Original Article

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# Assessing ABO Blood Group Relation with Collateral Coronary Circulation Development Quality

**Vahid Toupchi Khosroshahi[1], Amir Hossein Heydari[2]*, Ahmad Separham[1], Naser Aslan Abadi[1], Hamidreza Fallahabadi [2]**

1. *Cardiovascular Research Centre, School of Medicine, Tabriz University of Medical Science, Tabriz, Iran*
2. *Department. of Cardiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*

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**Corresponding Information:**
**Amir Hossein Heydari,**
Dept.of Cardiology,School of Medicine,Znjan University of Medical Sciences,Zanjan,Iran
**E-Mail:** amhohe@gmail.com

**ABSTRACT**

**Background & Objective:** Clinical outcomes of IHD depend on various factors, and coronary collateral circulation (CCC) development has recently been studied more. This study assessed blood groups' effect on CCC formation and patency.

**Materials & Methods:** In this retrospective study, all patients From January 2021 to August 2022, who had been hospitalized in the cardiac care unit of Shahid Madani Cardiology Hospital in Tabriz, Iran, were studied. ABO blood group typing was done with the Sinagene blood group determining kit. Collateral coronary circulation was assessed based on the Rentrop-Cohen grading scale for coronary arteries with 100% occlusion (CTO).

**Results:** 168 of 200 enrolled patients had well, and 32 had poor CCCs based on Rentrop scales. $A^+$ blood groups were significantly more prevalent in patients with a good Rentrop scale, and $A^-$, $B^-$ and $AB^-$ blood groups were significantly more prevalent in the poor CCC group. 21 patients in poor Rentrop and 68 in the good Rentrop group had hypertension (*P = 0.009*). Seventeen patients in the poor and 55 in the good Rentrop groups had DM (*P = 0.028*). The history of chronic kidney disease in poor Rentrop patients with 12 cases was significantly more than the good Rentrop group with 4 cases (*P=0.000*). The two groups had a significant difference in HLP prevalence (*0.026*).

**Conclusion:** This study showed DM, hyperlipidemia, hypertension, and $A^-$, $AB^-$ and $B^-$ blood groups were strong predictors of poor and $A^+$ for good CCC development.

**Keywords:** Coronary collateral circulation; RH blood type, O blood group, non-O blood groups

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## Introduction

Ischemic heart diseases (IHD) are the most important life-threatening type of Coronary artery disease (CAD) **(1)**. CAD is one of the world's three leading causes of death **(2).** Clinical outcomes of IHD depend on various factors, and coronary collateral development (CCC) has recently been studied more **(3)**. The relationship between blood group and coronary collateral arteries, which are small blood vessels that develop to help bypass blocked or narrowed coronary arteries, is an area of ongoing research. While some studies have suggested a potential association between the blood group and the development of coronary collateral circulation, the evidence is not yet conclusive, and further research is needed to fully understand the relationship **(4)**. The ABO blood group system categorizes individuals into four main groups: A, B, AB, and O, based on the presence or absence of specific antigens on the surface of red blood cells. Some studies have explored whether there is a link between the blood group and the presence or extent of coronary collateral circulation. The rationale behind these investigations is that the expression of certain blood group antigens may influence the development of collateral vessels **(5)**. For example, a study published

in the journal Circulation in 2012 suggested that individuals with blood group O may have better coronary collateral circulation compared to those with other blood groups. The study found that blood group O individuals had higher levels of a certain growth factor called hepatocyte growth factor (HGF), which is involved in angiogenesis (the formation of new blood vessels). The researchers hypothesized that higher HGF levels in blood group O individuals may promote the development of collateral vessels **(6)**. Understanding the potential relationship between ABO blood group and coronary collateral circulation is important for several reasons such as risk stratification, Treatment planning, Prognosis assessment, and Personalized medicine **(4).** Since Iranian peoples share most genetic specifications with Middle Eastern people, a study of the association of different blood groups with CCCs would help to set up future treatment and prevention approaches in this region.

