Influence of different clinical factors on collateral formation in patients with chronic total occlusion

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Background: The degree of coronary collateral development influences the outcome after acute myocardial infarction and long-term survival. This study aims to assess the factors that influence the development of collaterals in patients with chronic total occlusion (CTO).
Patients and methods: The study included 70 patients with coronary CTO. The patients were classified according to the presence and the degree of collateral formation using the Rentrop classification. Collaterals were present in 54 patients (77.1%), and 16 patients had no collaterals (22.9%). Patients with collaterals were significantly younger (51.76 ± 7.94) than those without collaterals (59.44 ± 6.26) ($P < 0.05$). Smokers and diabetic patients had fewer collaterals, while those with hypertension and dyslipidemia had more collaterals ($P < 0.05$). The duration of angina pectoris was significantly lower in patients without collaterals (8.44 ± 6.562) compared to those having collaterals (11.87 ± 5.45) ($P < 0.05$). Beta blockers were the only medication that showed significant collateral formation, with 11 patients (68.8%) having faintly visible collaterals, 31 patients (96.9%) partially filling collaterals, and six patients (100%) complete collateral filling versus two patients (12.5%) with nonvisible collaterals.
Conclusion: Beta blocker therapy, hypertension, and long duration of angina pectoris were associated with an increase in coronary collateral formation, while diabetes, dyslipidemia, advanced age, and previous MI were all associated with a decrease in collateral formation.

Key words: collaterals, chronic total occlusion, coronary arteries.

Vliv různých klinických faktorů na tvorbu kolaterál u pacientů s chronickým totálním uzávěrem

Úvod: Míra tvorby kolaterál věnčitých tepen ovlivňuje výsledek po akutním infarktu myokardu a dlouhodobé přežití. Cílem této studie bylo zhodnotit faktory, které ovlivňují vznik kolaterál u pacientů s chronickým totálním uzávěrem (CTO).
Pacienti a metody: Do studie bylo zařazeno 70 pacientů s CTO věnčité tepny. Pacienti byli roztříděni podle přítomnosti a míry tvorby kolaterál za použití Rentropovy klasifikace. Kolaterály byly přítomny u 54 pacientů (77,1 %), u 16 pacientů (22,9 %) přítomny nebyly. Pacienti s kolaterálami byli významně mladší (51,76 ± 7,94) než pacienti bez nich (59,44 ± 6,26) ($P < 0,05$). Kuřáci a diabetičtí pacienti vykazovali nižší míru tvorby kolaterál, zatímco u pacientů s hypertenzí a s dyslipidemií byly kolaterály četnější ($P < 0,05$). Doba trvání anginy pectoris byla významně nižší u pacientů bez kolaterál (8,44 ± 6,562) ve srovnání s těmi, kteří kolaterály měli (11,87 ± 5,45),($P < 0,05$). Beta-blokátory byly jediným lékem, u něhož byla prokázána významná tvorba kolaterál, přičemž 11 pacientů (68,8 %) mělo slabě viditelné kolaterály, 31 pacientů (96,9 %) částečně se plnící kolaterály a 6 pacientů (100 %) kompletně se plnící kolaterály oproti 2 pacientům (12,5 %) bez spontánně viditelných kolaterál.
Závěr: Léčba beta-blokátory, hypertenze a dlouhotrvající angina pectoris byly spojené s nárůstem tvorby kolaterál věnčitých tepen, zatímco cukrovka, dyslipidemie, pokročilý věk a předchozí infarkt myokardu souvisely se sníženou tvorbou kolaterál.

Klíčová slova: kolaterály, chronický totální uzávěr, korornární tepny.

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Tab. 1.

