muscle and interventricular septum [45].

In normal individuals even if the coronary collaterals are present, it cannot be visualised in angiogram due to its small size. Normal coronary collaterals are microvasculature and act as an alternative source of blood circulation during coronary occlusion when drastic functional and structural changes occur [14]. Fulton [24] explained that the size of normal collaterals in the absence of CAD ranges from 10–200 um and during CAD its diameter increases to 100–800 um. The development of stenosis in the epicardial artery causes ischaemia, which in turn produces pressure gradient between the donor and recipient artery and causes formation of collaterals by two processes: angiogenesis and arteriogenesis [60]. Natural coronary collaterals upon stimulation undergo remodelling to large arterioles with a calibre increment of 5–10 folds and exhibit tortuosity which distinguish it from other vessels. The expansion of natural collaterals into functional collaterals is known as arteriogenesis, while angiogenesis is the formation of new capillaries from already existing capillaries. Shear stress is the main factor leading to angiogenesis while arteriogenesis occurs without shear stress and factors affecting it are cytokines, monocytes, growth factors and stem cells [13]. Presence of collaterals maintains the viability of myocardium for longer period by extending the time buffer for successful reperfusion until the reperfusion of the occluded artery takes place by the process of thrombolysis or primary percutaneous interventions [10]. Stimulation of these coronary collaterals is the only procedure that can be done in patients having contra-indication to percutaneous intervention and bypass grafting.

CLASSIFICATION OF COLLATERALS

The collaterals include microvascular collaterals and native collaterals. Micro-vascular collaterals are arteriole-arteriole anastomoses between systemic arteries. Native collaterals are those present in healthy tissues that are free from arterial obstruction and function in normal physiological condition [79]. Anastomoses between left and right coronary arteries through native collaterals are seen abundantly during foetal life but their number decreases during the first year [16]. These channels which appear in adults range from 40–200 um in diameter and reach up the diameter of 800 um during coronary artery occlusion. The length of these coronary collaterals ranges from 1–2 cm to 4–5 cm [7]. Coronary collaterals are frequently formed in the following areas: the anterior aspect of the right ventricle, the apex of the heart, the posterior aspect of the left ventricle, and the crux of interatrial and interventricular groove [59]. Native collaterals provide an alternate source of blood during coronary occlusion and undergo drastic changes at the time of occlusion [14].

Wustmann et al. [74] classified the collateral anastomoses into homocollaterals anastomoses and intercoronary anastomoses. Homocoronary anastomoses occur everywhere except in the subepicardial layer of the heart and intercoronary anastomoses are more in subepicardial layer. Homocoronary collaterals are anastomoses between the parts of the same coronary artery and intercoronary collaterals are anastomoses between right and left coronary arteries. In his study collaterals were also classified into good and bad collaterals.

Table 1. Presence and extent of collateral supplying the occluded vessels from the homo coronary and hetero coronary collaterals are graded under a four-point scale under the Rentrop classification

Grades of collaterals	Classification
Grade 0	No filling of collateral vessels
Grade 1	Filling of collateral vessels without any epicardial filling of target artery
Grade 2	Partial epicardial filling by collateral vessel of target artery
Grade 3	Complete filling of main epicardial recipient artery by collateral vessels of target artery

Good collaterals are considered as the collaterals that can maintain the left ventricular function and bad were related with impaired ventricular function. The good collaterals with more than 100 um in diameter have protective role in maintaining the ventricular function. And these functional collaterals are formed from pre-existing arterioles by the process of arteriogenesis

METHODS OF EVALUATION OF COLLATERALS

There are various methods for assessment of coronary collateral function, which includes both invasive and non-invasive technique. The various methods of grading collaterals through invasive techniques are:

1. Grading of coronary collaterals was first described by Rentrop et al. [57] and was done by balloon occlusion of contralateral coronary artery. Collaterals were graded into grade 0, grade 1, grade 2, and grade 3 (Table 1). Collateral graded under a four-point scale under the Rentrop classification (Figs. 1, 2) [57].

   This method has limitations as it mainly depends on the pressure and flow of contrast during injection angiography. Rentrop et al. [58] documented the relation between the severity of stenosis and development of collaterals and found that collaterals increased in patients having beyond 70% occlusion. The shortfalls of the angiographic study were pointed out by Helfant et al. [26]. In their study on patients with 75% of stenosis, those with collaterals and without collaterals were compared in terms of their ventricular function. And the conclusion was made that the patients with more collaterals showed ventricular contraction abnormalities. The difference between the results of this and the previous studies was attributed to two reasons: the population selected by the earlier study had 90% of the occlusion and the samples selected were not homogenous in all respects.

