ORIGINAL ARTICLE

Influence of smoking habits on acute outcome of revascularization of chronic total occlusion

Kronik total oklüzyon sonucu üzerine sigara içme alışkanlıklarının etkisi

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ABSTRACT

Objective: Percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) remains a major challenge in interventional cardiology. The exact toxic components of cigarette smoke and the mechanisms involved in smoking-related cardiovascular dysfunction are largely unknown, but it increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol. There is only insignificant knowledge reported in the literature about the influence of smoking habits on acute outcome in CTO PCI.

Methods: Between 2012 and 2017, a total of 559 patients were included in the study. The patients all underwent PCI for at least 1 CTO. Antegrade and retrograde CTO techniques were applied. The Shapiro-Wilk test was used to test for normality of distribution. Continuous variables were tested for differences with the Kruskal–Wallis test or the Mann–Whitney U test, as appropriate. Categorical variables were tested using Fisher's exact test.

Results: Non-smokers were older than smoking patients (65.3±10.3 years *vs.* 58.3±9.2 years; p<0.001). The mean age of the cohort was 62.1 years (±10.5). Smokers were more often male (85.7% *vs.* 79.7%; p=0.074), suffered from longer lesion length (36.1±17.5 mm *vs.* 39.1±17.2 mm; p=0.023) and therefore needed longer stents (64.2±26.5 mm *vs.* 69.0±28.0 mm; p=0.084). The success rate was comparable for smokers and non-smokers. In-hospital procedural complications were rare and demonstrated no statistically significant difference.

Conclusion: The results of this retrospective study revealed no significant association between smoking and acute outcome in CTO PCI. Smokers did, however, have longer lesions and needed longer stents.

ÖZET

Amaç: Kronik total oklüzyon (KTO) için perkütan koroner girişim (PKG) girişimsel kardiyolojinin hâlâ önemli bir sorunudur. Sigara dumanının toksik bileşenleri ve sigara içimiyle ilişkili kardiyovasküler işlev bozukluğunun mekanizmaları geniş ölçüde bilinmemekle birlikte, bu durum enflamasyon, tromboz ve düşük yoğunluklu lipoprotein kolesterolün oksidasyonunu artırmaktadır. Sigara içme alışkanlıklarının KTO-PKG'nin akut sonucu üzerindeki etkisine ilişkin literatürde yalnızca önemsiz derecede bilgi vardır.

Yöntemler: 2012–2017 yılları arasında 559 hastayı çalışmaya aldık. Bu hastalar en az bir KTO için PKG geçirmişlerdir. Antegrat ve retrograt KTO teknikleri uygulanmıştır. Dağılımın normal olup olmadığını anlamak için Shapiro-Wilk testi kullanıldı. Sürekli değişkenlerde farklılıklar Kruskal–Wallis-testi veya uygun olduğunda Mann–Whitney-U testi ile sınandı. Kategorik değişkenler ise Fisher kesinlik testi ile sınandı.

Bulgular: Sigara içmeyenler içenlerden daha yaşlı idi (65.3±10.3 yıla karşın; 58.3±9.2 yıl; p=<0.001). Kohortun yaş ortalaması 62.1±10.5 yıl idi. Sigara içenler daha büyük bir sıklıkla erkekler olup (%79.7'ye karşın %85.7; p=0.074), lezyon uzunlukları daha fazla idi (36.1±17.56 mm'e karşın 39.1±17.2 mm). Bu nedenle daha uzun stentlere gerek duymuşlardır (69.0±28.0 mm'e karşın 64.2±26.5 mm; p=0.023). Sigara içenlerle içmeyenler arasında başarı oranları benzemekteydi. Hastanede yapılan işlemlerde nadiren komplikasyonlar görülmüş olup her iki grup arasında fark yoktu.

Sonuç: Geriye dönük çalışmamız sigara içen ve içmeyen hastalar arasında anlamlı bir ilişkin olmadığını düşündürmektedir. Buna rağmen sigara içenlerde lezyonlar daha uzun olup daha uzun stentlere gerek duyarlar.