Variable	No. (%)
Age	
Mean ± SD	53.23 ± 8.52
Range	34-74
Gender	
Female	16 (22.9%)
Male	54 (77.1%)
Duration of angina (in months)	
Mean ± SD	11.09 ± 5.86
Range	2-24
Risk factors	
Smoking	25 (35.7%)
DM	26 (37.1%)
HTN	43 (61.4%)
Previous CABG	8 (11.4%)
Dyslipidemia	32 (45.7%)
Family history of CAD	33 (47.1%)
Previous MI	18 (25.7%)
ECG	22 (31.4%
SWMA	17 (24.3%)
Medication	
ASA	65 (92.9%)
Beta blockers	50 (71.4%)
ACE inhibitors	34 (48.6%)
Statins	55 (78.6%)
Nitrate	60 (85.7%)
RCA	44 (61.1%)
LAD	22 (30.5%)
LCx	6 (8.4%)
Ipsilateral	35 (50%)
Contralateral	35 (50%)

Introduction

Coronary artery disease is the main cause of morbidity and mortality worldwide (1). Chronic total occlusion is a challenging subset of coronary artery disease due to low PCI success rate and high risk of complications (2). Therefore, patient selection plays a vital role in deciding to attempt PCI for CTO (2). The exact prevalence of CTO in the general population is unknown, as some patients are asymptomatic and never undergo diagnostic coronary arteriography (3). However, about 20% of patients undergoing coronary angiography have CTO (4).

The clinical presentation of a CTO patient might be very variable, depending on several factors, including the amount of viable myocardium and ischemia related to the CTO artery (3). Coronary collateral arteries serve as alternative conduits for blood flow that is capable of bypassing the site of obstruction and preserve the tissue that is jeopardized by ischemia (5). Adequate collateralization varies significantly among patients and correlates with long-term survival (1, 6). There is an ongoing debate on the relationship between coronary collateral artery growth (arteriogenesis) and clinical parameters such as age, diabetes, and medication (7).

Several clinical parameters and traditional risk factors are associated with the development of collateral circulation: among these, elevated cholesterol levels, diabetes mellitus, and hypertension are the most important (5, 8-10). In addition, the duration of angina pectoris is significantly associated with collateral artery formation (7). On the other hand, clinical studies do not show a consistent relation between collateralization and smoking (9, 11). However, in all of these studies, patients who were included had various degrees of stenosis. It is well known that the degree of stenosis is a major determinant of the arteriogenic response, and thus it has been a potential confounder in these studies (7). This study aims to assess the influence of different clinical factors on the development of collaterals in patients with chronic total occlusion (CTO).

Patients and methods

This observational study was approved by the institutional ethics committee and conducted in Ain Shams University Hospital between December 2017 and November 2018. It included 70 consecutive patients who had coronary chronic total occlusion (CTO) during coronary angiography. CTO was defined by a total occlusion (> 99% stenosis) of a coronary vessel for ≥ 3months (7). Patients who had previous coronary artery bypass surgery or poor angiographic image quality were excluded. All patients signed informed consent. Clinical, electrocardiographic, and echocardiographic data were collected in addition to details of coronary angiography.

The patients were classified into two groups according to the visibility of collaterals. Group A: patients had no visible collaterals; and Group B: visible collaterals. Further classification according to the Rentrop scoring system (12) was done by two independent experts who were blinded to patient data as follows:

0. no visible collateral channel filling;
I. faintly visible collaterals with a filling of branches but no filling of the distal stenotic (culprit) artery;
II. collaterals partially filling the branches of the stenosed artery;
III. complete collateral filling of the stenosed artery.

Data management

Data were collected, verified, revised, and then edited on PC. Categorical variables were expressed as an absolute and relative frequency (percentage), while continuous variables were presented as mean values +/- standard variation. Comparisons were made between the two groups using the t-test for continuous variables and the Chi-square Test and Pearson correlation coefficient for categorical variables. Statistical analysis was performed using SPSS (statistical software package version 12) (SPSS Science, Chicago, IL, USA).

Results

This study included 70 patients with coronary chronic total occlusion. The patients' age ranged from 34 to 74 years, with a mean of 53.23 years. Fifty-four patients were male, while 16 patients were female. The basic characteristics of the patients studied are shown in Table 1.

