Gender differences in coronary collateral circulation during acute and stable ischemic heart disease

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Abstract

Background: Diseases of the cardiovascular system are seen in the whole world as the main cause of death. In women, heart attack and stroke are associated with twice increased mortality rate. Collateral blood vessels during the coronary artery disease represent an alternative source of myocardial blood circulation. They reduce the infarction area, improve the functioning of the heart, avoid development of a ventricular aneurysm. The sex-related differences in patients with ischemic heart disease in relation to the anatomy of coronary blood vessels have been established. However, the existence of gender differences in relation to the coronary collateral circulation and its determining factors is unknown.

Method: We have used PubMed and Google Scholar medical databases and retrieved the articles for the last 10 years, containing the following keywords: Coronary artery disease, Ischemic heart disease, Human coronary collateral circulation, Vasculogenesis, Angiogenesis, Gender differences in coronary collateral circulation.

Conclusion: There was not detected any credible research in terms of gender differences in coronary collateral circulation, which is a pressing issue and is still a subject of research, in the scientific articles, searched for by us in PubMed and Google Scholar medical databases for 2006-2016. (TCM-GMJ April 2018; 3 (1):P25-P31)

Keywords: Coronary artery disease, Ischaemic heart disease, Human coronary collateral circulation, Vasculogenesis, Angiogenesis, Gender differences in coronary collateral circulation.

Urgency of Problem

Cardiovascular diseases (CVD) are considered as the main cause of death in the world at present. About half of the deaths caused by non-contagious diseases come for cardiovascular diseases. Experts estimate that this number will reach 23.6 million by 2030. Heart attack and stroke in women are associated with the twice increased mortality rate. About 3.4 million women die in the world with ischemic heart diseases per year.3

Historical issues

In 1669, Hens first described the existence of anastomosis between the right and left coronary artery, and in 1757 the Swedish Albert Von Haller described the coronary anastomosis structure. However, the decisive role was not attributed to them in patients with CAD till the middle of the 20th century10,11. In 1912, James Herik described coronary thrombotic obstruction in the presence of interoceanic anastomosis12,13,14, which evidenced that coronary collateral circulation is a significant determinant of the size and quality of myocardial cells. At the same time during, percutaneous coronary intervention in vivo coronary collateral measurements (PCI) was first performed in the late 1970s15,18. The existence of functional collaterals in the atherosclerotic coronary obstruction in vivo was not documented until 200319.

Coronary Collateral Circulation, Physiology, Classification

Coronary collateral arteries have been referred to as end-arteries for decades. Currently, they are known as relevant vascular anastomosis that connects the epicardial coronary arteries and represents the alternate source of myocardium at the occlusion of main coronary blood vessels. They preserve the contractile function of the myocardium. Their growth is initiated by ischemia, although collaterals are also found in individuals who do not have a coronary artery disease. The pilot studies have demonstrated the impact of such external factors on their development, like the growth factor, granulocyte colony stimulating factor (G-CSF)20,21,22. In some patients, the collateral flow is sufficient for the normal functioning of heart in the resting condition but not during exercise23,24. Also, there is an opinion that collaterals may not prevent myocardial ischemia in the coronary occlusion. For the prevention of myocardial ischemia in case of acute occlusion of blood vessels 20 to 25% of flow have to reach myocardium25. One of the four patients without CAD has enough collateral circulation, while in the patients with CAD the same index is one from three26. The reason for this is unknown, although there is an opinion on the important role of genetic factors27,28.

