

## The Correlation of Collateral Circulation and Age during Acute Ischemic Heart Disease

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### Abstract

**Background:** Coronary collaterals (CC) are alternative sources of blood supply to myocardium jeopardized by Ischemia. **Aim:** To investigate the dependence and influence of collateral circulation on age during acute ischemic heart disease. **Methods:** Analysis shows that 673 patients were studied from the SamgoriMedi Clinic (Tbilisi, Georgia) aged 27– 94 years (64.7+11.48) with acute coronary syndromes. Basic medical data such as sex, age, cardiovascular risk factors, angina pectoris, revascularization history, echocardiography, and laboratory data were obtained from the patient's medical records. CC vessels were graded according to the Rentrop grading system of 0 to 3. **Results:** The development index of collateral circulations visibly increases with age. Average age increases accordingly as follows: rentrop 0 - 62.85±12.01, rentrop 1 - 64.90±10.79, rentrop 2 - 66.84±10.49, and rentrop 3 - 69.04±9.68 (p<0.0001). There is positive significant correlation between the development of collateral circulation and age groups  $r=0.170^{**}$ ,  $p<0.001$ . The cases of female sex, hypertension, acute MI without ST elevation, CABG frequency (also EF% - 35-45%, <35%), and multiple vessel coronary lesion are noticed to increase with age, while the male sex and EF (ejection fraction) >45% cases decreases with age. **Conclusion** Collateral circulation shows significantly positive correlation with age and female sex. However, it should be mentioned that in elderly patients with a high ejection fraction and normal diastolic function, the development of collateral vessels is low.

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**Keywords:** Coronary collateral circulation, age, correlation

## Introduction

Coronary collaterals are alternative source of blood supply to myocardium jeopardized by ischemia (Seiler, 2010). Among individuals who are not suffering from coronary artery disease (CAD), collateral arteries are performed in preventing myocardial ischemia during a brief vascular occlusion in 20–25% (Meier et al., 2013). Determinants of such anastomoses are low heart rate and the absence of systemic arterial hypertension. In patients with CAD, collateral arteries preventing myocardial ischemia during a brief occlusion are presented in every third individual. Collateral flow is sufficient to prevent myocardial ischemia during coronary occlusion amounts from one-fifth to one-fourth the normal flow through the open vessel (Seiler et al., 2013; Bhatnagar et al., 2019). It is suggested that coronary collaterals are important in preserving left ventricular systolic and diastolic performance at least while resting. Not easily visible collaterals may also prevent systolic dysfunction (Carmel et al., 1998; Dai et al., 2020). The presence of CCC reduces postoperative myocardial injury, low cardiac output syndrome, and mortality rates (Ucak et al., 2019).

Collateral circulation does not occur until the age of 30, and it is observed only in 23% of patients with age range of 31-40 (Zimmerman et al., 2005). However, in case of stimulus for developing the collateral pathways – implying long-term angina, followed by severe coronary stenosis, the patient's age is crucial and this determines the development of collateral circulation. Moreover, collateral pathways develop more efficiently in young aged patients (Nakae et al., 2000). The total number of collateral pathways decreases with ageing in elder patients (Balci, 2004).

Regardless of the fact that studies have shown both age-related changes for blood vessels including arterial remodeling (Wang et al., 2010), as well as age-related functional decline of collateral circuits (Kurotobi et al., 2004), there are no studies which would let us define the specific influence of age on remodeling process so far (Balci et al., 2004).

Consequently, our research aims to study the dependence and influence of collateral circulation on age during acute ischemic heart disease.

## Materials and Methods

Analysis shows that 673 Patients, aged 27 – 94 years (64.7±11.48) with acute coronary syndromes, who underwent coronary angiography at the Department of Cardiology, SamgoriMedi Clinic (Tbilisi, Georgia) between January 2014 and January 2017 were evaluated and diagnosed with CAD.

Patients have given the consent to participate in the research study. The study protocol was approved by the local ethics committee. Clinical and laboratory data were obtained from the patients' medical records.

Basic clinical data, including sex, age, cardiovascular risk factors such

as hypertension, diabetes mellitus (DM), Dyslipidemia, TIA, smoking status, relevant medication, course of CAD, angina pectoris, revascularization (coronary artery bypass graft operation or percutaneous coronary intervention) history, ultrasound parameters of left ventricular systolic and diastolic function, ejection fraction, regional wall motion abnormalities, systolic and diastolic blood pressure were obtained from the patient's medical records. Diabetes Mellitus (DM) was defined as a history of DM, which is the use of antidiabetic drugs or fasting plasma glucose levels of  $\geq 7$  mmol/L. Hypertension (HT) was defined as a history of HT or use of antihypertensive drugs, or a blood pressure  $\geq 140/90$  mmHg. Smoking status was defined as current smoking.