The patients were divided into two groups according to the visibility of collaterals. Group A: sixteen patients who had no visible collaterals (22.9 %); and Group B: visible collaterals were seen in 54 patients (77.1%). A comparison between Groups A and B showed a significant difference between them regarding age. Group B had a younger age (51.76 ± 7.94) than Group A (59.44 ± 6.26), while there was no significant difference regarding gender. A statistical difference between Groups A and B concerning risk factors revealed that diabetes and smoking were associated with less collateral formation. At the same time, hypertensive and dyslipidemic patients had more visible collateral formation (Table 2), The duration of angina was significantly lower in Group A (8.44 ± 6.562) compared to Group B (11.87 ± 5.45), with a P value of 0.038. On the other hand, Group A had a higher rate of previous myocardial infarction and segmental wall motion abnormality than Group B with a statistical difference. There was no significant difference between the two groups concerning previous CABG or positive family history or ECG changes (Table 2).

Concerning medications, patients in Group B had collateral formation that was statistically highly significant in patients re-

ceiving beta blockers (48; 88.9%) versus patients in the group with no visible collaterals (2; 12.5%). ASA, ACE inhibitors, statins, and nitrate showed no significant effect on collateral formation between Groups A and B, and there was no statistical significance between the two groups regarding the affected artery (Table 2).

According to the presence and degree of collateral formation, the patients were divided into four grades: the groups were compared in regard to gender, age, duration of angina in months, risk factors of coronary artery disease, previous myocardial infarction, ECG changes, SWMAs, medications as well as the affected artery (Table 3). Patient age showed a statistically significant inversely proportional effect on collateral formation which was associated more with younger age 51.5 ± 8.29 for faintly visible collaterals, 51.94 ± 8.11 for partially filling collaterals, and 51.5 ± 7.4 for complete collateral filling. In comparison, for no visible collateral, an older age was seen (59.44 ± 6.26). Gender, as well as the duration of angina, showed no statistically significant difference in collateral formation between different grades of the Rentrop classification (Table 3). Patients with no collateral formation were statistically highly significant more prevalent in smokers (16; 100%) versus faintly visible collaterals (4; 25%), partially filling collaterals (4; 12.5%), and complete collateral filling (1; 16.7%). A similar statistically high significance was in diabetic patients with no collateral formation (16; 100%) versus faintly visible collaterals (7; 43.8%), partially filling collaterals (2; 6.2%), and complete collateral filling (1; 16.7%) (Table 3). However, the statistical significance of collateral formation was more prominent in hypertensive patients (11; 68.8%) for faintly visible collaterals, (23; 71.9%) for partially filling collaterals, (5; 83.3%) for complete collateral filling versus (4; 25%) for nonvisible collaterals.

On the other hand, patients with no collateral formation were statistically highly significant more present among dyslipidemic patients (14; 87.5%) versus faintly visible collaterals (7; 43.8%), partially filling collaterals (11; 34.4%), and complete collateral filling (0; 0%) (Table 3). Previous CABG, positive family history for coronary artery disease, prior myocardial infarction, electrocardiography, and resting segmental wall motion abnormalities showed no statistically significant effect on the formation of collaterals. Beta blockers were the only medication that was shown to be statistically significant for collateral formation as there were (11; 68.8%) patients with faintly visible collaterals, (31; 96.9%) for partially filling collaterals, (6; 100%) for complete collateral filling versus (2; 12.5%) for nonvisible collaterals. While for ASA, ACE inhibitors, statins, nitrates affected coronary artery as well as ipsilateral & contralateral showed no significant effect on collateral formation (Table 3).

Tab. 2.