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Physiology of development of collateral blood circulation (Arteriogenesis)

The most important trigger (which is also referred to as arteriogenesis) for collateral development is the indirect and variable stress on the endothelial cycle, which in parallel is occurring in the bone marrow where the mononuclear cells are worked out. In case of the main artery obstruction or occlusion, the pressure gradient is developed in the place of collateral anastomosis. It is a driving force and increases blood circulation in the collateral arteries, strengthens the vascular resistance, activates the endothelial of collateral arterioles. This process does not depend only on the patency of mechanosensory channels, and the endothelial surface. The cellular response is very important. The cytoplasm and endothelial glycoprotein, get involved in the process. Cationic channels, on the surface of cells, with their mechanical receptors and intercellular molecules (intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1) promote adhesion of circulating mononuclear cells and intermediate metabolites such as NO and other pro-angiogenic molecules. All of the mentioned lead to endothelial activation and collateral proliferation, after which protein 1 is released. The synthesis of NO occurs in the endothelial cells (NOS2 and NOS3) and it promotes not only the vasodilation but the proliferation of collateral arteries as well. The involvement of monocytes in this process, their circulation, and migration in endothelium enhances the activation of metalloproteinase (MMPs), the matrix product of cytoplasm, which is a factor of arterial remodeling. Finally, we get development and growth (angiogenesis) of the collaterals, new capillary vessels induced by ischemia. Their growth is promoted by the pressure gradient between the proximal part of the blood vessel and site of the coronary stenosis. Endothelial cells stimulate nitric oxide and MCP_1, monocytes that play a major role in collateral remodeling are involved in the process.

It is important that the collaterals are often regress. As soon as the reason is eliminated. The mentioned process is referred to as “pruning”.

Evaluation of Coronary Collateral Circulation, Classification

There is no technical and quantitative method of non-invasive evaluation during chronic total coronary occlusion. Evaluation is done visually with coronary angiography, which is known as the semi-quantitative method. It was described by Rentrop et al. and implies the balloon occlusion of the contralateral coronary artery. Collaterals from the occlusion area are classified as follows:

- grade 0-no collaterals;
- grade 1-side branch filling of the recipient artery without filling of the main epicardial artery;
- grade 2-partial filling of the main epicardial recipient artery;
- grade 3-complete filling of the main epicardial recipient artery

It should be noted that most clinicians and researchers evaluate the Rentrop classification without occlusion of collaterals, as the free (open) coronary artery increases back pressure in the collateral irrigation area and gradually reduces the degree of damage. The visual method has certain restrictions: there is no strictly objective evaluation method, affects pressure and contrast flow during injection during angiography. The second method of measuring is known as collateral flow index (CFI). 2 methods are available: First - is based on the Doppler velocity measurement, which is limited due to frequent artifacts. And second, more sophisticated considers pressure measurement. The simplest, cheaper, and most efficient method of measuring the collateral function is the intracoronary ECG.

All three methods (Rentrop score, CFI, and intracoronary ECG) are needed and represent the predictive clinical solution. There is another method of assessment, known as the washed collaterometer, which is determined by the time when distal collateral is filled with contrast substances. According to this method, the best collateral is washed more quickly.

Physiological Mechanisms of Collateral Circulation

A range of researchers has been conducted in order to clarify the physiological mechanisms of collateral circulation (Vasculogenesis, Angiogenesis, and Arteriogenesis). The role of coronary angiogenesis is important in the course of ischemic heart disease. Coronary collateral circulation preserves myocardial viability and functioning of the heart muscle. On the other hand, the risk of neurovascularization of atheromatous plaque is developed, which eventually ends with its destabilization and exclusion. That is why the study of the role of angiogenesis in the patients with ischemic heart disease is necessary.

Growth Factors (Angiogenesis and Arteriogenesis)

Angiogenesis is a well-regulated cascade reaction process, with the participation of growth factors, that eventually lead to a proliferation of endothelial cells in the new vascular network. Newly formed capillaries can restore effective perfusion only of a small area.

Arteriogenesis is a complex process involving a large number of different types of cells and growth factors as a result, large blood vessels are formed, with the well-developed media that promote restoration of the necessary effective perfusion, which in turn is the therapeutic goal of angiogenesis. Development of collateral circulation is a significant result of arteriogenesis in chronic coronary artery disease. Interaction of different factors and their involvement in the process of angiogenesis is not fully studied.

