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

S. Balakrishnan, B. Senthil Kumar, Factors affecting the formation of coronary collaterals

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ABSTRACT

Coronary artery disease is one of the major cause of death worldwide. Coronary artery disease are narrowing of coronary arteries that prevents adequate blood supply to the heart muscles 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 be done, as a remedy for these adverse cardiac events. Various methods of therapies have been focussed, for the promotion and sustenance of functional coronary collaterals. The determinants of human coronary collaterals give clear evidence for prognosis in coronary artery diseases and a new insight for further therapeutic promotion of coronary collaterals. This review mainly focus into various studies done on coronary collaterals and the affect of various demographic, morphological and cardiovascular risk factors in the formation of coronary collaterals during obstructive Coronary artery

disease. Many studies prove that various independent variables like morphology of coronary artery, location of the lesion, duration of the occlusion, coronary dominance, biochemical factors, cardiac risk factors like diabetes, hypertension also affects collateral formation. The current update review gives a holistic view on coronary collaterals and findings of various authors on the affect of these independent variables on collateral formation.

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

INTRODUCTION

Heart diseases are a major cause of death in India. One fifth of heart disease is caused due to complete or partial obstruction of the coronary arteries. Cardiovascular disease remains a major cause of death worldwide in 2013 [1]. Reperfusion is the only method of restoration of blood flow to 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. [2]

Coronary collaterals serve as an alternative conduits of blood flow during obstructive coronary heart disease. [3] The existence of coronary collaterals during coronary artery disease was first documented in 2003. [4] Coronary collateral circulation is an adaptive mechanism of the heart against Ischemia which aids in maintaining tissue perfusion. Collaterals are inter-arterial connection that maintain the blood flow so that the organ which is supplied by the artery is preserved from Ischemia. [5]

Based on studies done by Baroldi et al. [6] on angiograms and post mortem specimens it was found that coronary arteries are not end arteries but interconnected with an arteriolar network that expands during coronary occlusion. Zoll et al. [7] 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 which was found to be 9% in normal heart and 95% in complete stenosis. Habib et al .[8]showed in his studies that in humans the process of coronary collateralization reduced the severity of myocardial infarction as well as help maintain the ventricular function[8]. Elsman et al. [9] suggested that there was much difference in the survival rate of the patients with and without collaterals and found that the survival rate is less in patients without collaterals when compared with subject with well-developed coronary

collaterals. Evidences through various studies gathered the idea that the presence of coronary collaterals act as a great prognostic indicator during coronary heart disease. [10] It was found that the presence of functional collaterals benefited in mortality reduction, reduce myocardial infract size and which in turn reduces the risk of rapture of papillary muscle and inter ventricular septum. [11]

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 and occurs a drastic change functionally and structurally during occlusion. [12]. Fulton [13] explained that the size of normal collaterals in the absence of coronary artery disease ranges from 10-200um and during coronary artery diseases its diameter increases to 100-800um.The development of stenosis in the epicardial artery cause Ischemia which in turn produces pressure gradient between the donor and recipient artery and cause formation of collaterals by two processes Angiogenesis and Arteriogenesis.[14] Natural coronary collaterals upon stimulation undergo remodelling to large arteriole 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 called is known as Arteriogenesis, while Angiogenesis is the formation of new capillaries from already existing capillaries .Shear stress is found to be the main factor leading to angiogenesis while arteriogenesis occurs without shear stress and factors effecting it are cytokines, monocytes, growth factors and stem cells.[15]Presence of collaterals maintain 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.[16] Stimulation of these coronary collaterals is the only procedure that can be done in patients having contra-indication to percutaneous intervention and Bypass grafting.

Proximal part of right coronary artery is occluded, retrograde filling of Right posterior descending artery through via collateral channels from Left anterior descending artery (LAD)-red arrows-grade 3 collateral [23]