Variables	Group A: no visible collaterals	Group B: visible collateral formation	P value
	16 (22.9%)	54 (77.1 %)	
	Number (%)	Number (%)	
AGE Mean ± SD	59.44 ± 6.261	51.76 ± 7.943	0.001
DURATION Mean ± SD	8.44 ± 6.562	11.87 ± 5.45	0.038
SMOKING	16 (100%)	9 (16.7%)	0.000
DM	16 (100%)	10 (18.5%)	0.000
HTN	4 (25%)	39 (72.2%)	0.001
Dyslipidemia	14 (87.5%)	18 (33.3%)	0.000
Previous MI	14 (87.5%)	4 (7.4%)	0.000
SWMA	12 (75%)	5 (9.3%)	0.000
Beta blocker	2 (12.5%)	48 (88.9%)	0.000

Tab. 3.

Variables	Grade 0	Grade I	Grade II	Grade III	P value
	16 (22,9%)	16 (22,9%)	32 (45.7%)	6 (8.6%)	
	Number (%)	Number (%)	Number (%)	Number (%)	
Age (Mean ± SD)	59.44 ± 6.26	51.5 ± 8.29	51.94 ± 8.11	51.5 ± 7.4	0.01
Smoking	16 (100%)	4 (25%)	4 (12.5%)	1 (16.7%)	0.000
DM	16 (100%)	7 (43.8%)	2 (6.2%)	1 (16.7%)	0.000
HTN	4 (25%)	11 (68.8%)	23 (71.9%)	5 (83.3%)	0.007
Dyslipidemia	14 (87.5%)	7 (43.8%)	11 (34.4%)	0 (0%)	0.000
Beta blocker	2 (12.5%)	11 (68.8%)	31 (96.9%)	6 (100%)	0.000

Discussion

Coronary collateral vessels have functional and prognostic benefit in patients with chronic total occlusion. The interindividual differences in the number and extent of collateral vessels are influenced by multiple clinical, biochemical, and anatomical factors.

In this study, 70 patients with coronary chronic total occlusion were included. It showed that coronary collateral circulations were affected by several factors. Patient age is one of the factors related to the presence of collateral circulation. Well-developed collateral circulation was found in younger patients and decreased with advancing age. This result is consistent with previous angiographic studies which revealed that ageing decreased collateral formation (5, 13–15).

The underlying mechanisms could be due to suppression of collateral growth by reduced endothelial nitric oxide (NO) production in elderly patients (16). Alternatively, decrease response to inflammatory cytokines by leading to decrease arteriogenesis (17; 18). In comparison, the development of collaterals showed no significant difference between males and females in this study. This is in contrast to the results of Zhen et al. (15) who showed lower collateral development in females.

Regarding the risk factors for coronary artery disease, hypertensive patients had well-developed collaterals compared to non-hypertensive ones (72.2% versus 25%). This is concordant with the findings by Van der Hoeven and his colleagues (7), de Groot and his colleagues (5), and Zen and his colleagues (15). Hypertension leads to an increase in nitric oxide production and matrix metalloproteinase (MMP) activity through increasing fluid shear stress. Additionally, hypertension increases the angiotensin level leading to a rise in growth factor production. All these factors contribute to arteriogenesis and collateral formation (19).

Diabetes negatively affected the development of collateral circulation in this study. One hundred percent of patients with no collate-

rals had diabetes, while 18.5% of those with collateral formation had diabetes. These results are in line with the studies by de Groot and his colleagues (5) and Zen and his colleagues (15).

However, Van der Hoeven and his colleagues (7) showed no statistically significant difference in collateral formation between diabetic and non-diabetic patients. This may be because of an assessment of collateral circulation with invasive measurement techniques that show smaller collateral anastomoses in contrast to angiography that fails to do that (20, 21), especially in DM where microangiopathy is part of the disease (22).