Significant growth factors include:

a) Vascular endothelial growth factor (VEGF) that enhances migration and survival processes of endothelial cells, products of the plasminogen’s activator and interstitial collagens, as well as the migration of plain muscle.

b) Transforming growth factor (TGF-β), promotes the transformation of fibroblasts and stimulation of proliferation by activation of fibrosis processes.

c) Fibroblast growth factor (FGF) - Stimulates cell proliferation and migration of embryonic mesodermic and neurotoxic origin.
d) Inhibiting angiogenesis factor – endostatin-heparin connecting fragment - Specifically inhibits endothelial cell proliferation, thus inhibiting angiogenesis (Scheme 1)\textsuperscript{46,47}.

**Arteriogenesis** is the process of transformation of the earlier (collateral) arterial to functional (muscular) collateral artery\textsuperscript{48,49,50}.

The definition of **Angiogenesis** is used to determine the formation of new capillaries, which will emerge from the pre-existing post-capillary venules\textsuperscript{51}, the further growth and remodeling of these vessels to the complex vascular network is referred to as angiogenesis\textsuperscript{52}.

Vasculogenesis involves the growth processes inside the blood vessels when the endothelial cells migrate to various locations, they gather and produce endothelial chords, and then form the endothelial tubes\textsuperscript{52}. Thick muscle membrane is necessary for the vessel to acquire vaselastie and vasomotoric\textsuperscript{52,53}.

Collateralization in patients is different. In healthy individuals, it is correlated with hypertension and depressed heart rate, while there are variable on correlations between severity of coronary artery disease and coronary stenosis, duration of angina pain, vascular proximal localization damage and long-lasting occlusion in the patients\textsuperscript{54,55}.

**Pressure gradient and shear stress**

The mediators of the processes of arteriogenesis are the increased pressure gradient and shear stresses. During the hemodynamically significant stenosis of the main artery the pressure gradient, which promotes the formation of collaterals, is developed. Distally of the stenosis blood pressure is low. The blood flow will be distributed in the existing arterioles that connect the high-pressure area with the low-pressure area. This leads to the increase in flow rate and shear stress in the existing collateral arteries, which in turn result in the endothelial activation, advances in the growth monocyte adhesion and their transformation into the macrophages. This eventually leads to morphological changes and remodeling\textsuperscript{52,53,55}.

**Myocardial Ischemia**

Myocardial repeated ischemia is a stimulating factor for the development of coronary collateral circulation\textsuperscript{55}. In the process of angiogenesis, occurring in response to the hypoxia, other mechanisms are also involved, though there is the opinion that the development of collaterals through the arteriogenesis does not depend on the ischemia\textsuperscript{55}. Collateral arteries may be developed in the non-hypoxic tissue. While angiogenesis is induced by hypoxia, arteriogenesis is induced by shear stress. Both, chemokines and growth factors are involved in the process, though in different ways. Factors TGF-α, VEGF, b-FGF induce Angiogenesis and proliferate the endothelial cells; while the factors, like TGF-β, GM-CSF, b-FGF, which stimulate arteriogenesis, proliferate smooth (plain) muscle\textsuperscript{53,54,55}.

According to the research by Takeshita et al in case of the recurrent myocardial ischemia, when a vascular occlusion occurs, collaterals begin functioning instantly, while in a state of rest they are inactive\textsuperscript{56}. According to the Herlitz et al Patients with chronic angina, who have recently suffered from acute myocardial infarction, were compared to patients with newly emerged angina and an acute myocardial infarction\textsuperscript{57}. For the last one year, they had a high risk of death rate and reinfarction. Based on the mentioned the myocardial ischemia was named as the grounded stimulator for the development of coronary collaterals\textsuperscript{57}.

**Eosinophilia**

Monocytes, neutrophils, lymphocytes and vascular growth factors (such as endothelial growth factor, fibroblasts growth factor and transformational growth factor [TGF-β]) play an important role in the development of coronary collateral blood circulation, however, they can not fully explain the development of the mechanism of the coronary collateral blood circulation\textsuperscript{65}.

