The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 3692-3698

Effect of Lesion Age on Short Term Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention

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ABSTRACT

Background: Chronic total occlusions (CTO) represent a continuously increasing lesion subset in contemporary angioplasty practice, which is observed in about 15% of patients undergoing coronary angiography with a higher prevalence in those with previous coronary artery bypass grafting (CABG).

Objective: To determine the impact of lesion age on procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI).

Patients and methods: Sixty six patients with CTO having significant angina or recent acceleration of previously chronic stable angina, admitted to National Heart Institute and Zagazig University Hospitals were included in this cohort study to determine the impact of lesion age on procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). According to the CTO age, our study population was subdivided into 3 groups: group 1 (CTO age of > than 3 to 12 months), group 2 (CTO age of 12 to 24 months) and group 3 (CTO age of >24 months). All patients were subjected to PCI for coronary chronic total occlusion.

Results: There was statistically significant relation between the studied groups regarding gender. Within the group with CTO from 3 to 12 months, 54.5% were females versus 22.7% and 18.2% within the groups of 12 to 24 and >24 months respectively. There was statistically significant relation between time for PCI and time of CTO. On doing Turkey HSD test, the difference was significant between 3 to 12 months and each other group (as in this group, time of PCI was significantly the lowest time). **Conclusion:** Success of CTO - PCI in the current era of new dedicated CTO equipment is unlikely to be affected by CTO lesion age.

Keywords: Chronic total occlusions, Lesion Age, Percutaneous Coronary Intervention.

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide[(1)]. CAD is mainly caused by atherosclerosis plaques that progressively enlarge and cause luminal obstructions, many atherosclerotic plays become vulnerable and are precursors of acute coronary syndromes[(2)].

A chronic total occlusion is defined as an atherosclerotic complete vessel occlusion with thrombolysis in myocardial infarction (TIMI) grade 0 flow within the occluded segment, and an estimated occlusion duration of ≥ 3 months. CTO are commonly encountered, occurring in approximately 20% of all patients referred for coronary angiography[(1)]. In patients who are undergoing cardiac catheterization and have a prior diagnosis of CAD, the frequency with which at least one CTO is encountered ranges from 30% to 50%[(3)].

CTO consists of an atherosclerotic plaque and a thrombotic component that can be homogeneous or made up of several layers of differently organized tissues as a result of multiple thrombotic episodes occurring at different times[(4)]. There is frequently a compelling indication to open a CTO (which is either for symptomatic and/or prognostic indication) [(5)].

Advances in guidewires, stents, and devices to cross chronically occluded arteries are evolving, so that more patients with chronic total occlusions (CTOs) are being successfully treated percutaneously[(6)].

Despite progress in techniques to open CTO's and corresponding imaging modalities, either invasive or non-invasive, there still is a paucity of information regarding effect of CTO age on the success rates of PCI and the short-term outcome of the procedure[(7)]. This study amid to determine the impact of lesion age on procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI).

PATIENTS AND METHODS

This prospective, cross sectional cohort study enrolled sixty six consecutive patients admitted to National Heart Institute and Ahmed Maher Teaching Hospitals with CTO having significant angina or recent acceleration of previously chronic stable angina. According to the CTO age, our study population was subdivided into 3 groups: group 1 (CTO age of > than 3 to 12 months), group 2 (CTO age of 12 to 24 months) and group 3 (CTO age of >24 months).

Inclusion criteria: Patients selection on the basis of the presence of symptoms, viability, and inducible ischemia (>10%) in the CTO artery territory, demonstrated by functional imaging tests. In presence of impaired left ventricular ejection fraction (LVEF), CTO revascularization was only considered for lesions subtending viable myocardial territory judged to be of hemodynamic importance, by LGE CMR. The decision of the revascularization strategy (PCI or CABG, and lesions to be revascularized) for each patient was left to the local heart team in the participating center. In case of surgical indication rejected by the patient, PCI was

Received: 24/03/2022
Accepted: 23/05/2022

proposed if considered to be feasible by the local heart team.

Exclusion criteria: Patient proved by initial angiography to be non-candidate for CTO re-canalization. Patient with scarred non-viable myocardium proved by viability testing modality (scar was defined as either a bright thinned out echo-reflective area of less than 6 mm thickness, which is akinetic or dyskinetic in the entire territory of CTO or an area of scar found by other viability studies in the territory of the CTO artery). Pregnancy. Significant valvular disease. Informed consent to participation in the study was not obtained. Uncontrolled hypertension. Hemodynamic instability.