## Materials and Methods

### Study Population

In this retrospective study, documents of all patients From January 2021 to August 2022, who had been hospitalized in the cardiac care unit of Shahid Madani Cardiology Hospital in Tabriz, Iran, were studied. The study was approved by Tabriz University of Medical Science ethics committee (code: IR.TBZMED.REC.1402.290). Since this study was a retrospective research informed consent from patients was not needed according to ethics committee's discretion. 796 patients diagnosed with stable and unstable angina and ischemia, proven by non-invasive exercise tests, were enrolled. From all primary study populations, 200 patients with at least one 100% (TIMI-1) occluded coronary artery (CTO) in angiography movie were chosen based on inclusion and exclusion criteria. Inclusion criteria were age older than 18 with at least one 100% occlusion in a coronary artery with thrombosis in myocardial infarction patients with TIMI grade one coronary blood flow. Exclusion criteria were chronic kidney disease (CKD) with a glomerular filtration rate of fewer than 30 milliliters per 1.73 $m^2$ of the body surface, acute myocardial infarction, liver cirrhosis, cerebrovascular diseases, hematologic diseases, severe valvular heart diseases (VHD).

Patients with a history of antihypertensive drug usage, systolic blood pressure of more than 140 mm Hg, or diastolic blood pressure of more than 90 mm Hg were considered hypertensive (HTN) **(7)**. Diabetic patients (DM) were those who were using anti-diabetic medications or had a fasting blood glucose (FBS) of more than 125 mg/dl or random blood glucose (BS) of more than 200 mg/dl in two different measurements (Glucose Assay Kit (ab65333)) **(8)**. Hyperlipidemia was considered LDL > 130 mg/dl, cholesterol> 200 mg/dl or triglyceride > 150 mg/dl (ab65390). Patients who were using lipid-lowering medications were also considered HLP patients **(9)**. Smokers or past smokers (patients with a smoking history until at least six months before being enrolled in the study) were considered smokers (SMH).

Laboratory Parameters: Patients had been kept fasting for 12 hours prior to the angiography procedure. We used the study's pre-angiography (right before the procedure) peripheral test results of venous blood samples. ABO blood group typing was done with the Abcam blood group determining kit (ab270207).

Echocardiography: We used 2D Prob to measure left ventricular Ejection Fraction (LVEF %). The echocardiography device was the GE Vivid 7 Dimension® ultrasound system, General Electric Company, Fairfield, Connecticut.

Coronary Angiography Procedure: Cardiologists had done angiography procedures in the hospital. All procedures were based on the Judkins method **(10, 11)**. Documented recorded movies of procedures were evaluated by the different blinded interventional cardiologists, and collateral coronary circulation was assessed based on the Rentrop-Cohen grading scale for coronary arteries with 100% occlusion. The Rentrop-Cohen grading scale categorizes collateral coronary arteries filling into four grades. Grade 0 indicates that there is no collateral filling with contrast on angiography or the filling is not detectable in the movie. Grade 1 shows the filling in branches of collateral arteries, excluding its main trunk. Grade 2 is the partial filling of the epicardial portion of coronary arteries through the collateral coronary artery, and Grade 3 collateral coronary artery (CCA) fills the epicardial coronary arteries entirely with blood. The highest Rentrop grade was used in the case of multiple CCAs. The severity of CAD was determined based on the number of coronary arteries with 100% occlusion. Rentrop grades 2 and 3 were considered good collateral flow, and 0 and 1 grades were poor.

Statistical Analysis: Statistical analysis and graph designing were performed using IBM SPSS Statistics v.24 and GraphPad Prism v9. Continues variables were analyzed by a 2-sample t-test, and $\chi^2$ was used for categorical qualitative variables. Quantitative variables were analyzed with the Mann-Whitney. Univariate analysis with a significance of $p\text{-}value < 0.05$ was done to determine significant effective factors in CCCs potency.

