Chronic Total Artery Occlusions in Noninfarct-Related Coronary Arteries

Ozcan Ozeke, MD¹ Mutlu Gungor, MD² Serkan Topaloglu, MD¹ Dursun Aras, MD¹ Can Ozer, MD²

¹Department of Cardiology, Türkiye Yüksek İhtisas Hospital, Ankara, Turkey

²Department of Cardiology, Bayindir Hospital, Ankara, Turkey

Address for correspondence Ozcan Ozeke, MD, Türkiye Yüksek İhtisas Hastanesi, Kardiyoloji Klinigi, Ankara 06100, Turkey (e-mail: ozcanozeke@gmail.com).

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Abstract

It has been rarely encountered some patients in clinical practice with coronary artery chronic total occlusion (CTO) on angiography but no any clinical history or electrocardiographic, echocardiographic, or left ventriculographic evidence of previous myocardial infarction. These noninfarct-related artery CTO (non-IRA CTO) lesions may be used as a clinical role model of endogenous cardioprotective mechanisms in addition to continuing the process of atherosclerosis. The objective of this study was to characterize the clinical characteristics of patients with non-IRA CTO patients and compared them to those with infarct-related CTO (IRA-CTO). We reviewed our invasive cardiology database searching for the CTO of any major coronary arteries, and assessed whether or not they have the clinical history or electrocardiographic, echocardiographic, and left ventriculographic evidence of previous myocardial infarction. Interestingly, we detected that all these patients with non-IRA CTO had diabetes mellitus, and the clinical and demographic features of these non-IRA CTO patients were compared with age- and sex-matched diabetic IRA-CTO patients with regard to conventional coronary risk factors and the angiographic collateral grading system. There were total 99 CTO patients (49 patients with non-IRA CTO and 50 patients with IRA-CTO). All patients with non-IRA CTO had better collateral circulation (96 vs. 40% $p < 0.001$) compared with those having IRA-CTO. The only significant difference between the groups was the status of current smoking (4 vs. 88%; $p < 0.001$). The present study showed that the non-IRA CTOs were associated with diabetes mellitus and better collateral development compared with IRA-CTO. In diabetic patients, the concomitant smoking use may be harmful by preventing endogenous cardioprotective mechanisms.

Keywords

- chronic total coronary occlusion
- cardioprotection
- diabetes

Coronary atherothrombosis and atherosclerosis remain significant causes of morbidity and mortality in the population as a whole. The presence of atherosclerosis is necessary but not sufficient for atherothrombosis. There are separate factors involved that predispose to plaque rupture and thrombosis. Coronary artery chronic total occlusions (CTOs) are generally associated with late organization of an acute thrombotic total occlusion generated by atheromatous vulnerable plaque rupture causing acute ST elevation myocardial infarction (STEMI) and segmental wall motion abnormality (SWMA).¹ However, all total occlusions may not always

lead to or caused by infarction. In clinical practice, it has been encountered in some patient with CTO on angiography but without clinical history and cardiac imaging evidence of previous myocardial infarction probably due to progressive occlusion of a long-term high-degree stenosis.^{2–5} Therefore, CTO are of two origins, (1) “infarct-related artery CTOs (IRA CTO),” those resulting from an STEMI and usually associated with a loss of viability and SWMA, (2) “non-IRA CTOs (non-IRA CTO),” those resulting from a progressive chronic stenosis that eventually evolves into a complete occlusion; those are associated with preserved viability and left ventricular

contractility because of the adaptive collateral network.⁵ Both two CTO groups differed in terms of the type of ischemia (STEMI vs. stable coronary artery disease [CAD]). These patients are able to maintain good left ventricular function and sustain a reasonable quality of life despite their CTO. We believe that the characteristics of patients with non-IRA CTO might provide new information about endogenous cardioprotective mechanisms in addition to continuing the process of atherosclerosis. Although severe stenosis may progress to complete occlusion, the presence of collateral flow and other endogenous cardioprotective mechanisms may protect against the development of myocardial infarction and SWMA.^{6,7} Therefore, we sought to characterize the features of non-IRA CTO patients.