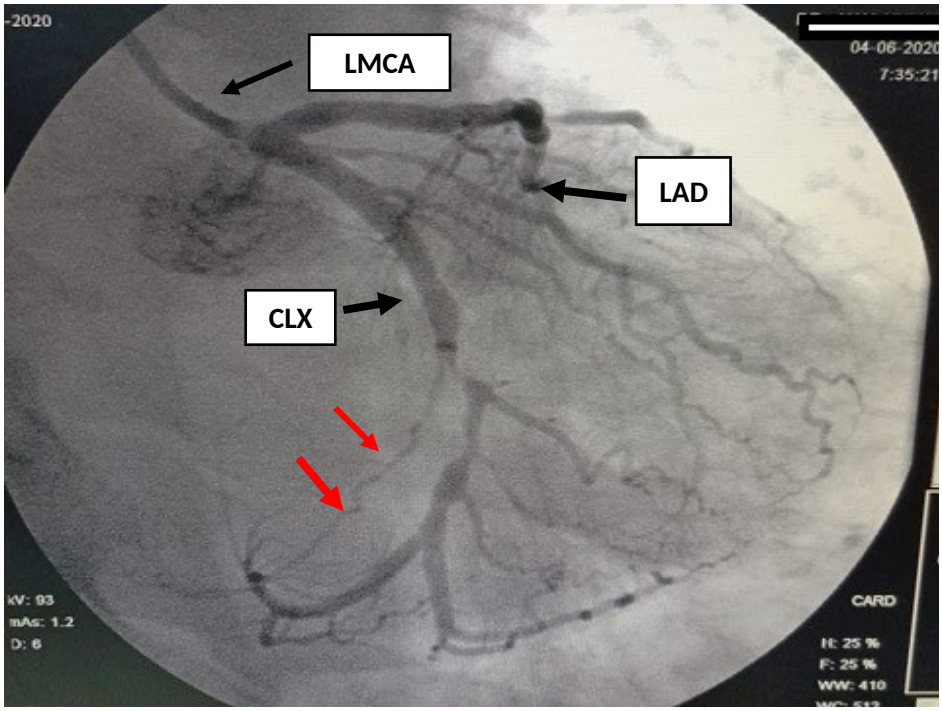

Figure 1. Coronary angiogram -complete filling of distally occluded circumflex artery CLX via homo collateral channels (red arrows-grade 2 collateral [23]

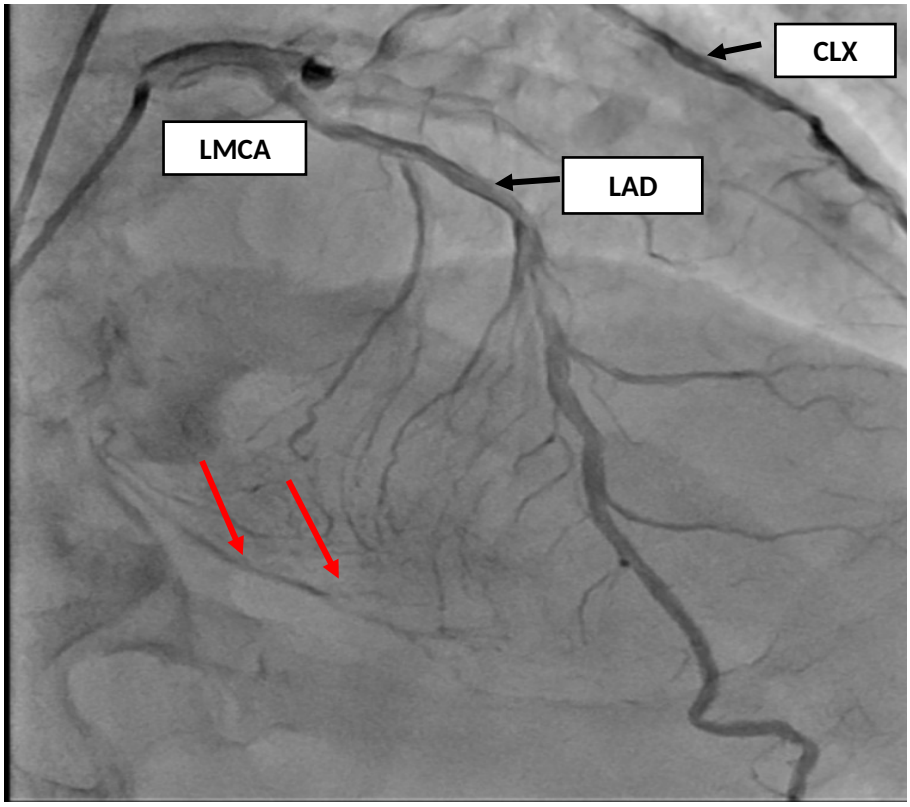

Figure 2. Coronary angiogram with injection of radiographic contrast into Left main coronary Artery (LMCA).