## Results

168 of 200 enrolled patients had well, and 32 had poor CCCs based on Rentrop scales. The mean age of patients in the poor Rentrop group was 63.66 ± 8.27, and good Rentrop was 64.48 ± 10.01 years ($P = 0.633$). 8 of 32 patients with poor Rentrop and 44 of 168 with good Rentrop were female ($P = 0.005$ and $P = 0.000$, between two groups $P = 0.888$). Types of blood groups were significantly different between the two Rentrop groups. The $A^+$ blood group was significantly more prevalent in patients with a good Rentrop scale, and $A^-$, $B^-$ and $AB^-$ blood groups were significantly more

prevalent in the poor CCC group (*p = 0.028*). 21 patients in poor Rentrop and 68 in the good Rentrop group had hypertension (*P = 0.009*). Seventeen patients in the poor and 55 in the good Rentrop groups had DM (*P = 0.028*). The Number of patients with a smoking.

history was not significantly different between the two groups (poor = 1, good = 2, *P = 0.409*). The history of chronic kidney disease in poor Rentrop patients with 12 cases was significantly more than the good Rentrop group with 4 cases (P=0.000). The two groups had a significant difference in HLP prevalence (*0.026*). There was no difference in the number of occluded vessels (single vessel disease (SVD) and multiple vessel disease (MVD)) between the two groups (*P = 0.098*). The two studied groups had no significant difference in the occluded vessel type (*P = 0.099*). The mean of LVEF in patients with poor Rentrop was 41.09 ± 9.44% and 44.11 ± 11.12% in the good Rentrop group (*P = 0.152*). All described data can be seen in Table 1.

**Table 1. Relation of different parameters with quality of CCC**

| Parameters | Poor Collateral | Good Collateral | P-value |
|---|---|---|---|
| **Age, years (mean±SD)** | 63.66 ± 8.27 | 64.48 ± 10.01 | 0.633 |
| **Gender, male (n (%))** | 24 (75%) | 124 (73.8%) | 0.888 |
| **Hypertension, n (%)** | 11 (34.4%) | 100 (59.5%) | 0.009 |
| **Diabetes mellitus, n (%)** | 17 (53.1%) | 55 (32.7%) | 0.028 |
| **Smoking, n (%)** | 1 (3.1%) | 2 (1.2%) | 0.409 |
| **Hyperlipidemia, n (%)** | 21 (65.6%) | 80 (47.6) | 0.026 |
| **Mean LVEF (%)** | 41.09 ± 9.44% | 44.11 ± 11.12% | 0.152 |
| **$O^+$ blood type, n (%)** | 9 (28.1%) | 80 (29.8%) | 0.028 |
| **$O^-$ blood type, n (%)** | 1 (3.1%) | 9 (5.4%) | |
| **$A^+$ blood type, n (%)** | 6 (18.8%) | 56 (33.3%) | |
| **$A^-$ blood type, n (%)** | 3 (9.4%) | 2 (1.2%) | |
| **$B^+$ blood type, n (%)** | 39 (23.2%) | 7 (21.9%) | |
| **$B^-$ blood type, n (%)** | 3 (9.4%) | 2 (1.2%) | |
| **$AB^+$ blood type, n (%)** | 1 (3.1%) | 6 (3.6%) | |
| **$AB^-$ blood type, n (%)** | 2 (6.3%) | 4 (2.4%) | |

The two groups had no significant difference in the number of patients with LAD, RCA, or LCX involvement (*P = 0.601, P = 0.720, P = 0.936*). No correlation existed between the number of involved coronary arteries and the Rentrop scale (0.098). (Table 2).

**Table 2. Relation of three main branches of coronary arteries with CCC quality**

| Parameters | Poor Collateral | Good Collateral | P-value |
|---|---|---|---|
| **Multivessel coronary stenosis, n (%)** | | | 0.098 |
| **LAD, n (%)** | 11 (34.4%) | 57 (33.8%) | 0.601 |
| **RCA, n (%)** | 18 (56.3%) | 98 (58.3%) | 0.720 |
| **LCx, n (%)** | 3 (9.4%) | 13 (7.7%) | 0.936 |

Univariate Regression Analysis for Independent Predictor of poor collateral coronary artery development showed that diabetes (P = 0.028, CI = 95%, OR = 1.883), $A^-$, $B^-$ and $AB^-$ blood groups were independent predictors of poor CCC and blood groups $A^+$, and hypertension were independent predictor of good CCC (P = 0.050, CI = 95%, OR = 1.917 and *P = 0.009*, CI = 95%, OR = 1.764).