There are few studies on the relation of coronary artery disease and eosinophilia. According to a study by Jiang et al, it is described that low levels of eosinophils are associated with serious myocardial damage and that eosinophils play an important role in thrombosis in patients with the acute coronary syndrome\textsuperscript{64}. According to the research conducted in China in 2008-2014, the correlation between eosinophilia and coronary collateral circulation was detected in 502 patients with unstable angina. It was found that EOS was associated with and could independently predict high-grade CCC in patients with UAP with epicardial coronary arteries stenosis 80%\textsuperscript{67}. The reressive analysis has shown that the specified quantity of eosinophils (odds ratio: 1.969; 95% confidence interval [CI]: 1.210–3.205; \(P=0.006\)) and neutrophils (odds ratio: 0.757; 95% CI: 0.584–0.981; \(P=0.035\)) are independent predictors of coronary collateral circulation. Eosinophils in quantities of 0.12×10⁹/l can independently be the predictors of high-quality coronary collateral circulation with 72.5% probability and 58.4% specificity \textsuperscript{68}. Coronary collateral circulation and epicardial coronary collaterals normally are not visualized on the angiogram until the coronary artery stenosis reach 80%, when the pressure is reduced and the coronary collateral circulation becomes noticeable. Inflammatory mediators, monocytes, neutrophils, lymphocytes, cytokines play an important role in the formation of coronary collateral circulation\textsuperscript{69,70}.

Jiang et al suggest that the reduced number of eosinophils indicate severe myocardial infarction, eosinophils play an important role in forming thrombosis during acute coronary syndrome. According to the study of Verdoia et al number of eosinophils is higher in patients with well-developed collateral circulation compared with patients with poorly developed coronary collateral blood circulation. Eosinophils play an important role in inflammatory
response regulation in patients with unstable angina. Finally, it is suggested that eosinophilia may be an independent predictor of high-quality coronary collateral circulation in patients with unstable angina in case of the stenosis of 80% of epicardial coronary arteries.

Collateral Circulation, Reserve of Coronary Flow and Its Prognostic Significance

Collateralization in patients is different. Years ago there was an opinion that the ischemia was the basis for the development of collateral circulations. However, studies did not prove this fact. Structurally coronary collaterals were found in 80% of newborns, indicating vasculogenesis in the embryogenesis. Coronary circulation in humans has a wide network of the anastomosis, even when the coronary artery disease is not formatted. Eventually, in case of necessity, they will transfer into coronary collaterals and can prevent signs of myocardial ischemia in the short-term coronary occlusions in ¼ of individuals. There are variable data on the links between the severity of the coronary artery disease and the severity coronary stenosis, the lesion of proximal localization and the long-term occlusion in the patients. It is known that the correct functioning of collaterals is associated with low frequency of heart rate and absence of arterial hypertension. Along the development of the disease of coronary arteries, well-developed coronary collaterals reduce mortality in patients. The protective effect of coronary collaterals in case of acute myocardial infarction is represented in the following way: decreasing infarction zone and fatal arrhythmias (such as arrhythmias with extended QT intervals), improving left ventricular function and preventing of an aneurysm. As we face difficulties in evaluating the collateral blood circulation, studies have shown the opposite prognostic significance of collateral fertility. Their high impact on mortality is still controversial. Few studies, reflecting the effect of the collateral circulation on mortality, have been conducted up to now. Only 3 of them clearly reflect the advantages of collateral blood circulation. The disparity is still a subject of discussion. This is partially explained by the method of evaluation of collateral blood circulation used in most studies. The collateral is assessed visually by coronary angiography, while the use of intracoronary flow or pressure measurement method (collateral flow index) with the Doppler is more accurate.

The significance of the collateral circulation in chronic total occlusion of the coronary artery, with the preservation of the left ventricular function, is vivid. There are also some examples of patients with the occlusion of a left coronary artery or three-vessels and light symptoms correlation between collateral and restenosis is also investigated. Clinical trials confirm rapid regression of collaterals following the PCI in chronic total coronary occlusion.