Method

We reviewed our invasive cardiology database searching for the CTO of any major coronary arteries, and assessed whether or not they have the clinical history or electrocardiographic (Q wave, precordial R loss), echocardiographic (SWMA), and left ventriculographic (SWMA) evidence of previous myocardial infarction. Interestingly, we detected that all CTO patients without SWMA had diabetes mellitus, and the clinical and demographic features of these patients (Group 1; non-IRA CTO) were compared with age- and sex-matched diabetic patients with IRA CTO with SWMA (Group 2; IRA CTO). The patients with a history of coronary artery bypass grafting were excluded from the study.

Conventional cardiovascular risk factors, including cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia, and family history of early CAD, were the targets for evaluation. The diagnosis of diabetes was made according to HbA1c levels in accordance with 2010 American Diabetes Association Guidelines⁸; HbA1c lower than 5.7% (normal), HbA1c: 5.7–6.4% (prediabetic group), and HbA1c higher than 6.4% (diabetic group). Hyperlipidemia was defined as lipid-

lowering medication use, and/or a total cholesterol level above 200 mg/dL. The premature family history of CAD (first grade family member, i.e., men < 55 years and women < 65 years) data were also recorded.

Some other echocardiographic data including left ventricular ejection fraction evaluated by the modified Simpson method were recorded.

The collateral filling of the recipient artery was assessed according to modified Rentrop and Thrombolysis In Myocardial Infarction collateral grading system (“recipient filling grade”).⁹ Based on this grading system, Grade 0: no collaterals; Grade 1: collaterals extend to region with no angiographically apparent recipient vessel; Grade 2: minimal recipient filling by collaterals, that is, minor side branch filling but no epicardial or major branch filling; Grade 3: moderate recipient filling, that is, complete major side branch and partial epicardial filling; Grade 4: complete filling of major epicardial segment. The poor collateral circulation was accepted as the modified Rentrop collateral scores 0 to 2 and good collateral circulation as modified Rentrop collateral scores 3 to 4.

The SPSS statistical software package (version 16.0; SPSS Inc., Chicago, IL) was used to perform all statistical calculations. Continuous variables were expressed as mean ± standard deviation. The independent samples *t* test or Mann-Whitney *U* test were used to compare continuous variables, when appropriate according to normality test results. Categorical variables were expressed as numbers and percentages, and compared using the χ^2 test. For all tests, a value of *p* < 0.05 was considered significant.

Results

A total of 99 consecutive patients with CTO were included in the study. There were 49 diabetic patients with non-IRA CTO and 50 diabetic patients with IRA CTO. The clinical and demographic features of patients were presented in ►Table 1. The collateral circulation was better in non-

Table 1 Comparison of the demographic and clinical features of diabetic patients with IRA versus non-IRA CTO

Diabetic CTO patients	Non-IRA CTO (N: 49)	IRA CTO (N: 50)	<i>p</i> value
Age (y)	60 ± 9	59 ± 7	0.318
Sex (male)	34/49 (69)	35/50 (70)	0.825
HbA1c (%)	7.6 ± 1.2	8.2 ± 2.1	0.068
Hypertension (%)	34/49 (69)	33/50 (66)	0.719
Family history for early CAD (%)	14/49 (29)	10/50 (20)	0.320
Hyperlipidemia (%)	24/49 (49)	23/50 (46)	0.767
Current smoking (%)	2/49 (4)	44/50 (88)	< 0.001
CTO in LAD (%)	10/49 (20)	20/50 (40)	0.034
CTO in Cx (%)	13/49 (26)	13/50 (26)	0.952
CTO in RCA (%)	26/49 (53)	17/50 (34)	0.056
Good collateral circulation (%)	47/49 (96)	20/50 (40)	< 0.001
LVEF (%)	67 ± 7	40 ± 8	< 0.001

Abbreviations: CAD, coronary artery disease; CTO, chronic total occlusion; Cx, circumflex artery; IRA, infarct-related coronary artery; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery; SWMA, segmental wall motion abnormality; y years.