## Discussion

This study showed that blood group $A^+$ could be associated with good CCC, and $A^-$, $B^-$ and $AB^-$ with poor CCC. The $A^+$ blood group was a weak independent predictor of good CCC in enrolled patients. There is one study that has examined the relationship between blood group and CCC Rentrop score. This study carried out in Turkey, showed that the O blood group is a predictor of good CCC. The most important difference between this study and ours is that they have stated that the O blood group is the most prevalent in their country and have not reported other blood groups in detail. Our study studied all blood groups; even different RHs were included **(4)**. Figure 1.

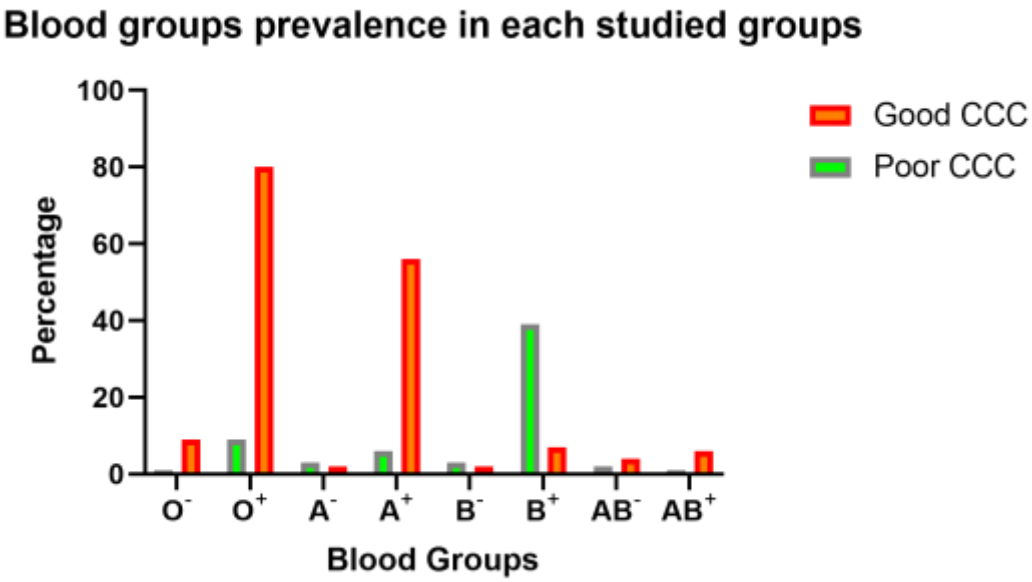



**Figure 1. Blood group distribution in both groups.**

Collateral coronary circulations are the most important bypass tracts for the blood supply of the myocardium. Poor CCCs are not able to provide enough blood flow for myocytes. The result of poor CCC would be myocardial ischemia and further cardiac complications in states of coronary artery occlusion **(12)**. There could be many factors affecting CCCs development, some are changeable, and some cannot be manipulated. Nevertheless, all these factors are essential for predicting CCC's patency condition **(13)**. Responsible factors for developing CCC can be categorized into two categories; the first is the factors that relate to endothelium and vasculature properties of coronary arteries (e.g., endothelial dysfunction) **(3, 14).** The other factors could be attenuated externally with medications and changing lifestyles (e.g., smoking and DM) **(15, 16)**.