2. The more recently described angiographic classification, collateral connection (CC) grades, is based on the size of the collaterals (Table 2) [73].

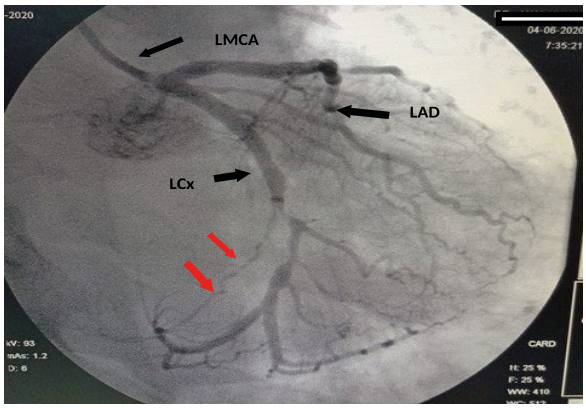

Figure 1. Coronary angiogram — complete filling of distally occluded circumflex artery via homo collateral channels (red arrows — grade 2 collateral); LAD — left anterior descending artery; LMCA — left main coronary artery; LCx — left circumflex artery.

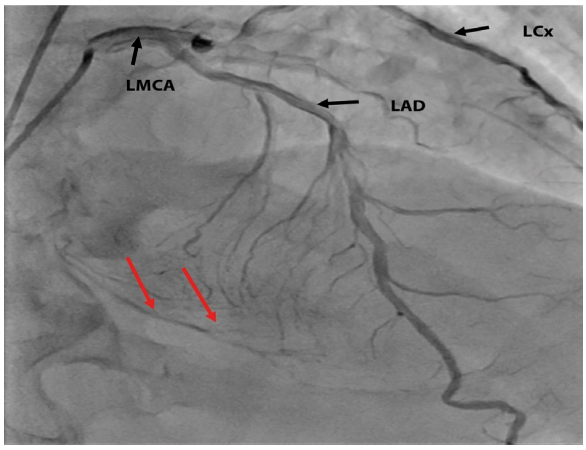

Figure 2. Coronary angiogram with injection of radiographic contrast into left main coronary artery (LMCA) (red arrow — grade 1 collaterals); LAD — left anterior descending artery; LCx — left circumflex artery.

Table 2. Collateral score evaluated according to the presence of connection between donor and recipient artery

Collateral grades	Classification
CC0	No continuous connection between the recipient and the donor artery
CC1	Continuous thread-like connection
CC2	Continuous side-branch-like size throughout the course of collateral

CC — collateral connection

3. Measuring collateral flow index (CFI). There are two methods available, one is Doppler velocity measurement and the other is pressure measurement. The use of Doppler wire to access the effect of occlusion was demonstrated first by Morton Kern's lab. But while assigning the phasic flow of collaterals it showed higher magnitude in systole which differed from diastole [55].
4. Measuring the collateral function using intracoronary electrocardiogram (ECG) lead where coronary pressure guide wire is used as ECG lead and ST segment elevation > 0.1 mV is used as threshold level to detect the ischaemia [44].

VARIABILITY IN FORMATION OF COLLATERALS

Great variability exists in the formation of collaterals in patient with similar severity of coronary heart disease. This variability depends mainly on the various factors and has individual differences [39]. Studies show that various independent variables affect the collateralisation. This includes factors like morphology of coronary artery, location of the lesion, coronary dominance, various biochemical factors, age, sex, and duration of the occlusion [42]. Collateral vessel formation is also seen impaired in metabolic syndromes such as diabetes mellitus, hyperlipidaemia and hypertension [1].