Patients with renal dysfunction (serum creatinine level  $>132.6$   $\mu\text{mol/L}$ ), revascularization (coronary artery bypass graft operation or percutaneous coronary intervention) history, severe valvular disease, myocardial or pericardial disease, and technically inadequate coronary angiography were excluded from the study. Patients who were diagnosed with hematological disease, cancer, systemic inflammatory or autoimmune disease, thrombocytopenia, and the use of anticoagulant agents were also excluded from the study.

### **Angiographic Evaluation and CC Grading**

Coronary angiography was performed through the Radial artery to all patients using the Seldinger technique. Each angiogram was interpreted by two experienced cardiologists who were not familiar with the clinical details and results of the other investigations of each patient.

CC vessels were graded according to the Rentrop grading system of 0 to 3:

0 = no filling of any collateral vessel;

1 = filling of the side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment;

2 = partial filling of the distal epicardial segment by collateral vessels;

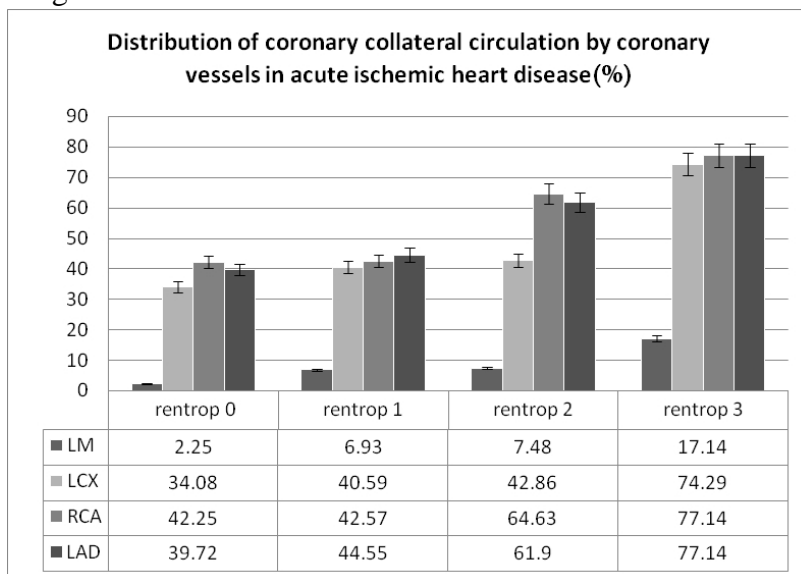
3 = complete filling of the distal epicardial segment by collateral vessels.

### **Statistical Analysis**

Continuous variables are expressed as  $\pm$  SD, and categorical variables as frequencies and %. Continuous variables were compared with the use of the one way ANOVA and Post Hoc Tests, while categorical variables were compared with the use of the Fisher's Exact Test. Correlation analysis between categorical variables was performed by Spearman correlation analysis. P value  $<0.05$  was considered as statistically significant. All statistical analysis was performed using SPSS version 23.

## Results

Collateral circulations that were explored and performed in our study appeared to be related with both singular and multiple vessel occlusions. Thus, the distribution of collateral circulation degree by involved blood vessels is given in Figure 1.



**Figure 1.** Frequency of LAD, LCX and RCA increases with rentrop. For LM, collateralization is little and does not show any significant variation related to rentrop.

Age data of patients according to collateral circulation degrees is given in Table 1.

**Table 1. Distribution of patients' age data according to rentrop**

	N	Mean+SD	Minimum	Maximum	F	P
Rentrop0	355	62.85+12.01	27.00	92.00	<b>8.40</b>	<0.0001
Rentrop1	101	64.90+10.79	40.00	94.00		
Rentrop2	147	66.84+10.49	41.00	87.00		
Rentrop3	70	69.04+9.68	47.00	87.00		

According to the chart represented above, the development index of collateral circulations confidently increases with age. In addition, in case of rentrop 0, minimal age is 27 years. On the other hand, rentrop 1-2 corresponds to 41-42 years, and rentrop 3 corresponds to 47 years. The mean age is confidently low in rentrop 0 case. In addition, this group includes the lowest index of minimum age, which also shows the tendency of growth with age. Multiple comparisons (Post Hoc Tests) show that there is a significant age difference in the following groups: rentrop 0 - rentrop2(p<0.0001), rentrop1- rentrop3(p=0.0190), and rentrop0 - rentrop3 (p<0.0001).