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Recanalization of a chronic total occlusion (CTO) remains a challenging procedure in interventional cardiology. A CTO of a coronary artery is identified in as many as 20% of patients with a clinical indication for coronary angiography. With the implementation of novel recanalization techniques and emerging devices, percutaneous coronary intervention (PCI) has become a promising treatment option for these patients.[1–5] If there is significant myocardial ischemia combined with clinical symptoms due to ischemia, recanalization is indicated. In suitable cases, left ventricular function can be improved and more invasive therapies, like coronary artery bypass graft (CABG) surgery, can be avoided and complication rates are lower. The prognosis of the disease can be improved with both a short-term and long-term survival benefit.[6,7]

Tobacco use is one of the most important avoidable causes of cardiovascular diseases.[8] Several trials have shown that smoking substantially increases the risk of myocardial infarction, sudden cardiac death and stroke.[9,10] Smoking not only increases the risk of the development of coronary heart disease (CAD), but also increases morbidity and mortality in patients with known coronary atherosclerosis.[11] It has been suggested that increased thromboxane production or increased fibrinogen levels might be responsible for this.[12,13]

The exact toxic components of cigarette smoke and the mechanisms involved in smoking-related cardiovascular dysfunction are largely unknown, but it increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol.[14]

This study assessed the impact of smoking on the procedural success and features of CTO PCI.

METHODS

Between 2012 and 2017, a total of 559 patients who underwent CTO PCI in a German high volume CTO center were included in the research. All of the patients had a clinical indication for CTO PCI and/or a positive functional ischemia test in the territory of the occluded coronary artery as assessed with magnetic resonance imaging or stress-echocardiography.

The patients were classified according to their smoking status as never-smokers or current smokers. Smokers were identified as patients who reported having smoked cigarettes within 30 days.

Abbreviations:

CABG	*Coronary artery bypass graft*
CAD	*Coronary artery disease*
CART	*Controlled antegrade and retrograde tracking*
COPD	*Chronic obstructive pulmonary disease*
CTO	*Chronic total occlusion*
DES	*Drug-eluting stent*
DM	*Diabetes mellitus*
HDL-C	*High-density lipoprotein cholesterol*
PAD	*Peripheral artery disease*
PCI	*Percutaneous coronary intervention*
TIMI	*Thrombolysis in Myocardial Infarction*

To prevent thromboembolic complications, heparin was administered during the intervention guided by the activated clotting time (>300 seconds). All of the procedures were performed via both femoral arteries using 7-F guiding catheters; in the majority of cases, bilateral injections of contrast fluid were used to determine the length of the lesion and the existence and extent of intercoronary collaterals. Dual injections were made in most cases to identify contralateral collaterals and define the length of the lesion.

The antegrade approach was used as first step. Coronary wiring started with tapered polymer soft-tip guidewires and ended with super-stiff guidewires (up to 12-g wires). The retrograde approach was used for complex lesions with ambiguous proximal caps and a poor distal target. The techniques used in the retrograde approach were the standard “true” retrograde wire crossing, the kissing wire technique, controlled antegrade and retrograde tracking (CART), and the reverse CART technique, with or without a knuckle wire. If required, the maneuvers were guided using intravascular ultrasound to understand the local anatomy and to identify the exact entry point of the CTO. The Japanese-CTO score, which combines several parameters of a CTO, including the degree of calcification of the lesion, >45° bend in the CTO segment, blunt proximal cap, length of occluded segment (>20 mm) and a previously failed recanalization attempt, was calculated for all of the patients.

Drug-eluting stents (DES) were implanted in almost all cases. After the PCI, dual antiplatelet therapy consisting of 100 mg of aspirin once daily indefinitely and 75 mg of clopidogrel daily for at least 6 months was continued. An Angio-Seal vascular closure device (St. Jude Medical Inc., St. Paul, MN, USA) was used after the arterial puncture. Procedural success was defined as successful recanalization of the CTO with residual stenosis <30% and restoration of grade 3 Thrombolysis in Myocardial Infarction (TIMI) flow.

The primary endpoint of this study was determination of the impact of smoking on the success rate of CTO PCI. The secondary endpoints were the influence of smoking on the clinical and angiographic characteristics of patients with CTO and on hospital safety parameters, examining severe complications, such as all-cause mortality, vessel perforation, ST-elevation myocardial infarction and thromboembolic events.

Statistical analysis

The distribution of continuous variables was characterized using the median and minimum-maximum, and the distribution of categorical variables was described with absolute and relative frequencies. The Shapiro-Wilk test was used to test for normality of the data. Since normality was rejected for all of the continuous variables of interest, the differences in the distribution of continuous variables between smoker and non-smoker were tested with the Mann-Whitney U test. Differences in the distributions of categorical variables were tested using Fisher's exact test. According to the exploratory character of the analysis, all p values were interpreted as descriptive measures rather than as definitive inferential measures.