All patients were investigated by history taking, clinical examination, 12-lead surface electrocardiogram (ECG) with special concern for ischemic manifestations in the form of Q waves, ST and T changes, routine pre-PCI labs were ordered shortly before procedure to rule out significant renal impairment or bleeding tendency, echocardiography was done using Philips machines, studies were done shortly before procedure and 3 months after procedure, angiography, angioplasty and CTO re-canalization. All patients were subjected to percutaneous coronary intervention (PCI) for coronary chronic total occlusion.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8. Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages and were compared by Chi square test (χ^2). Quantitative data were expressed as mean ± SD (Standard deviation) and range. Post Hoc tests: Tukey honestly significant difference (Tukey-HSD) test was used as a post hoc test to adjust for multiple comparisons after significant ANOVA test to indicate which significant difference between pairs of groups whereas Bonferroni post hoc test was used after significant Kruskal-Wallis test. P value < 0.05 was considered significant.

RESULTS

Table 1 showed that there was statistically ***non-significan****t* relation between the studied groups regarding age, presence of comorbid hypertension, dyslipidemia, ischemic heart disease, family history of IHD or smoking. There is statistically ***significant*** relation between the studied groups regarding gender and presence of comorbid diabetes.

Table (1): Comparison between the studied groups regarding demographic data

Parameter	CTO			P
	3- 12 months N=22	12 – 24 months N=22	>24 months N=22	
Age (year): Mean ± SD Range	 62.09 ± 8.3 47 – 77	 63.05 ± 6.5 53 – 74	 64.05 ± 6.48 53 – 74	0.664
Gender: Male Female	 10 (45.5%) 12 (54.5%)	 17 (77.3%) 5 (22.7%)	 18 (81.8%) 4 (18.2%)	0.01*
Risk factors				
Diabetes	20 (90.9%)	10 (50%)	13 (59.1%)	0.026*
Hypertension	16 (72.7%)	19 (86.4%)	17 (77.3%)	0.714
Dyslipidemia	13 (59.1%)	13 (59.1%)	14 (63.6%)	0.759
IHD	15 (68.2%)	20 (90.9%)	17 (77.3%)	0.464
Family history	12 (54.5%)	9 (40.9%)	9 (40.9%)	0.367
Smoking: No Smoker Ex-smoker	 13 (59.1%) 8 (36.4%) 1 (4.5%)	 10 (45.5%) 12 (54.5%) 0 (0%)	 11 (50%) 11 (50%) 0 (0%)	0.561

*: statistically significant

Table 2 showed that there was statistically ***non-significant*** relation between J-CTO Score and time of CTO. On comparing each two individual groups, the difference was ***significant*** between 3 to 12 months and >24 months.

Table (2): Comparison between the studied groups regarding J-CTO score

J-CTO score	CTO			P
	3- 12 month N=22	12 – 24 months N=22	>24 month N=22	
2 3 4 5	5 (22.7%) 10 (45.5%) 5 (22.7%) 2 (9.1%)	4 (18.2%) 5 (22.7%) 10 (45.5%) 3 (13.6%)	0 (0%) 5 (22.7%) 12 (54.5%) 5 (22.7%)	0.106
p	P_1 0.201	P_2 0.079	P_3 0.003*	

*: statistically significant
p1 the difference between group of 3 -12 months and from 12 to 24 months
p2 the difference between group of >24 months and from 12 to 24 months
p3 the difference between group of 3 -12 months and > 24 months

Table 3 showed that there was statistically ***non-significant*** relation between the studied groups regarding collaterals. There was statistically ***significant*** relation between grades and time of CTO. On comparing each two individual groups, the difference was significant between 12 to 24 months and each other group.