Therefore, Figure 2 shows age-related distribution of collateral circulation.

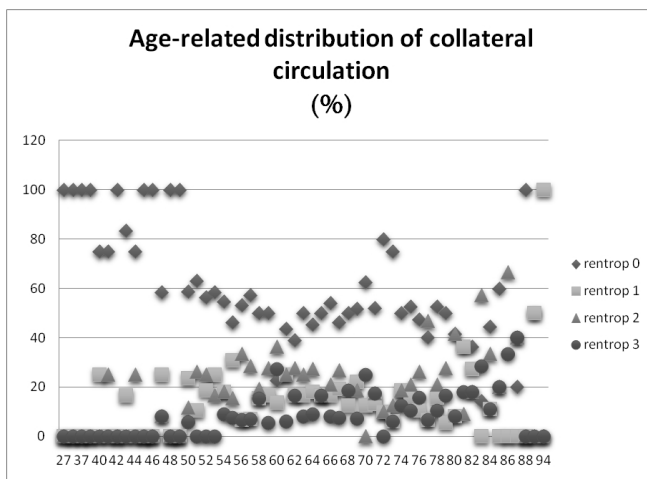


Figure 2.

As shown in the diagram above, undeveloped collateral circulation is observed with high frequency among all age groups. The maximum age for 0-1 degree is 92-94 years, and 87 years for 2-3 degree. Correlation analysis proved statistically confident positive link between development of collateral circulation and age groups  $r=0.170^{**}$ ,  $p<0.001$ . To determine what defines the age-related variations of collateral circulation, we studied the distribution of ischemic heart disease characteristics in different age groups (Table 2).

Table 2. Distribution of ischemic heart disease characteristics according to age

	<56		56-65		66-75		>75		F	p
	abs	%	Ab s	%	ab s	%	ab s	%		
Female	20	13.25	53	26.63	81	43.78	82	59.42	30.05	<0.0001
Male	131	86.75	146	73.37	104	56.22	56	40.58	30.05	<0.0001
Hypertension	94	62.25	146	73.37	157	84.86	122	88.41	12.88	<0.0001
Diabetes melitus	20	13.25	44	22.11	54	29.19	28	20.29	4.27	0.0053
Dyslipidemia	50	33.11	89	44.72	93	50.27	54	39.13	3.73	0.0112
Acute myocardial infarction with ST elevation	51	33.77	83	41.71	59	31.89	46	33.33	1.63	0.1814
Acute myocardial infarction without ST elevation	47	31.13	60	30.15	72	38.92	55	39.86	1.92	0.1256
Unstable angina	53	35.10	56	28.14	54	29.19	37	26.81	0.97	0.4066
>5 years	6	3.97	15	7.54	18	9.73	21	15.22	4.02	0.0076
TIA	10	6.62	13	6.53	12	6.49	11	7.97	0.12	0.9499

Past history of MI	30	19.87	61	30.65	62	33.51	41	29.71	2.77	0.0407
Past history of coronary intervention	25	16.56	49	24.62	40	21.62	31	22.46	1.14	0.3341
Stenosis of Culprit vessel	109	72.19	154	77.39	142	76.76	107	77.54	0.55	0.6490
Multiple vessel coronary lesion	14	9.27	47	23.62	40	21.62	42	30.43	7.04	0.0001
EF>45%	118	78.15	123	61.81	94	50.81	65	47.10	12.90	<0.0001
EF - 35-45%	25	16.56	57	28.64	66	35.68	52	37.68	6.82	0.0002
EF<35%	8	5.30	19	9.55	25	13.51	21	15.22	3.10	0.0261
Foci of regional asynergy	98	64.90	165	82.91	151	81.62	117	84.78	8.03	<0.0001
Normal diastolic function	56	37.09	22	11.06	19	10.27	11	7.97	23.66	<0.0001

The incidence of female sex, hypertension, acute MI without ST elevation, CABG frequency (also EF% - 35-45%, <35%), and multiple vessel coronary lesion increases with age. On the other hand, the male sex and EF (ejection fraction) >45% case is decreasing with age. In patients with age range of 56-75 years, the occurrence of diabetes, dyslipidemia, and past history of MI increases with age. However, these indices decrease in patients older than 75 years.

Table 3 shows the results of correlation analysis between the indices of collateral circulation and patient age, sex, and acute coronary syndrome indices.