Coronary collaterals are also developed with the higher degrees of coronary occlusion. A study has been conducted to demonstrate the existence of latent coronary collateral in humans. They start functioning immediately after coronary obstruction. Despite the changes in time, the way collateral change under the coronary collateral pressure does not fully reflect the changes that are developed in case of acute coronary occlusion and thus can not be compared to the same changes in the chronic coronary occlusion. The positive effect of the collateral circulation on the outcome of patients who have been subjected to the mechanical intervention in the first hours of acute myocardial infarction is not still fully investigated. In the study conducted with the participation of 1,164 patients 6 months death rate was low in patients with coronary collateral, compared to patients with no collateral (4% vs 9%, p = 0.011).

After multivariate analysis, CC did not emerge as a significant variable in relation to 6-month clinical and angiographic outcomes. CC does not exert a protective effect in patients who undergo mechanical intervention in the first 6 hours of AMI onset.

Gender Differences, What Makes Gender Aspect Interesting?

Cardiovascular disease develops 7 to 10 years later in women than in men and is still the major cause of death in women. The risk of heart disease in women is often underestimated due to the misperception that females are ‘protected’ against cardiovascular disease. The underrecognition of heart disease and differences in clinical presentation in women lead to less aggressive treatment strategies and a lower representation of women in clinical trials. Over the past 2 decades, MI prevalence has increased among midlife women, while declining among similarly aged men. Also, although the risk of future hard cardiovascular events remains higher in midlife men compared with midlife women, the gap has narrowed in recent years. Greater emphasis on vascular risk factor control in midlife women might help mitigate this worrisome trend.

Women in their midlife years have historically been at a lower risk for overall vascular events than similarly aged men. We recently reported, however, that in a nationally representative sample of the US population that participated in the National Health and Nutrition Examination Surveys (NHANES), self-reported stroke prevalence among women aged 45 to 54 years was double that of similarly aged men.

It is often argued that women have smaller coronary arteries, coronary circulation, and thus worse coronary outcomes, simply because their bodies are smaller. The results of this investigation reaffirm that body size is positively correlated with coronary artery size and collaterals. Many of the major studies of vessel dimensions discussed, including the previous Intravascular ultrasound investigation, found that after correcting for body or heart size, sex differences lost statistical significance.

The mechanisms that underlie the sex difference are unknown. It may be because of differences in levels of hormones that control vascular tone and size.

The rates of collateralization between men and women remain unclear and there are few studies concerned with gender differences in coronary collateral circulation in CAD patients. Shi Lui and co-authors investigated 868...
patients with obstructive CAD. Patients were assessed for collateral grades based on the Rentrop grading system. Overall, 53% of participants had collaterals. Difference between sex groups was found. Men had higher rates of collaterals than women (P-value = 0.000175)102.

Some studies showed that there was no significant effect of sex on collateral vessel development103. In a study conducted by Tahiti E and co-authors eighty-four of the 1236 patients who had acute myocardial infarction and total proximal occlusion in only the left anterior descending coronary artery (LAD) or the right coronary artery (RCA) were selected. 74 patients were included (49 men, 25 women) in the study. None of the patients had repulsion criteria (ie, decrease in early ST elevation and repulsion arrhythmia). In this study, factors such as age, sex, BMI, HT, and smoking did not have a significant effect on CCV development103. However, others showed that in acute coronary syndrome men tended to develop greater collateral circulation than women104.

The opposite was reported in another study, where collaterals were more frequent in women than in men with multivessel disease105 Waldebecker b. et al. Studied angiograms from consecutive and unselected patients with acute coronary syndrome men tended to develop greater collateral circulation than women.

Further studies should be conducted to identify sex-related differences in coronary circulation in CAD patients and clarify the existence of “female pattern” of coronary collateral circulation.

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