DISCUSSION

Classification of collaterals

The collaterals include micro vascular collaterals and native collaterals. Micro vascular collaterals are arteriole -arteriole anastomosis present in Systemic artery. Native collaterals are those present in healthy tissues that are free from arterial obstruction and function in normal physiological condition.[17] Anastomosis of left and right coronary arteries through native collaterals are seen abundantly during foetal life and reduces during first year. [18] These channels which appears in adult ranges from 40-200um in diameter and reaches up to the diameter of 800um during coronary artery occlusion. The length of these coronary collaterals ranges from 1-2cm to 4-5 cm.[19] Coronary collaterals are frequently formed in the areas like- anterior aspect of the right ventricle, apex of the heart, posterior aspect of the left ventricle, crux of Interatrial and Interventricular groove. [20] Native collaterals provide an

alternate source of blood during coronary occlusion and undergo drastic changes at the time of occlusion. [21]

Baroldi [22] classified the collaterals anastomosis into Homo collaterals anastomosis and Inter coronary anastomosis. Homocoronary anastomosis occurs everywhere except in the subepicardial layer of heart and intercoronary anastomosis are more in subepicardial layer. Homocoronary collaterals anastomosis between the parts of same coronary artery and intercoronary collaterals anastomosis between Right and left coronary artery. In his study collaterals were also classified into good and bad collaterals. 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 for 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 and was done by balloon occlusion of contralateral coronary artery.[23]

Collaterals was graded into grade 0, grade 1, grade 2, grade 3.

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

This method has limitations as it mainly depends on the pressure and flow of contrast during injection Angiography. Rentrop documented the relation between the severity of stenosis and development of collaterals and found that collaterals increased in patients

having beyond 70% occlusion.[24] The shortfalls of the angiographic study was made by Helfant, Kemp and Grolin .[25] In their study on patients with 75% of stenosis, those with collaterals and without collaterals are compared on their ventricular function. And the conclusion was made that the patients with more collaterals showed ventricular contraction abnormalities. The change of results from the previous studies was attributed, two reasons that the population selected by the earlier study had 90% of the occlusion and the sample selected were not homogenous in all respects.

(2) The more recently described angiographic classification is based on collateral connection (CC) Grades-size based classification. [26.]

Collateral grades	**Classification**
CCO	No continuous connection between the recipient and the donor artery
CCI	Continuous thread like connection
CC2	Continuous side branch like size throughout the course of collateral

(3) By measuring collateral flow index (CFI). In these two measurements are 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 differs from diastole.[27]

(4) Measuring the collateral function is intra coronary ECG lead were coronary pressure guide wire is used as ECG lead and ST segment elevation >0.1mv is used as a tool to detect the Ischemia.[28]

Variability in formation of collaterals

Great variability exists in the formation of collaterals in patient with similar kind of severity of coronary heart disease. This variability depends mainly on the various factors and has individual differences [29]. Studies show that various independent variables effects on the collateralisation. This includes factors like Morphology of coronary artery, location of the lesion, Coronary dominance, various biochemical factors, Age, Sex, duration of the

occlusion.[30] Collateral vessel formation is also seen impaired in metabolic Syndromes like Diabetes mellitus, Hyperlipidaemia and Hypertension.[31]

Affect of morphology of coronary artery in formation of collaterals

The concept of collateral development are based on careful anatomical studies done by James and Baroldi.[32] There are two main coronary artery that supply oxygenated blood to the myocardium. They are left coronary artery (LMCA) and Right coronary artery (RCA) LMCA originate from the left sinus of Valsalva while the RCA originate from the Right sinus of vasalva.[33] The difference in the diameter of the Ostia and its location in the sinus of vasalva effect the amount of coronary blood flow. Usually LMCA bifurcates to LAD and CLX Artery. LAD gives septal branch and 1-3 obtuse marginal branches while RCA give only one large acute marginal branch.[34] Studies shows that Anatomic variation in orifice, courses, branching pattern and abnormalities of coronary artery, presence of myocardial bridges and coronary fistula effect the hemodynamic characters of the artery.[35]Various morphological changes have been noticed in studies conducted on coronary arteries. The common trunk of left coronary artery is described as 15mm in length. Long common trunk is present in between 11.5% to 18% of cases and the short trunk which is less than 5cm is considered as important risk factor for coronary artery sclerosis. Banchi in 1904 found in his studies that the common trunk trifurcates in 25% of the cases. Schleringer et al .[36] in 1946 found in his studies that the presence of third coronary arteries varies between 33% and 51% cases. Absence of LMCA is common anomaly that can be detected in 0.4 -8% of the population. [37]The difference in the diameter and branching pattern of the artery effect the amount of blood flow which in turn effect the collateralization.