Table (3): Comparison between the studied groups regarding collaterals and rentrop collaterals classification

Parameter	CTO			P
	3- 12 months N=22	12 – 24 months N=22	>24 months N=22	
Collaterals Epicardial Septal	 4 (18.2%) 18 (81.8%)	 7 (31.8%) 15 (68.2%)	 8 (36.4%) 14 (63.6%)	0.383
Rentrop class **1** **2** **3**	 8 (36.4%) 11 (50%) 3 (13.6%)	 2 (9.1%) 8 (36.4%) 12 (54.5%)	 0 (0%) 5 (22.7%) 17(77.3%)	<0.001**
p	P_1 0.003*	P_2 0.069	P_3 <0.001**	

**: statistically highly significant
p1 the difference between group of 3 -12 months and from 12 to 24 months
p2 the difference between group of >24 months and from 12 to 24 months
p3 the difference between group of 3 -12 months and > 24 months

Table 4 showed that there was statistically ***significant*** relation between time for PCI and time of CTO. On doing Turkey HSD test, the difference was significant between 3 to 12 months and each other group (as in this group, time of PCI was significantly the lowest time). There was statistically ***significant*** difference between the studied groups regarding radiation dose. On doing pairwise comparison, the difference was ***significant*** between 3 to 12 months group and each other group (lowest dose was associated with recent CTO). There was statistically ***non-significant*** relation between contrast volume and time of CTO. All patients had successful outcome.

Table (4): Comparison between the studied groups regarding time of PCI, radiation dose, length of hospital stay and outcome

	CTO			P
	3- 12 month N=22	**12 – 24 months N=22**	**>24 month N=22**	
Time of PCI Mean ± SD Range (min)	 66.68 ± 25.13 30 – 140	 88.14 ± 28.98 45 – 150	 117.23 ± 56.21 52 – 243	<0.001**
Turkey HSD	P_1 0.174	P_2 0.044*	P_3 <0.001**	
Radiation dose Mean ± SD Median Range	 4.273 ±2.513 3.2 1.7 – 10.8	 7.455 ± 3.019 7.2 2.1 – 12.9	 8.405 ± 2.728 8.95 3.2 – 13.1	<0.001**
Pairwise	P_1 0.003*	P_2 <0.001**	P_3 0.944	
Contrast volume Mean ± SD Range (ml)	 249.09 ± 87.17 120 – 410	 258.18±101.07 100 – 450	 284.55 ± 101.5 120 – 490	0.456
length of hospital stay and outcome				
LOS (Days) Median Range	 0 0 – 3	 0 0 – 5	 0 0 – 3	0.319
Same day **1 – 3** **4 – 5**	16 (72.7%) 6 (27.3%) 0 (0%)	13 (59.1%) 7 (31.8%) 2 (9.1%)	13 (59.1%) 9 (40.9%) 0 (0%)	0.364
Outcome: Success	 22 (100%)	 22 (100%)	 22 (100%)	1

**: statistically highly significant   *: statistically significant
p1 the difference between group of 3 -12 months and from 12 to 24 months
p2 the difference between group of 3 -12 months and > 24 months
p3 the difference between group of >24 months and from 12 to 24 months

Table 5 showed that there is statistically ***non-significant*** relation between cost and age of CTO. It was non-significantly higher in the groups of CTO of 12 months and >24 months.

Table (5): Comparison between the studied groups regarding cost by CTO time

COST BY CTO AGE	**X (within normal PCI cost)**	2X	>2X	P
CTO Age >3m to 12m	4	16	21`	
CTO Age of 12m to 24m	2	14	6	0.164
CTO Age > 24m	0	12	10	

Table 6 showed that there was statistically ***non-significant*** relation between technique used and age of CTO. Regarding RDR and ADR technique, it was ***non-significantly*** higher in the groups of CTO of 12 months and >24 months.

Table (6): Comparison between the studied groups regarding CTO technique used by CTO time

CTO technique used	AWE	ADR	RWE	RDR	P
CTO Age >3m to 12m	16	1	4	1	
CTO Age of 12m to 24m	8	4	6	4	0.161
CTO Age > 24m	5	6	6	5	

AWE: antegrade wire escalation ADR: antegrade dissection re-entry
RWE: retrograde wire escalation RDR: retrograde dissection re-entry

Table 7 showed that there was statistically **significan**t relation between the studied groups regarding presence of immediate complications. No patients within 3 to 12 months had been complicated while 18.2% and 27.3% within 12 to 24 months and those >24 months had been complicated. There was statistically **non-significan**t relation between the studied groups regarding complications at 6 and 12 weeks as none of them had been complicated.