RESULTS

In this study group, 82.5% of the patients were men. The mean age was 62.1 years (±10.5). In all, 259 (46.3%) patients were smokers. Table 1 illustrates the baseline characteristics. Non-smokers were older than smoking patients (65.3±10.3 years *vs*. 58.3±9.2 years; p=<0.001). Of the smokers, 22.8% suffered from diabetes mellitus (DM), 81.7% had arterial hypertension, and 10.4% had peripheral artery disease (PAD).

Smoking patients had a greater prevalence of chronic obstructive pulmonary disease (COPD) (13.5% *vs*. 6.3%; p=0.006), a familiar liability for a coronary artery disease (CAD) (37.5% *vs*. 19.3%; p=<0.001) and male gender (85.7% *vs*. 79.7%; p=0.074). Among the non-smokers, prior CABG surgery was more frequently seen (12.0% *vs*. 6.9%; p=0.046) and a total cholesterol <200 mg/dL, as

Table 1. Baseline and periprocedural characteristics

	Non-smoker (n=300)	Smoker (n=259)	*p*
Age (years), median (min-max)	66 (38–87)	59 (33–83)	<0.001
Hypertension, n (%)	245 (81.7)	207 (79.9)	0.666
Diabetes, n (%)	87 (29.0)	59 (22.8)	0.101
Gender (male), n (%)	239 (79.7)	222 (85.7)	0.074
Chronical obstructive pulmonary disease, n (%)	19 (6.3)	35 (13.5)	0.006
Body mass index, median (min-max)	27.4 (17.0–45.0)	27.5 (18.8–46.7)	0.826
Total cholesterol >200 mg/dL, n (%)	34 (16.5)	43 (26.9)	0.020
LDL cholesterol >100 mg/dL, n (%)	97 (47.1)	82 (51.3)	0.461
Peripheral artery disease, n (%)	42 (14.0)	27 (10.4)	0.246
Family history, n (%)	58 (19.3)	97 (37.5)	<0.001
Prior myocardial infarction, n (%)	103 (34.3)	89 (34.4)	1
Prior coronary artery bypass graft, n (%)	36 (12.0)	18 (6.9)	0.046
Prior CTO PCI attempt, n (%)	118 (39.3)	111 (42.9)	0.438
Ejection fraction >40%, n (%)	290 (96.7)	242 (93.4)	0.112
Multivessel disease, n (%)	232 (77.4)	186 (71.8)	0.231
Chronic total occlusion location, n (%)			0.208
Left anterior descending	89 (29.7)	62 (23.9)	
Left circumflex	33 (11.0)	38 (14.7)	
Right coronary artery	177 (59.0)	156 (60.2)	

CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention.

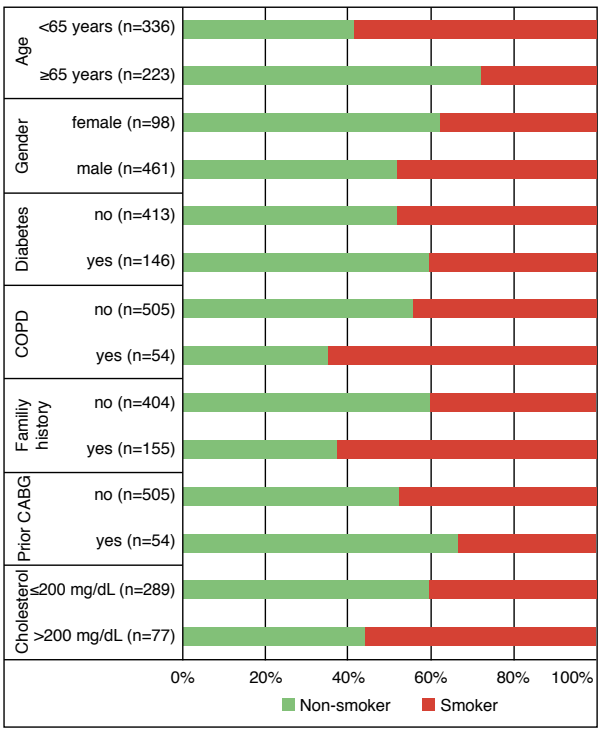

Figure 1. Distribution of cardiovascular variables according to smoking status.