EFFECT OF THE MORPHOLOGY OF CORONARY ARTERY ON THE FORMATION OF COLLATERALS

The concept of collateral development is based on careful anatomical studies done by Jamies [33] and Baroldi et al. [7]. There are two main coronary arteries that supply oxygenated blood to the myocardium. These are left main coronary artery (LMCA) and right coronary artery (RCA). LMCA originates from the left sinus of Valsalva while the RCA originates from the right sinus of Vasalva [47]. The difference in the diameter of the ostia and their location in the sinus of Vasalva affect the amount of coronary blood flow. Usually LMCA bifurcates to left anterior descending artery and left circumflex artery. Left anterior descending artery gives septal branch and 1–3 obtuse marginal branches while RCA gives only one large acute marginal branch [65]. Studies shows that anatomic variation in orifice, courses, branching pattern and abnormalities of coronary artery, presence of myocardial bridges and coronary fistula affects the haemodynamic characteristics of the artery [4]. Various morphological changes have been noticed in studies conducted on coronary arteries. The common trunk of left coronary artery is described as 15 mm in length. Long common trunk is present in 11.5% to 18% of cases and the short trunk, which is less than 5 cm, is considered as important risk factor for coronary artery sclerosis. Banchi [6] in 1904 found in his studies that the common trunk trifurcates in 25% of cases. Frescura et al. [22] in 1946 found in his studies that the presence of third coronary artery varies between 33% and 51% of cases. Absence of LMCA is common anomaly that can be detected in 0.4–8% of the population [69]. The difference in the diameter and branching pattern of the artery influences the amount of blood flow, which in turn affects the collateralisation.

EFFECT OF MYOCARDIAL BRIDGES ON COLLATERAL FORMATION

Myocardial bridges are myocardial fibres that spread over a segment or branch of a coronary artery. The presence of myocardial bridges causes a typical angina if it is long and deep [34]. Myocardial bridges occur in 60% of normal hearts. The length of the bridges ranges from 9.69 mm to 50 mm. The myocardial bridge usually occurs around the right marginal branch and posterior interventricular branch of RCA. It is very important when present in the proximal part of the artery. It causes compression during systole and the severity ranges from tachyarrhythmia and myocardial infarction [18].

It is now accepted that coronary obstruction is an important stimulus that promotes the development of coronary collateral network. Proximal location of the lesion is found to be an independent variable determining the collateral development other than the severity of the angina pectoris [23]. The percentage of diameter and coronary artery narrowing is also an independent predictor of collateral channel.

CORONARY DOMINANCE

Identification of coronary dominance has been found to be important in the interpretation of myocardial ischaemia. Angiographic records of 2029 consecutive patients by Ajayi et al. [3] showed that right dominance influences much excellent collateralisation between the coronary arteries. Hence, coronary dominance can be considered as an important factor determining the collateral formation in CAD. In patients

with left coronary dominance, the RCA will be smaller, which have a disastrous consequence, as the potential for rapid development and reopening of collateral vessel is likely diminished. Left dominance seems to be associated with higher mortality due to acute infarction and higher incidence of atherosclerosis [11].

MECHANICAL AND CHEMICAL FACTORS AFFECTING COLLATERAL FORMATION

Shear stress

Increase in shear stress affects the collateral growth. The difference in pressure gradient during occlusion between the occluded artery and the feeding artery of the collaterals acts as a driving force to produce shear stress. The endothelial cells sense the change in this shear stress through the mechanoreceptors present in the endothelial glycocalyx. Cell adhesion is regulated by certain molecules such as cell adhesion molecule and vascular cell adhesion molecule which facilitates the adhesion of mononuclear cells in the circulatory system and mononuclear cells which induce angiogenesis [32]. Angiogenesis is the process of formation of capillaries as a result of fluid shear stress which can only partly contribute to tissue perfusion; the conversion of these capillaries into functional collateral is termed as arteriogenesis [2].

Patel et al. [52] suggested those collaterals can be formed without shear stress and ischaemia can cause collateral growth which is mainly mediated by stem cells, chemical and genetic factors.

Effect of exercise on shear stress

Exercise was found to have a positive impact on collateral growth. Nickolay et al. [49] in his studies found that exercise increases the myocardial demand, which increases coronary flow and acts as a driving force for arteriogenesis, which helps in formation of collaterals in patients with stable CAD. However, exercise would also exacerbate ischaemia during coronary stenosis; hence, shear stress was found to have minimal effect on collateralisation [45].

GRANULOCYTE MACROPHAGE COLONY STIMULATING FACTOR

Granulocyte macrophage colony stimulating factor was introduced in a randomised placebo-controlled trial to improve collateralisation and it was noticed that it in turn caused rupture of the plaque [50].

Neutrophil-lymphocyte ratio

Neutrophil-lymphocyte ratio was considered as a marker of inflammatory cardiovascular diseases [29]. Neutrophils are involved in inflammatory responses and lymphocytes play an important role in immune responses and there exist a relation between immune responses and infarction aggravation. A decrease in the lymphocyte count is associated with a poor outcome in acute coronary syndrome [51].