Table (7): Comparison between the studied groups regarding complications

	CTO			P
	3- 12 months	**12 – 24 months**	**>24 month**	
	N=22	**N=22**	**N=22**	
Immediate: No Yes	22 (100%) 0 (0%)	19 (86.4%) 3 (13.6%)	16 (72.7%) 6 (27.3%)	0.009*
6 weeks: no	22 (100%)	22 (100%)	22 (100%)	1
12 weeks: no	22 (100%)	22 (100%)	22 (100%)	1

*: statistically significant

DISCUSSION

In this study, there was statistically non-significant relation between the studied groups regarding age. But, there was statistically significant relation between the studied groups regarding gender. Within the group with CTO from 3 to 12 months, 54.5% were females versus 22.7% and 18.2% within the groups of 12 to 24 and >24 months respectively. **Danek** ***et al.***[5] determined the impact of lesion age on procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) in 394 patients. Mean age of the study patients was 66 ± 10 years, and 86% were men.

Regarding risk factors, there was statistically non-significant relation between the studied groups regarding presence of comorbid hypertension, dyslipidemia, ischemic heart disease (IHD), family history of IHD or smoking. But, there was statistically significant relation between the studied groups regarding presence of comorbid diabetes. Within the group with CTO from 3 to 12 months, 90.9% had diabetes versus 50% and 59.1% within the groups of 12 to 24 and >24 months respectively. **Danek** ***et al.*** [5] found high prevalence of hypertension (88%), hyperlipidemia (96%), and diabetes mellitus (43%).

Regarding J-CTO score, there was statistically non-significant relation between grades and time of CTO. On comparing each two individual groups, the difference was significant between 3 to 12 months and >24 months and each other group. **Danek** ***et al.*** [5] found that lesions of known age tended to be more complex, with greater incidence of proximal cap ambiguity and higher J-CTO score.

In our study, there was statistically non-significant relation between the studied groups regarding collaterals (septal collaterals were in 81.8%, 68.2% and 63.6% of those in groups with CTO 3 to 12 months, 12 to 24 months and >24 months respectively). **Danek** ***et al.*** [5] found that interventional collaterals were more common among lesions of known age (66% vs. 54%, p<0.001).

In this study, there was statistically significant relation between J-CTO scores and time of CTO. On comparing each two individual groups, the difference was significant between 12 to 24 months and each other group, looking specifically at the J-CTO score sheet criteria in our study, there was statistically ***non-significant*** relation between the studied groups regarding J-CTO score sheet criteria and time of CTO except for re-entry lesions, There was statistically ***significant*** difference between the studied groups regarding reentry CTO, which indicated that failure of CTO recanalization is more frequent CTO of more than 24 months.

Fu ***et al.***[8] concluded in their resent study that prior failed CTO lesions were associated with higher complexity of morphology; however, 81.1% of CTOs could be recanalized safely and effectively by experienced operators at repeat attempts. There was a definite relationship between lesion complexity and the increasing need for multiple approaches and technologies during CTO-PCI to achieve success, considering lesion complexity and prior failure, reattempted CTO-PCIs could still achieve an overall success rate of 81.1% by high-volume operators with acceptable complications.

Regarding time for PCI, there was statistically significant relation between time for PCI and time of CTO. On doing Turkey HSD test, the difference was significant between 3 to 12 months and each other group (as in this group, time of PCI was significantly the lowest time). **Danek *et al.***[5] compared 728 lesions of unknown duration with the 394 lesions of known age. Patients with known lesion age had higher incidence of prior PCI, prior CABG, prior MI, and prior failed CTO PCI as compared with those of unknown lesion age.

Regarding radiation dose, there was statistically significant difference between the studied groups regarding radiation dose. On doing pairwise comparison, the difference was significant between 3 to 12 months group and each other group (lowest dose was associated with recent CTO).

Regarding CTO revascularization cost there was statistically ***non-significant*** relation between cost and age of CTO. It was non-significantly higher in the groups of CTO of 12 months and >24 months.

In a recent publication by the OPEN-CTO investigators[9], in hospital costs were measured. The authors noted that the procedural costs were similar to the costs of multivessel or left main PCI in the SYNTAX trial (Synergy Between PCI With Taxus and Cardiac Surgery) and FREEDOM trial (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease), although the equipment requirements in this registry seem higher.