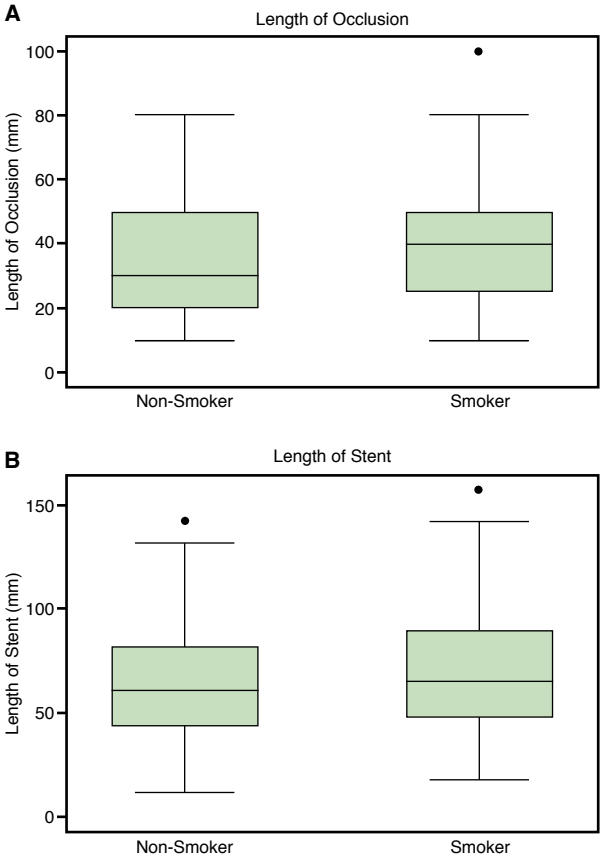

Figure 2. Comparison of **(A)** length of occlusion and **(B)** length of stent in smokers and non-smokers.

shown in Figure 1. An ejection fraction better than 40% (96.7% *vs*. 93.4%; statistical trend p=0.112) was also observed more often in patients without a smoking habit.

Table 2 presents the procedural and angiographic characteristics. The lesion length was longer (36.1±17.5 mm *vs*. 39.1±17.2 mm; p=0.023) in smoking patients, and the length of the stents used was also subsequently longer (64.2±26.5 mm *vs*. 69.0±28.0 mm; statistical trend p=0.084) (Fig. 2). Approximately 70% of all of the patients had a high grade of calcification, independent of smoking status (non-smokers: 71.0% *vs*. smokers: 69.1%; p=0.644). The median Japanese CTO score was 3 (p=0.616). The retrograde technique was used in 20.3% of non-smokers and 22.4% of smokers (p=0.605).

There were no significant differences with respect to the quantity of contrast medium (non-smokers: 247±125 mL *vs*. smokers: 245±115 mL; p=0.659), fluoroscopy time (non-smokers: 35.6±19.3 minutes *vs*. smokers: 36.7±20.8 minutes; p=0.713), examination time (non-smokers: 102±41.4 minutes *vs*. smokers: 102±44.1 minutes; p=0.977), diameter of the stents used (non-smokers: 3.07±0.37 mm *vs*. smokers: 3.05±0.34 mm; p=0.649) or the number of the stents (non-smokers: 2.1 *vs*. smokers: 2.0; p=0.512).

The success rate was comparable for smokers and non-smokers (p=0.813). In-hospital, acute procedural complications were rare and revealed no statistically significant difference (p=0.266). They included mostly vascular complications, such as a local hematoma at the puncture site, and 1 cardiac tamponade, which was treated with pericardiocentesis and had no further consequences. No severe complications, such as periprocedural death or ST-elevation myocardial infarction, were observed.

DISCUSSION

Not smoking is probably the most important step one can take to decrease the chance of developing CAD. In the United States, smoking accounted for 30% of all deaths from cardiovascular disease and 20% of deaths from ischemic heart disease. Smoking results in approximately 100,000 deaths due to coronary

Table 2. Procedural and angiographic characteristics

	Non-smoker (n=300)	Smoker (n=259)	*p*
Complication rate, n (%)	20 (6.8)	11 (4.3)	0.266
Success rate, n (%)	256 (85.3)	219 (84.6)	0.813
Length of lesion*	30 mm (10–80)	40 mm (10–100)	0.023
Calcification, n (%)	213 (71.0)	179 (69.1)	0.644
Tortuosity >90°, n (%)	154 (51.3)	138 (53.3)	0.672
Blunt stump, n (%)	194 (64.7)	160 (61.8)	0.483
Japanese CTO score, n (%)			0.507
0	12 (4.0)	12 (4.6)	
1	42 (14.0)	23 (8.9)	
2	61 (20.3)	58 (22.4)	
3	74 (24.7)	68 (26.3)	
4	81 (27.0)	76 (29.3)	
5	30 (10.0)	22 (8.5)	
Retrograde technique, n (%)	61 (20.3)	58 (22.4)	0.605
Stent type, n (%)			0.224
Drug eluting stent	250 (98.0)	218 (99.5)	
Bare metal stent	5 (2.0)	1 (0.5)	
Number of stents*			
Diameter of stent	3.0 mm (2.25–4.0)	3.0 mm (2.5–4.0)	0.649
Lenght of stent	61 mm (12–142)	65 mm (18–157)	0.084
Amount of contrast medium	200 mL (90–650)	240 mL (70–800)	0.659
Fluoroscopy time	31 min (4–104)	33 min (5–113)	0.713
Examination time	100 min (15–300)	100 (11–240)	0.977