Monocytes

The arterial remodelling was induced by the circulating mononuclear cells, monocytes. The monocytes secrete metalloproteinases which help in arterial remodelling. Hence, it was noticed that factors such as monocyte chemoattractant protein-1 (MCP-1) and platelet-derived growth factors can induce the level of collateralisation [28]. Monocyte adhesion is associated with arteriogenesis. Shear stress caused by the change in the blood flow in the occluded and feeding artery causes activation of the endothelial cells, which increases the adhesion of monocytes. This process is supported by vascular endothelial growth factor (VEGF-A); it acts on the endothelial cells which cause an increase in the adhesion of monocytes by activation of cellular adhesion molecule [15]. Thus, VEGF-A has been shown as an inducer of collateralisation. The differences in the genetic makeup in forming monocytes also depend on formation of collaterals during CAD [40].

Eosinophils

According to studies of Toor et al. [67] eosinophils are new biomarkers for risk stratification in patients with CAD. Eosinophil count $> 0.12 \times 100$ can predict abundant coronary collateral circulation with 72.5% probability and 58.4% specificity. According to Verdoia et al. [68] the number of collaterals is higher in patients with high level of eosinophils. Wang et al. [72] investigated the relation between the eosinophil count and collateral development and found that the number of eosinophils is high in people with high level of collateral development.

EFFECT OF VEGF ON THE PROCESS OF ARTERIOGENESIS

Studies show that by increasing the level of VEGF-A by recombinant gene coding for VEGF-A, a great improvement in the formation of collaterals is observed [41]. The growth factors released during angiogenesis are induced by VEGF mRNA [17].

Impaired VEGF-A in diabetes mellitus causes low collateralisation [70]. VEGF-A induces monocyte migration, which is disturbed in diabetes mellitus [71]. Kranz et al. [38] studied on the level of VEGF-A in the blood serum during acute myocardial infarction with the help of immuno-radiometric assay. The level of VEGF-A in the serum was measured in healthy individuals and in patients with unstable angina pectoris. This was also compared with the level of VEGF-A in the blood of sub-coronary sinus in patient with sub-acute myocardial infarction. The level of VEGF-A in healthy controls was 98 (75–137) pg/mL and in patients with unstable angina ii was 116 (57–140) pg/mL. The level of VEGF-A taken from the coronary sinus was noted as 61 (43–83) pg/mL, which shows that the main source of VEGF in the serum is not the infracted myocardium. Hung et al. [30] assessed the diagnostic value of serum VEGF-A for distinguishing acute coronary syndrome from stable angina in 248 CAD patients and 48 healthy subjects. They concluded that the level of VEGF-A was higher in CAD patients compared to those with stable angina pectoris.

IMPAIRED COLLATERALS AND CARDIAC RISK FACTORS

Gender and age

Aging reduces the arterial remodelling, which in turn decreases collateral-depended flow that acts as a recovery for acute obstruction in coronary arteries [21]. Aging compromises mobilisation and homing of stem cells and inflammatory cells, which induces collateral remodelling. Aging reduces the stem cell capacity to secrete cytokines which help in remodelling of collaterals [75].

Studies shows that gender is not related to the collateralisation, but still some studies shows that collateralisation is more in females with multi-vessel disease. Chigogidze et al. [12] conducted a review of all articles of the last 10 years and found that no research was on gender differences in collateral formation and circulation. About 96% of the female affected by coronary heart disease are above the age of 50 and post-menopausal, which may lead to the inference that oestrogen directly modulates angiogenesis by its effect on the endothelial cells [48].

The protection against cardiovascular disease in women during reproductive age is believed to be related at least in part to oestrogen, since endogenous levels of oestrogen and the expression of oestrogen receptors differ considerably between sexes. Oestrogen mediates its cardio protective actions by increasing angiogenesis and vasodilation and decreasing reactive oxygen species, oxidative stress, and fibrosis. Through these mechanisms, oestradiol limits cardiac remodelling and attenuates heart hypertrophy [31].

Smoking and alcohol

Koerselman et al. [36] conducted a cross-sectional study on the effect of smoking and alcohol on the coronary collaterals and found association between the lifestyle behaviours and the level of collateralisation.

EFFECT OF METABOLIC SYNDROMES SUCH AS DIABETES MELLITUS AND HYPERTENSION ON COLLATERALISATION

Patients with metabolic syndrome had increased risk of cardiovascular mortality and morbidity. The metabolic syndrome which is accepted as a cardiovascular risk factor includes impaired glucose metabolism, elevated blood pressure, dyslipidaemia and central obesity. The metabolic syndrome is highly prevalent in patients with vascular diseases [20].

Hypertension

Koreselman et al. [35] found in his studies that high blood pressure with coronary obstruction causes impaired collateral formation. Studies showed that diastolic prolongation is also associated with improved collateral growth. Patel et al. [53] found that patients with heart rate of 50 beats develop more collaterals compared to patients with 60 beats per minutes. Pressure increases fluid shear stress on the endothelial cells, which in turn increases the level of collateralisation or remodelling pressure [66].