In our study, there was statistically ***non-significant*** relation between technique used and time of CTO. Regarding RDR and ADR technique, It was non-significantly higher in the groups of CTO of 12 months and >24 months.

Brilakis *et al.*[10] concluded that in general, each score is only applicable to the population from which it was derived and validated. Calculating ≥1 scores can promote detailed review of the angiogram and facilitate decision making. For example, medical therapy may be preferred over CTO-PCI in mildly symptomatic patients with highly complex occlusions. Complex CTOs (such as those with J-CTO score ≥2) are more likely to require dissection reentry and retrograde crossing techniques and should be performed by experienced operators.

Regarding contrast volume, there was statistically non-significant relation between contrast volume and time of CTO. It was non-significantly higher in the group of CTO>24 months. Also, **Danek *et al.***[5] found that contrast volume did not differ significantly among the groups.

Regarding outcome, all patients had successful outcome with no significant difference between the studied groups, that was consistent with the study published by **Han *et al.***[11] who reported that the overall success rate was 88.9%. **Barlis *et al.***[12] showed that indeterminate CTO age independently predicts CTO PCI failure (p=0.002). **Tomasello *et al.***[13] showed that CTOs of longer duration (>12 months) and indeterminate duration can be treated with no impact on procedural outcomes and one-year MACE. The presence of severe calcifications, longer CTO length, and small vessel diameter were independent predictors of technical failure, suggesting that revascularization of older CTOs can be safely and effectively attempted.

Regarding complications, there was statistically significant relation between the studied groups regarding presence of immediate complications. No patients within 3 to 12 months had been complicated while three patients within CTO from 12 to 24 months (13.6%) had immediate complications (one had CIN, one had hypotension with mild septal hematoma and the last one had perforation sealed with covered stent, pericardiocentesis and blood transfusion) and six patients within CTO > 24 months (27.3%) had immediate complications (one had hypotension, one had LCX, one had septal perforation, one had pulmonary edema, one had septal perforation sealed with ballon inflation and the last one had one had perforation sealed with cover stent). **Danek *et al.***[5] found no difference in the incidence of major adverse cardiac events for older vs. more recent occlusions. There were 8 cases of MACE in the lowest tertile of lesion age: 3 perforations, 4 MIs requiring re-PCI, and 1 ischemic stroke. The middle and highest lesion age tertiles had 4 cases of MACE each. MACE in the middle tertile comprised of perforation and ischemic stroke in 1 patient, 1 stent thrombosis requiring repeat PCI, and 2 myocardial infarctions, 1 of which was caused by donor artery damage. MACE in the highest tertile of lesion age was caused by 2 perforations causing tamponade and death, and 2 myocardial infarctions.

Prior studies have shown an association between lesion age and severity of calcification. A study of post-mortem CTO lesion morphology has shown age-related differences in occlusion histologic composition. **Srivatsa *et al.***[4] studied 96 CTOs from autopsies in 61 patients and found that cholesterol and foam cells were seen more frequently in younger lesions, while older lesions tended to have a greater fibrocalcific component. An IVUS study by **Suzuki *et al.*** [14] also demonstrated increasing calcification with increasing CTO age (correlation between arc of calcification and lesion age r=0.445, p<0.0001; correlation between length of calcification and lesion age r=0.397, p=0.001).

This study has some limitations. This study involved single team experience, multi-center studies are required to potentiate our findings. Lack of precise dating of lesion age is another potential limitation, although we only included cases with angiographic or solid clinical documentation of lesion age in our study. Determining the exact age of a CTO is very challenging, as serial coronary artery imaging is infrequently performed and even when it is performed the exact onset of the occlusion is often unclear. We relied on follow up echocardiography studies to assess evolution of systolic function and WMSI. More advanced imaging modalities would have been more accurate as CMR.

CONCLUSION

Success of CTO - PCI in the current era of new dedicated CTO equipment is unlikely to be affected by CTO lesion age.

RECOMMENDATIONS

Percutaneous coronary intervention (PCI) for coronary chronic total occlusion (CTO) should be performed for proved viable myocardium in the territory supplied by the occluded vessel. Proper evaluation of the clinical and angiographic data of the patient should be done to choose the proper plan for the intervention starting from the guiding catheter, the approach and the instruments that will be used. Larger multi-center studies, longer follow up, serial echocardiographic studies, use of CT angiography might modify patient selection and contrast amount.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

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