Dyslipidemia has a role in the development of atherosclerosis, but its correlation with the development of collaterals is not specified. This study suggests that dyslipidemia inhibits the development of collaterals as it was more prevalent in patients with no collaterals than those with collaterals. This is similar to the findings of both de Groot and his colleagues (5) and Zen and his colleagues (15). A possible mechanism is that dyslipidemia impairs monocyte chemotaxis leading to reduced monocyte/macrophage influx (23). Secondly, it leads to a delayed and impaired arterial growth (24).

On the other hand, by using quantitatively by measuring the intracoronary derived collateral flow index (CFI), there was no association between hyperlipidemia or actual cholesterol level and collateral development, as reported by Van der Hoeven and his colleagues (7).

Smoking has a negative effect on collateral development; in our study, 100% of patients with no collateral formation were smokers, while in those with collateral formation, 16.7% were smokers. These results are in line with those of de Groot and his colleagues (5). However, they are not in agreement with those of Zhen and his colleagues (15) and Van der Hoeven and his colleagues (7) who failed to show a consistent relation between collateralization and smoking.

The effect of smoking depends on its duration, with current nicotine exposure leading to induced stimulation of EC proliferation, migration and tube formation, which increases arteriogenesis. While chronic smoking causes endothelial dysfunction and alters inflammatory responses leading to decreased collateral formation, thus observed positive effect disappears (25).

Regarding symptoms, an increased duration of angina pectoris leads to an increase in collateral formation. These results were concordant with Van der Hoeven and his colleagues (7) who showed that the duration of angina pectoris was positively associated with collateral formation. The possible explanation of this positive correlation is that the increased duration of angina produces more acute inflammatory mediators and cytokines, which result in vascular remodeling and arteriogenesis (26).

In terms of medication, patients receiving beta blockers had better collateralization than those who did not receive them. This finding corresponds with the results of Van der Hoeven and his colleagues (7). On the other hand, it is discordant with those of Zen and his colleagues (15).

The effect of low heart rate induced by beta blockers leads to improved fluid shear stress at the endothelial wall, which stimulates coronary collateral cross (27, 28). This is supported by the study by Schirmer et al. (29) which showed positive effects of ivabradine on arteriogenesis in mice.

Statins have pleiotropic effects and stimulate new vessel formation; this finding is supported by patient studies conducted by Dincer et al. (30), Nishikawa et al. (31), and Ovbiagele et al. (32). However, no correlation was found in our study between statins and collateral development. This result was similar to that in the study done by Van der Hoeven and his colleagues (7).

Concerning the vasodilator effect of nitrate, there was no significant effect on collateral development. This finding is supported by those of Goldstein et al. (33) and Feldman et al. (34). They found that a reduction in coronary collateral resistance was not associated with angiographically visible collateral vessels.

As for previous MI, this study shows that a history of prior MI is associated with decreased collateral formation, as is also reported by Van der Hoeven and his colleagues (7).

We found no correlation between collateral development and either ECG finding or echocardiographic measurement. On the other hand, Akgullu el al (35) showed a negative correlation between the Rentrop score and the LVEF values of patients with stable angina pectoris. As a patient with previous MI who had depressed LVEF in addition to inadequate blood supply through collateral leads to regional wall myocardial dysfunction. Furthermore, Werner et al. (36) reported that regional wall motion was best preserved in patients without prior Q-wave myocardial infarction and with grade CC2 collaterals.

In summary, this study has shown that in patients with coronary artery disease and chronic total occlusion, beta blocker therapy, hypertension, and long duration of angina are directly proportional to coronary collateral formation. At the same time, DM, dyslipidemia, advanced age, and previous MI were inversely proportional to collateral formation. On the other hand, gender, positive family history of coronary artery disease, ACE inhibitor therapy, treatment with statins, nitrates, and ASA medications did not show a statistically significant effect on the formation of collaterals.

Conclusion

In patients with chronic coronary total occlusion, beta blocker therapy, hypertension, and long duration of angina were associated with an increase in coronary collateral formation. By contrast, DM, dyslipidemia, advanced age, and previous MI were associated with a decrease in collateral formation.

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Compliance with ethical standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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