Affect of myocardial bridges on collateral formation

Myocardial bridges are myocardial fibres that spread over a segment or branch of coronary artery. The presence of myocardial bridges cause a typical type of angina if it is long and deep.[38] Myocardial bridges occur in 60% of normal hearts. The bridges ranges from 9.69mm and 50mm.It usually occurs around the right marginal branch and posterior Interventricular branch of Right coronary Artery. 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.[39]

It is now accepted that coronary obstruction is an important stimulus that makes 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.[40] The percentage of diameter and coronary artery narrowing is also an independent predictor of collateral channel.

Coronary dominance

Identification of coronary dominance is found to be important in the interpretation of myocardial ischemia. An angiographic records of 2029 consecutive patients by Ajayi et al .[41] found that right dominance influence much excellent collateralization between the coronary arteries. Hence coronary dominance can be considered as an important factor determining the collateral formation in coronary artery diseases. In patients with left coronary dominance the right coronary artery 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. [42]

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 act 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 like 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.[43] Angiogenesis is the process of formation of capillaries as 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.[44]

Bhamini Patel et al. [45] suggested those collaterals can be formed without shear stress and ischemia can cause collateral growth which is mainly mediated by stem cells, chemical and genetic factors.

Affect of exercise on shear stress

Exercise was found to have a positive impact on collateral growth. Nickolay et al.[46] in his studies found that exercise increase the myocardial demand which increases coronary flow and act as a driving force for arteriogenesis which helps in formation of collaterals in patients with stable coronary artery disease. But exercise would also exacerbate ischemia during coronary stenosis, hence shear stress have found to be have minimal out come in collateralization.[47]

Granulocyte macrophage colony stimulating factor

Granulocyte macrophage colony stimulating factors was introduced in randomized placebo-controlled trial to improve collateralisation and was noticed that it in turn cause rupture of the plaque.[48]

Neutrophil-lymphocyte ratio

Neutrophil-lymphocyte ratio was considered as a marker of inflammatory cardiovascular diseases. [49] Neutrophil 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 shows a poor out come in acute coronary syndrome.[50]

Monocytes

The arterial remodelling was induced by the circulating mononuclear cells, Monocytes. The monocytes secrete metalloproteinases which helps in arterial remodelling. Hence it was noticed that the factors like Monocyte chemo attracted protein MCP-1 platelet derived growth factors can induce the level of collateralization.[51] The (vascular Endothelial

growth Factors) VEGF–A act on the Endothelial cells which cause increase in the adhesion of monocytes by activation of cellular adhesion molecule. 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 VEGF –A, it acts on the endothelial cells which cause increase in the adhesion of monocytes by activation of cellular adhesion molecule.[52] Thus VEGF-A has been shown as an inducer of collateralisation. The differences in the genetic makeup in forming monocytes also depend in formation of collaterals during coronary artery diseases [53]

Eosinophil

According to studies of Toor et al. [54] Eosinophil are new biomarkers for risk stratification in patients with coronary artery diseases. Eosinophil in quantities > 0.12x 100 can predict high quantity coronary collateral circulation with 72.5% probability and 58.4% specificity. According to Verdoia et al.[55] the number of collaterals are more in patients with high level of eosinophil. JU Wang et al.[56] investigated the relation between the eosinophil and collateral development and found that the level of eosinophil is high in people with high level of collateral development.

Affect of vasculoendothelial growth factors (VEGF) in the process of arteriogenesis

Studies shows that by Increasing the level of VEGF-A by recombinant gene coded for VEGF-A great improvement in the formation of Collaterals is observed.[57] The growth factors released during Angiogenesis is induced by VEGF m RNA.[58] Impaired VEGF-A in Diabetes mellitus causes low collateralization.[59]VEGF-A induces monocyte migration which is disturbed in Diabetes Mellitus.[60]A Kranz et al .[61] 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 is measured as 98 (75-137) pg/ml and with unstable angina is 116(57-140). The level of VEGF –A taken from the coronary sinus is noted as 61(43-83) pg/ml and shows

that the main source of VEGF in the serum is not from the Infracted myocardium. Anan Hung and et al. [62] studied on the diagnostic value of serum VEGF– A on Acute Coronary Syndrome from stable angina on 248 CAD patients and 48 healthy subjects concluded that the level of VEGF-A was higher in CAD patients compared to stable angina pectoris.