IRA CTO group compared with IRA-CTO group (96 vs. 40%; $p < 0.001$). Of the 49 patients, 35 (71%) patients in non-IRA CTO group presented with typical angina pectoris, 4 (8%) with atypical angina but positive stress test, and 10 (20%) with positive treadmill test with diagnosis of silent ischemia on routine checkup. In non-IRA CTO group, no patient had a history of STEMI, whereas all patients in IRA-CTO group had a history of previous/old acute STEMI. There were no significant differences between the groups regarding the conventional coronary risk factors including the presence of hypertension, hyperlipidemia, and family history for early CAD except for status of current smoking (4 vs. 88%; $p < 0.001$).

Discussion

There were some interesting findings of this small study. The first one was that all non-IRA CTO patients had diabetes mellitus. Although it is well known that diabetes mellitus is accepted as CAD equivalent even in the presence of normal coronary artery on coronary angiography, this finding may mean that some endogenous protective mechanisms also might be more effective in diabetics in the background of continuing the process of atherosclerosis.^{10,11} The second interesting finding of the study was that the only significant difference between the groups regarding the presence of conventional coronary risk factors was the status of smoking. Almost all diabetic CTO patients with preserved left ventricular contractile function had almost no history of current or ex-smoking.

It is unclear which factors have an important role for preserved left ventricular function despite the CTO; however, some mechanisms may have an important role in this cardioprotective effect. It is speculated that coronary remodeling patterns are associated with the clinical presentation of CAD, and reported that there were likely many things that prevent or lead to plaque instability or rupture. The coronary arteries may respond to plaque growth by either outward expansion of the vessel wall (positive remodeling) or vessel shrinkage (negative remodeling).¹² Many nonstenotic lesions undergo "expansive," "positive," or "outward" remodeling, which is observed more frequently in the culprit lesion of acute coronary syndromes than in stable CAD.^{13,14} The classical definition of these plaques encompasses histopathological features such as a large lipid core, the presence of inflammatory cells, and a thin fibrous cap in positive remodeling. In contrast, lesions with constrictive "negative remodeling" are associated with higher grade stenoses with a stable fibrous plaque phenotype.¹⁵ We need to know which factors convert or protect stable patients to/from vulnerable ones. These factors will provide us more detail information about cardioprotection. Some of these known cardioprotective factors, conditions, or mechanism in the presence of CAD are the development of collateral circulation, ischemic conditioning, and life style changes or measures (such as regular walking/exercise, quit smoking, good control of diabetes, and hypertension).^{16,17}

Ischemic preconditioning (IPC) has been recognized as a major cardioprotective phenomenon for two decades.^{18,19} This "conditioning" the heart can be initiated through the application of several different mechanical and pharmacological strategies (pharmacological preconditioning and postconditioning).²⁰ One of the most striking features of this study was that all CTO patients without clinical, electrocardiographic, echocardiographic, and left ventriculographic evidence of previous myocardial infarction had diabetes. Although diabetes is well-known CAD risk factors, some endo/exogenous protective mechanisms might be more effective in some diabetic patients. Although some have been reported that preconditioning protection against infarction and stunning do not develop in diabetic hearts,²¹ this topic has remained unclear. Up to date, there are no clear evidence against or stimulate for IPC in diabetics. It is well known that adenosine triphosphate (ATP)-sensitive potassium (KATP) channels in coronary myocytes contribute to the control of coronary blood flow at rest and in hypoxia. These in the sarcolemma of cardiomyocytes (sarc KATP channels) are required for adaptation of the heart to stress. The opening of sarc KATP channels and KATP channels in the inner membrane of mitochondria (mito KATP channels) plays a central role in IPC.²² Sulfonylureas and glinides close β cell KATP channels to increase insulin release. However, the closure of cardiovascular KATP channels by these drugs in the setting of acute coronary syndromes may lead to increased mortality,²³ although the recently published studies^{24,25} did not identify an increased mortality risk with sulfonylureas. It should be effective in some diabetic patients and may be in some coexisting conditions stimulating or preventing these endogenous cardioprotective mechanisms in diabetics.