Diabetes mellitus

The mortality in CAD is found to be higher in diabetic patients and the adverse effect of diabetes mellitus on prognosis of coronary artery is well known [9]. Great difference in recruitment of coronary collaterals in diabetic and non-diabetic patients have been shown in angiographic studies. The influence of diabetes mellitus on CAD is in controversy. It is mainly based on angiographic study, as angiographic method is considered as semiquantitative method for assessing the collateral formation in diabetes mellitus [62]. Diabetes mellitus causes endothelial dysfunction and structural changes in microcirculation, which negatively influence the development of collaterals [61]. The difference in

the collateral development in the diabetic patients is due to the impaired endothelial function in diabetes [70]. Microvascular resistance is higher in diabetic patients and this resistance determines the bloods flow distal to the occluded vessels, which results in impaired collateral recruitment [54]. Kornowski [37] showed that collateral grade is associated with hyperlipidaemia and is negatively associated with diabetes mellitus. Studies based on CFI show that collateral formation is independent of diabetic mellitus and the degree of collaterals depends on the coronary artery stenosis. It was found that collateral score is similar in patients with duration of stenosis less than 5 years. And the difference is showed only in patients with duration between 5 and 10 and more than 10 years. Hyperinsulinaemia brings both functional and structural changes in blood vessels. Functional changes are through nitric oxide by receptor-mediated resistance, which maintains the vasodilation, and structural changes occur by proatherogenic responses mediated by MAP kinase pathway, causing significant changes over a period of time [64]. Earlier studies suggested that diabetic patients had poor collateral formation [43], but recent studies have shown that it is independent of diabetes mellitus and the degree of collateral formation is only depended on the degree of coronary artery stenosis [46]. Zbinden et al. [77] studied 200 patients of which 100 were diabetic and 100 non-diabetic, of this 174 had stenosis and 26 were angiographically normal. Doppler guide wire was used to calculate the coronary flow velocity. The patients were homogenous in all respects and this study found no difference in the coronary flow index between the diabetic and non-diabetic patients.

Pohl et al. [56] conducted a study in 450 patients who underwent angioplasty and collateral flow was measured using Rentrop classification. Also, CFI was measured using sensor-tipped percutaneous transluminal coronary angioplasty guide wire. Multivariate analysis of factors such as gender, age and various cardiovascular risk factors was performed and found that myocardial ischaemia and coronary lesion severity are the only factors that determine the collateral flow. Ansari Anvil et al. [5] studied on the clinical determinants of collateral formation. Medical history was correlated with the angiographic evidence of collateral blood flow and there was no relation between the grades of collateral formation and the risk factors. Still, there are few studies that reported the set of variables such as age, gender, smoking status, history of type 2 diabetes mellitus, hypertension, hyperlipidaemia, alcohol conceptions as predictors of collateral circulation.

THERAPEUTIC PROMOTION OF COLLATERALS

Stem cells therapy

Stem cells therapy with vascular progenitor for vascular endothelial cells stimulates collateral in rat models. When these stem cells are engrafted into the blood vessels it was found better than pluripotent stem cells and mesenchymal cells in preclinical studies [76]. If the preclinical model mimics all the risk factors that inhibit the growth of collaterals, it would make an effective therapeutic strategy. If we consider these factors, the young healthy animals are not any way similar to the aged human with lots of risk factors. Thus, the administration of vascular endothelial factors given directly into the cardiac tissue doesn't cause any useful clinical impact. It has been found that arteriogenic therapies by growth factors showed subsequent development of collaterals in patients with stable angina, but in some patients it progressed to unstable angina [78].

CONCLUSIONS

Collateral formation and its remodelling depends on multiple factors, which leads to variability in the quality and function of collaterals during CAD. The effect of various demographic, morphological and cardiac risk factors on formation of coronary collaterals remains as an inconclusive issue. Therapeutic promotion of these collaterals is essential as these are alternative sources of blood flow, which results in long term mortality reduction. Further studies should be conducted on various factors affecting the collateral formation in obstructive coronary diseases to open new strategies for therapeutic promotion of collateralisation. Aiding and promoting collateralisation can help overcome the severe limitation of therapies available in cardiovascular diseases treatments and also can open new horizons in the treatment of CAD. A complete knowledge about various factors causing variability in the formation of these collaterals give way for more effective methods of understanding and employing therapeutic strategies.

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