Impaired collaterals in cardiac risk factors

Gender and age

Aging reduces the arterial remodelling which in turn decrease collateral depended flow that act as a recovery for acute obstruction in coronary arteries. [63] Aging compromises mobilization 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. [64]

Studies shows that gender is not related with the collateralization, but still some studies shows that collateralization is more in females with multi vessel disease .Chingogide et al.[65]conducted a review of all articles of the last ten years and found that no research was on gender differences in collateral formation and circulation .About 96% of the female effected with coronary heart disease is above the age of 50 and post-menopausal which may lead to the inference that Oestrogen directly modulates angiogenesis by their effect on the endothelial cells.[66]

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 ERs differ considerably between sexes. Oestrogen mediates its cardio protective actions by increasing angiogenesis and vasodilation and decreasing ROS, oxidative stress, and fibrosis. Through these mechanisms, E2 limits cardiac remodelling and attenuates heart hypertrophy.[67]

Smoking and alcohol

Jeroen Koerselamn et al. [68] conducted cross-sectional study on the effect of smoking and alcohol on the coronary collaterals and found association between the life style behaviours and the level of collateralization.

Affect of metabolic syndromes like diabetes mellitus and hypertension on collateralization

Patients with metabolic syndrome had increased risk of cardio vascular mortality and morbidity. The metabolic syndrome which are accepted as cardiovascular risk factors includes impaired glucose metabolism, elevated blood pressure, dyslipidaemia and central obesity. This metabolic syndrome is high in patients manifested with vascular diseases.[69]

Hypertension

Koreselman et al .[70] add in his studies that high blood pressure with coronary obstruction cause impairs in collateral formation. Studies showed that diastolic prolongation also associated with improved collateral growth. Patel et al .[71] have found that the patients with heart rate of 50 beats develop more collaterals compared to patients with 60 beats per minutes. As pressure increases fluid shear stress on the endothelial cells which in turn increase the level of collateralization or remodelling pressure.[72]

Diabetes mellitus

The mortality in coronary artery disease is found to be more in Diabetic patients and the adverse effect of diabetes mellitus on prognosis of coronary artery is well known.[73] Great difference in recruitment of coronary collateral in diabetic and non-diabetic patients have been shown in angiographic study. The influence of diabetes mellitus on coronary artery diseases is in controversy. These are mainly based on angiographic study, as angiographic method is considered as semiquantitative method for assessing the collateral formation in diabetes mellitus.[74] The diabetes mellitus causes endothelial dysfunction and structural changes in microcirculation which have negative influence in development of collaterals [75]. The difference in the collateral development in the diabetic patients is due to the impaired endothelial function in diabetic patients. [76] Micro vascular resistance is more in diabetic patients and this resistance determine the bloods flow distal to the occluded vessels which makes impaired collateral recruitment.[77] Korwashy [78] showed that collateral grade is associated with Hyperlipidaemia and is negatively associated with diabetes mellitus. Studies

based on CFI shows that collateral formation is independed of diabetic mellitus and degree of collateral depends on the coronary artery stenosis.It was found that collateral score is similar in patients with duration of stenosis less than five years. And the difference is showed only in patients with duration between 5-10 and more than 10 years. Hyper Insulinemia brings both functional and structural changes in blood vessels. Functional changes are through nitric oxide by receptors –mediated resistance which maintain the vasodilation and structural changes occur by proatherogenic responses mediated by MAP kinase pathway, cause significant changes over a period of time. [79]. Earlier studies shows that the diabetic patients had poor collateral formation and recent studies shows that it is independent of diabetes mellitus and the degree of collateral formation is only depended on the degree of coronary artery stenosis. [80] R Zhinden et al. [81] studied in 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 respect and this study found no difference in the coronary flow index between the diabetic and non-diabetic patients.

Tilmann et al.[82] conducted a study in 450 patients who underwent angioplasty and collateral flow was measured using Rentrop classification also CFI was measured using sensor tipped PTCA guide wire. Multivariate analysis of factors like gender, age and various cardiovascular risk factors were analysed and found that myocardial Ischemia and coronary lesion severity is the only factors which determine the collateral flow .Zahra Ansari anvil et al .[83]studied on the clinical determinants of collateral formation. Medical history were correlated with the angiographic evidence of collateral blood flow and found no relation between the grades of collateral formation and the risk factors. Still there are few studies that reported the set of variables like age, gender, smoking status, history of type II 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 vasculoendothelial 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.[84] If the

preclinical model mimic 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 vasculoendothelial factors given directly into the cardiac tissue doesn't cause any useful clinical impact. It is found that arteriogenic therapies by growth factors showed subsequent development in collaterals in patients with stable angina but in some it developed unstable angina.[85]

CONCLUSIONS

Collateral formation and its remodelling depends on multiple factors which leads to variability in the quality and function of collaterals during coronary artery diseases. The affect 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 source of blood flow which benefits 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 coronary artery diseases. A complete Knowledge about the various factors causing variability in formation of these collaterals give way for more effective methods of understanding and employing therapeutic strategies.

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