Enhancement of coronary collateral function is another important endogenous protective mechanism for the preservation of ischemic myocardium. It can protect and preserve myocardium around the time of coronary occlusion, contribute to better residual myocardial contractility, and lessen symptoms and it is compatible with better survival if adequately exist.^{7,26} In general, there are two different forms of endogenous compensatory vessel formation: (1) "angiogenesis," which is defined as hypoxia-induced "formation of new capillaries" through the activation and proliferation of endothelial cells in ischemic tissue and (2) "arteriogenesis," which is defined as the physical forces (local hemodynamic and mechanical)-induced "transformation of pre-existent immature bridging collateral arterioles" into a much larger functional conductance vessels to restore the perfusion distal to the occluded artery and compensate for the loss of function of occluded artery, and does not require hypoxia-ischemia as a stimulus.²⁷ Since the severity of stenosis for "arteriogenesis" and the presence of residual ischemic stimulus for "angiogenesis" are important triggers, arteriogenesis should be a much more efficient mechanism to compensate for the gradual or intermittent occlusion of a major epicardial artery, and will probably result in a greater increase in blood flow to the ischemic tissue, than the stimulation of angiogenesis. This can be explained by the difference in diameter between the collateral vessels formed in arteriogenesis and the capillaries formed in angiogenesis. Physically, flow is

inversely proportional to resistance and will be greater if the collateral circulation offers less resistance in comparison to occluded or stenosed native vessels. Higher flow in turn will be associated with greater shear stress and this will lead to endothelial cell activation and an increase in size of the collaterals in an attempt to normalize shear forces. For these reasons, the severity of the coronary stenosis (CTO or not) plays a part in the intensity of arteriogenesis.²⁸ Although these vessels do not have an important role as an acute mechanism,²⁹ the support of collateralization needs time to develop.¹⁸ This mechanism may be important in increasing the capacity of a poorly developed collateral circulation over time, particularly in CTO patients due to progressive occlusion of a long-term high-degree stenosis.^{5,30} Although the influence of the diabetes on collateral development is debatable,^{8,9,14,31} it has been reported that diabetics generally have a poor acute collateral response because of the diffusely impaired endothelial function.³² However, after the acute phase (> 3 months), this mechanism may be irrelevant. In the present study, all diabetic patients in never smokers had good collateral circulation compared with diabetic smokers. The concomitant presence of diabetes and current smoking as a deadly duet may impair the collateral development and prevent endogenous cardioprotective mechanisms.³³ The effect of smoking and nicotine on coronary arterial function has been proved with various invasive and noninvasive techniques; however, their effects on coronary collateral development are debatable. Tobacco smoke contains more than 4,000 chemical compounds that might have an effect on human coronary collaterals.³⁴ In addition to smoking-induced chronic hypoxia and endothelial dysfunction, nicotine was shown to be a potent physiological and/or pathological angiogenic agent effective through an endogenous nicotinic cholinergic pathway in endothelial cells and in part by activation of endothelial-monocyte interactions involved in arteriogenesis.³⁴ Despite to this stimulating effect on collateralization, the other clinical studies revealed that smoking was negatively and independently correlated with reduced coronary collateralization.³⁵ In the light of these findings, smoking cessation should be firmly recommended to particularly diabetic patients³⁶ and emphasized the impact of smoking on their disease process.

There were some limitations of present study such as its retrospective design, small size sample, and possible under-detection of SWMA by echocardiography or left ventriculography. In fact, ventriculography is much less sensitive than echocardiography in the SWMA detection. Cardiac magnetic resonance imaging would be more effective in detecting previous myocardial infarction.

We detected that the concomitant presence of diabetes and smoking impairs the collateral development in CTO diabetic patients. Although it is well known that diabetes mellitus aggressively induces atherosclerosis and may be more susceptible to infarction; it can also activate endogenous cardioprotective mechanism protecting the left ventricular contractile function from ischemia/reperfusion injury. However, these cardioprotective mechanisms might be blunted in diabetics particularly in the presence of active

smoking. A better understanding of the mechanisms or conditions causing this cardioprotection will be important for the design of more effective strategies for the treatment of patients with CAD, thus decreasing the morbidity and mortality associated with diabetes.

Conflict of Interest

The authors declare no conflict of interest.

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