**Table 3. Correlations between coronary collateral circulation degrees and acute ischemic heart disease indices**

		rentrop0	rentrop1	rentrop2	rentrop3
<56	r	0.174**	0.003	-0.112**	-0.137**
	p	<0.001	0.930	0.004	<0.001
56-65	r	-0.091*	0.010	0.067	0.046
	p	0.018	0.789	0.081	0.235
66-75	r	0.029	0.012	-0.052	0.008
	p	0.446	0.765	0.181	0.831
>75	r	-0.109**	-0.028	0.097*	0.080*
	p	0.005	0.469	0.012	0.038
Female	r	-0.059	-0.039	0.079*	0.035
	p	0.125	0.318	0.041	0.362
Hypertension	r	-0.013	-0.039	-0.003	0.070
	p	0.746	0.318	0.936	0.071
Diabetes	r	-0.094*	0.061	0.062	-0.002
	p	0.015	0.111	0.108	0.955
Dyslipidemia	r	-0.077*	0.043	0.069	-0.017
	p	0.045	0.268	0.072	0.656

Acute MI with ST elevation	r	<0.001	0.019	-0.002	-0.019
	p	0.991	0.631	0.968	0.624
Acute MI without ST elevation	r	-0.028	-0.027	-0.023	0.109**
	p	0.473	0.481	0.543	0.005
Unstable angina	r	0.029	0.009	0.026	-0.094*
	p	0.448	0.816	0.499	0.015
Angina more than 5 years >	r	-0.216**	-0.044	0.163**	0.184**
	p	<0.001	0.256	<0.001	<0.001
TIA	r	-0.097*	0.068	0.028	0.043
	p	0.011	0.080	0.471	0.268
Past history of MI	r	-0.147**	0.054	0.076*	0.073
	p	<0.001	0.161	0.048	0.057
Past history of coronary angioplasty or bypass	r	-0.054	0.083*	0.020	-0.036
	p	0.160	0.031	0.598	0.345
LM	r	-0.155**	0.023	0.042	0.170**
	p	<0.001	0.545	0.276	<0.001
LAD	r	-0.200**	-0.039	0.135**	0.191**
	p	<0.001	0.314	<0.001	<0.001
RCA	r	-0.181**	-0.069	0.146**	0.179**
	p	<0.001	0.072	<0.001	<0.001
LCX	r	-0.152**	-0.005	0.018	0.229**
	p	<0.001	0.901	0.637	<0.001
Stenosis of Culprit vessel	r	-0.105**	0.021	0.145**	-0.049
	p	0.006	0.585	<0.001	0.209
Multiple vessel coronary lesion	r	-0.316**	-0.086*	0.174**	0.382**
	p	<0.001	0.026	<0.001	<0.001
EF>45%	r	0.091*	0.025	-0.032	-0.135**
	p	0.018	0.515	0.407	<0.001
EF - 35-45%	r	-0.049	-0.027	0.042	0.055
	p	0.206	0.477	0.279	0.151
EF - Up to 35%	r	-0.072	0.001	-0.011	0.132**
	P	0.062	0.988	0.777	0.001
Sites of regional asynergy	r	-.096*	0.044	0.062	0.021
	p	0.013	0.255	0.109	0.585
Normal diastolic function	r	0.154**	-0.036	-0.094*	-0.083*
	p	<0.001	0.346	0.015	0.032

\* - P&lt;0.05, \*\* - p&lt;0.01

Rentrop 0 - absence of coronary collateral pathways – shows a significantly positive correlation with EF>45% and normal diastolic function with age <56 years. However, it shows negative correlation with diabetes, dyslipidemia, past history >5 years, TIA, past MI, LM, LAD, RCA, LCX, stenosis of culprit vessel, multiple vessel coronary lesion, age 66-75, >75, and sites of regional synergy. Retrop 1 shows confidently positive correlation with multiple vessel coronary lesion and past history of coronary angioplasty or bypass. Retrop 2 shows confidently positive correlation with age > 75years, female sex, past history > 5 years, past history of MI, LAD, RCA, stenosis of

culprit vessel, multiple vessel coronary lesion, and negative correlation with normal diastolic function for age < 56 years. Rentrop 3 shows clearly positive correlation with age > 75 years, acute MI without ST elevation, past history > 5 years, LM, LAD, RCA, LC, multiple vessel coronary lesion, and EF < 35%. However, negative correlation is observed with age < 56 years, unstable stenocardia, EF > 45%, and normal diastolic function.