Our study showed that females were relatively less troubled with CAD, but being male did not significantly predict CCC development quality. There is a comprehensive review article that shows that there is not any solid evidence of the relationship between gender and CCC quality **(17)**. There was a relationship between diabetes and poor development of CCC. Patients with a history of diabetes mellitus showed a higher probability of having poor CCC. Other studies confirm this finding of our study **(18, 19).**

Contrary to DM, hypertension was another related factor to good CCC. There are controversial findings about hypertension's effects on CCC development; some studies have shown that hypertension is a significant factor in the quality of CCCs, and others have shown the opposite **(3, 14, 20)**. Hyperlipidemia is not only a significant factor for CAD occurrence but also a potential factor for the poor development of CCCs. Other studies have also proven this study's findings **(21, 22).**

Previous studies have shown that the O blood type population is less susceptible to having CAD in their lifetime. Conversely, the non-O blood group population is more in danger of severe CAD and a higher mortality rate **(23, 24)**. These differences between CAD outcomes of different blood groups demonstrate that people with different blood groups have genetic differences in other risk factors for CAD **(25)**. Although non-O blood groups increase the mortality rate in patients with CAD based on our study, it could be because of other risk factors than CCC development.

ABO differences make a variation in other genomic specifications of individuals. For example, the endothelial marker is one of the most important factors in angiogenesis, which can differ between persons with different blood groups **(26)**. Angiogenesis is the core procedure for the development of CCC, so this could be one of the reasons that ABO differences can change CCC development progression. The impact of blood groups on coronary angiogenesis, the formation of new blood vessels in the coronary arteries, is an area of ongoing research. While there is no definitive consensus on the direct influence of blood groups on coronary angiogenesis, some studies have suggested potential associations and

mechanisms. Here are a few factors that have been investigated.

Certain blood group antigens, such as the H antigen present in blood type O, have been associated with higher levels of specific growth factors involved in angiogenesis. For example, individuals with blood type O have been found to have higher levels of hepatocyte growth factor (HGF), which is known to stimulate angiogenesis. This suggests that blood group antigens may influence the production or activity of growth factors that regulate angiogenesis **(27)**.

Endothelial cells line the inner walls of blood vessels and play a crucial role in angiogenesis. Studies have suggested that blood group antigens, particularly ABO antigens, can affect endothelial cell function. For instance, blood group A antigens have been associated with reduced endothelial nitric oxide synthase (eNOS) activity, which could impact endothelial function and potentially influence angiogenesis **(28)**.

Blood group antigens can affect the immune response and inflammatory processes, which are involved in angiogenesis. Some studies have suggested that certain blood groups may have different inflammatory and immune profiles, potentially influencing the angiogenic response **(29).**

Understanding the potential relationship between ABO blood group and coronary collateral circulation is important for several reasons, the outmost important one is “risk stratification”; If a significant association is established between blood group and coronary collateral circulation, it could provide valuable information for risk stratification in individuals with coronary artery disease (CAD). It would help identify individuals who are more likely to develop collateral vessels as a compensatory mechanism for blood flow restoration in the presence of blocked or narrowed coronary arteries **(30)**. The second importance would be “Treatment planning”; the presence and extent of coronary collateral circulation can have implications for the management of CAD. If individuals with certain blood groups are found to have better collateral circulation, healthcare professionals may consider different treatment strategies for them. For example, individuals with poor collateral circulation may require more aggressive interventions, such as revascularization procedures like angioplasty or coronary artery bypass grafting, whereas those with better collateral circulation might benefit from less invasive approaches **(31)**. The third importance is “Prognosis assessment”; the presence and functionality of coronary collateral circulation have been associated with better outcomes in CAD, including reduced risk of myocardial infarction (heart attack) and improved long-term survival. If a relationship between blood group and collateral circulation is established, it may help refine prognostic evaluation and provide additional information for predicting outcomes in individuals with CAD **(32)**. Last but not least important would be “Personalized medicine”; Understanding the relationship between blood group and collateral circulation could contribute to personalized medicine approaches in the management of CAD. If blood group is found to be a relevant factor, it could be considered alongside other patient-specific characteristics when determining the most appropriate treatment options and interventions (4).