heart disease each year.[15] Several trials have shown a close association between coronary heart disease and tobacco use.[16,17]

Beyond its status as an independent risk factor, smoking appears to have a multiplicative interaction with other major cardiovascular risk factors, such as high serum levels of lipids, arterial hypertension, and diabetes. Furthermore cigarette smoking is a risk factor for the development of DM, including an increased risk of microvascular and macrovascular complications of DM.[18,19] Compared with non-smokers, smokers have been found to have higher levels of serum cholesterol, triglycerides, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and lower serum concentrations of high-density lipoprotein cholesterol (HDL-C), and apolipoprotein.[20] Our data were consistent with these findings, revealing a higher total cholesterol level in smokers. Recently Mouhamed et al.[21] demonstrated that tobacco consumption was associated with alterations in the lipid profile, particularly low levels of HDL-C and increased triglycerides, which may explain the atherosclerosis risk.

It has been suggested that there may be a cigarette dose–response relationship between smoking and subclinical coronary atherosclerosis. Kim et al.[22] reported that current smoking with a substantial number of pack-years was a significant risk factor for mixed plaques.

Stallones et al.[23] showed that smokers have about twice as much CAD as non-smokers, whether measured by deaths, prevalence, or the incidence of new events. This excess risk in smokers compared with non-smokers tends to decrease with age: over 60 years of age there is probably no difference between the 2 groups, and with increasing age the differential dimin-

ishes. Interestingly, some trials have demonstrated the so-called "smokers paradox," a higher mortality in non-smokers than in smokers after acute myocardial infarction.[24] But Teo et al.[25] reported that the extent of risk is closely related to the number of cigarettes smoked, with even low levels of smoking associated with a considerable risk of myocardial infarction.

Our data emphasized some important aspects. First, dyslipidemia and family risk for CAD were more frequent in CTO patients who smoked. Second, the success and complication rates were comparable for smokers and non-smokers. Third, a statistical trend indicated that a longer lesion in CTO patients was associated with a smoking habit and a longer stent, though it did not reach the point of significance. Kastrati et al.[26] indicated that long lesions represented an independent risk factor for restenosis after bare metal stent placement, while newer data from Chang et al.[27] suggested that lesion length had no impact on short-term or long-term outcomes in the era of DES.

Ichiki et al.[28] provided evidence that platelet-derived nitrogen monoxide release was significantly impaired in long-term smokers, resulting in the augmentation of platelet aggregability, and Hioki et al.[29] added that smoking induced a prothrombotic state in smokers via increased platelet-dependent thrombogenesis. Matetzky et al.[30] suggested increased plaque tissue factor expression and thrombogenicity as a further mechanism for the increased risk of atherothrombotic events in smokers.

Lee et al.[31] demonstrated in a large cohort study that in patients with a revascularized CTO lesion, cigarette smoking was associated with fewer thrombotic events but with a greater incidence of target vessel revascularization. In contrast, we demonstrated a need for longer stents as a result of longer lesion length.

To the best of our knowledge, this is the first study to show this close relationship in CTO patients between lesion and stent length and a smoking habit.

Study limitations

Our study is a retrospective analysis and all of the data were collected from a single center. The results may have been influenced by selection criteria, operator experience, and varying techniques used by the operators. Furthermore, we have no data about the impact of the long term follow-up of AIP in CTO patients and data concerning kidney function were not collected. Another limitation may be that the matched and un-matched data used in this study were already collected. Thus, the analysis was based on an observational study.

Conclusions

Our retrospective study suggests that CTO patients who smoke suffer from longer lesions and need longer stents. Nevertheless, no significant association between smoking and acute outcome in patients undergoing CTO PCI was seen. PCI of CTO lesions in smokers is feasible and can be safely performed.

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Keywords: Chronic total occlusion; percutaneous coronary intervention; smoking habits.

Anahtar sözcükler: Kronik total oklüzyon, perkütan koroner girişim; sigara içme alışkanlıkları.