## Discussion

Definitive diagnostic data on the effects of aging on collaterals in humans are very limited (Epstein et al., 2012). While studying collateral development with age, it was observed that though the prevalence of coronary collaterals was highest in Group 51 to 70 years, but prevalence of adequate collaterals (Rentrop 2-3) were seen to be increasing with age. In cases with age > 50 years, collaterals were significantly more prevalent compared to less than 50 years (Puri, 2017). Nakae et al. also observed higher prevalence of collaterals among cases with age ranging from 55 - 63 years (Nakae et al., 2000), but well developed collaterals were less documented in older patients in their study group. Also, Pohl et al. did not find any significant correlation between age and collateral development (measured by coronary flow index) (Pohl et al., 2001). According to other data, High-grade collaterals were significantly more in middle-aged individuals compared to the elderly (Chandra et al., 2019). This study showed that absence of collateral circulation correlates with age less than 56 years. The minimal age of patients on rentrop 0 group is 27 years, while the minimal age of patients who show the presence of collateral circuits is more than 64 years and increases with the degree of development of collateral pathways. Age less than 56 years shows confidently positive correlation with absence of collateral circulation. Also, a positive correlation exists with 2 and 3 degree rentrop. 56-65 age groups have negative correlation with absence of collaterals. The authors concluded that advanced age was an independent factor predicting impaired collateral circulation (Kurotobi et al., 2004) which is not confirmed by this study. Age > 75 years shows confidently negative correlation with rentrop 0 and confidently positive correlation with 2 and 3 degrees. According to literature, good coronary collateral circulation has an indirect beneficial effect on the prognosis for primary PCI. Moreover, a longer time after onset and a more advanced age are associated with higher mortality (Chu et al., 2019).

The factors influencing the collateralization, whose cases increases with age, can also involve diabetes and dyslipidemia. According to our study, this shows a negative correlation with rentrop 0 and their rate is obviously lower in patients aged < 56 years. This also accounts for the absence of collaterals in young age. TG/HDL ratio is an independent risk factor for predicting poor development of CCC in elderly patients with STEMI and acute



total occlusion (Liu et al., 2018). According to this study, Rentrop 0 shows significantly negative correlation with dyslipidemia.

This data is confirmed by authors as diabetic patients with CAD develop more extensive coronary collateral circulation than nondiabetic subjects, especially men aged <55 years. The collateral circulation mainly develops at the LAD and RCA. Patients with diabetes mellitus were observed to have III degree collateral circulation more frequently compared with patients without diabetes (13.2 vs 8.5%,  $p<0.01$ ). This conclusion was further outlined in male patients with diabetes aged <55 years. It was also compared with male patients without diabetes (20 vs 3.4%,  $p<0.001$ ) and female patients with diabetes (20 vs 2.2%,  $p<0.001$ ).

It was confirmed that III degree collateral circulation develops more during complete occlusion of arteries arising from anterior descendent (LAD) and right coronary artery (RCA) (Melidonis et al., 1999). According to this data, collateral circulation developed during lesion of both LAD and RCA, as well as LCX. In case of LM, collateralization degree is low and does not show confident correlation with rentrop. LAD, LCX, and RCA incidence increases with rentrop degree. Due to the function of LV, patients with better coronary collateral grades had a higher importance EF (Ajayiet al., 2017). Patients with coronary artery disease reportedly have an impaired left ventricular filling (Nii et al., 1994). It is suggested that coronary collaterals are important in preserving left ventricular systolic and diastolic performance. Not readily visible collaterals may also prevent systolic dysfunction (Carmel et al., 1998). The data  $EF>45\%$  shows clearly positive correlation with rentrop 0 and negative correlation with rentrop 2-3 at the same time.  $EF>45\%$  incidence confidently decreases with age, which also can be considered as a reason for growing degree of collateralization with age. Normal diastolic function shows vividly positive correlation with rentrop 2 and 3 and negative correlation with rentrop 0. The diameter of the coronary arteries were larger in male subjects than females (ShukrI et al., 2014). Males showed higher degree of collateral circulation compared to females (Liu et al., 2017). This paper shows that the cases of female sex increases with age which correlates with rentrop 2.

More extensive studies are recommended to verify these results, in particular, at the molecular and cellular level.

## **Conclusion**

In conclusion, collateral circulation shows significantly positive correlation with age and especially in female sex. However, it should be considered that in elderly patients with a high ejection fraction and normal diastolic function, the development of collateral vessels is low.

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