## Conclusion

Blood group differences are not strange to any scientist, but the exact pathophysiological pathway that makes it able to change the process of CCC development is unknown yet. This study showed that besides DM and hyperlipidemia were independent predictors of poor CCC, hypertension, $A^-$, $B^-$ and $AB^-$ blood groups could be considered as strong predictors of poor CCC development (Figure 2). $A^+$ patients have good collateral coronary blood flow compared to other blood group patients. Based on the mentioned results it seems that having a conservative approach to individuals with $A^+$ blood group would be suitable for them and the health care system. On the other hand, individuals with $A^-$, $B^-$ and $AB^-$ blood groups need to be approached more intensively and the cardiologist should be prepared to implement intervention-based treatment on them rather than medical and conservative approaches.

Our study had some limitations; for example, we could not measure more biochemical indexes in patients and needed access to other heart centers to grow our study population. We recommend that other scientists in the future further study the pathophysiology of ABO's effects on CCC development.

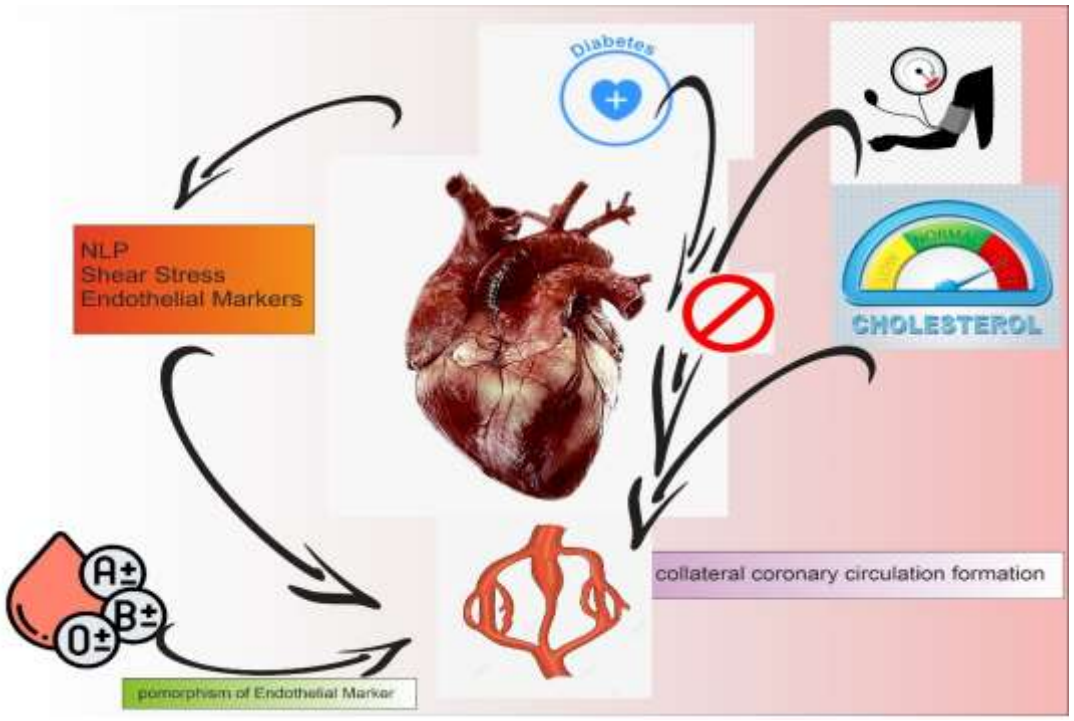



**Figure 2.** **The outline of the results.**

## Ethical approval and consent to participate

All the procedures were followed in accordance with the Declaration of Helsinki guidelines.All experimental protocols were approved by the Tabriz Medical University Ethics committee.Written informed consent was not needed to be obtained.

## Funding

No funding source is to be reported.

## Conflict of Interest

There is no conflict of interest with any of the authors to be declared.

## Contributions

VTK, NAA, HF, and AS collected data, AHH wrote the draft and final version, AHH analyzed data with Pythone, GraphPad prism, SPSS, and Excel. AS supervised methodology design and implementation.

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