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Original Article

Long-term changes in ischemic burden after chronic total occlusion percutaneous coronary intervention: a retrospective observational study

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Abstract: Objective: There is uncertainty of the benefit of percutaneous coronary intervention (PCI) for chronic coronary total occlusion (CTO). The study aimed to investigate potential long-term changes in ischemic burden in patients with CTO after PCI. Methods: Patients who underwent CTO PCI with available records of ^{15}O-H_2O positron emission tomography within 3 months prior to and at least 6 months after successful CTO PCI were retrospectively included. Data on perfusion defect size, hyperemic myocardial blood flow (MBF), and coronary flow reserve (CFR) within the CTO area before and after CTO PCI were extracted and compared for evaluating ischemic burden. The comparisons were also performed after stratifying by baseline perfusion defect sizes. Results: A total of 74 eligible patients were included with an average age of 62.0±7.5 years. Significant decrease in perfusion defect size (3 (2-4) versus 1 (0-2) segments, P<0.001) and significant increase in hyperemic MBF (1.32±0.39 versus 2.27±0.52 mL/min/g, P<0.001) and CFR (1.72±0.47 versus 2.73±0.73, P<0.001) were observed after CTO PCI when compared to that at baseline. When stratifying by baseline perfusion defect size, no significant differences were observed between groups in changes of hyperemic MBF (P=0.301) and CFR (P=0.850), but patients with larger perfusion defect size exhibited greater reduction in perfusion defect size (P<0.001). Conclusions: CTO PCI relieved ischemic burden for at least 6 months, and patients with larger baseline perfusion defect size might benefit more from CTO PCI in terms of ischemic burden.

Keywords: Chronic coronary total occlusion, prognosis, percutaneous coronary, intervention, positron emission tomography

Introduction

Chronic coronary total occlusion (CTO) is defined as a 100 percent stenosis of a coronary artery with Thrombolysis in Myocardial Infarction (TIMI) 0 flow for more than three months based on angiography or symptoms [1]. It is often found in patients who underwent diagnostic coronary angiography, with a prevalence of about 25-33% [2-6]. CTO not only causes symptoms such as angina, but also lead to poor prognosis. Patients with CTO usually are older and have more comorbidities [2-4]. In addition, unrevascularized CTO was associated with higher mortality and major adverse cardiovascular events when compared to revascularized CTO [7, 8]. Percutaneous coronary intervention (PCI) is one of the interventions for revascularization when indicated, but the procedure is much more challenging compared to non-CTO PCI. The success rate of CTO PCI was reported to be about 50-70%, while it is about 95% for non-CTO PCI [9-11]. Although increased success rates have been reported in experienced centers in recent years with advance in the technique [12-15], there is uncertainty of the benefit of PCI for CTO patients. Evidence from limited studies supports the effect of CTO PCI on relief of ischemic burden and symptoms, and on improvement in myocardial perfusion [16-19]. Current guideline suggests CTO patients with a marked ischemic burden to receive PCI

[20]. A recent study indicated that at 3 months after CTO PCI, patients with a larger perfusion defect showed more reduction in defect size, and significant increase in hyperemic myocardial blood flow (MBF) and coronary flow reserve (CFR) within the CTO area irrespective of baseline defect size [21]. However, it remains unclear whether the observed benefits in reducing ischemic burden would exist after a longer follow-up. In this study, we aimed to investigate potential long-term (i.e., 6 months) changes in ischemic burden in patients with CTO after PCI.

Methods

Study design and study participants

The study retrospectively included patients who underwent CTO PCI between 2015/01/01 and 2020/12/31 with available records of ^{15}O-H_2O positron emission tomography within 3 months prior to and at least 6 months after successful CTO PCI. Detailed inclusion criteria: (1) patients who were diagnosed with CTO and received CTO PCI between 2015/01/01 and 2020/12/31 in our hospital (see below for detailed diagnosis criteria); (2) patients who performed examinations of ^{15}O-H_2O positron emission tomography within 3 months prior to and at least 6 months after CTO PCI. Exclusion criteria: (1) patients who received an unsuccessful CTO PCI, or received repeat revascularization after the CTO PCI; (2) patients without records of ^{15}O-H_2O positron emission tomography either within 3 months prior to or at least 6 months after CTO PCI; (3) patients who received coronary artery bypass grafting identified by patient files. The study was approved by the medical ethics committee of our hospital (No. 2021-03-B018), and informed consent was waived given the nature of a retrospective study design and use of anonymous data.

Diagnosis of CTO and successful revascularization

To identify patients with a diagnosis of CTO, medical records of invasive coronary angiography of the patients were screened, and CTO was defined as a total occlusion of the vessel on invasive coronary angiography with complete interruption of antegrade blood flow (TIMI grade 0) for an estimated time of at least 3 months [1]. Successful revascularization was defined as TIMI flow grade 3 and <30% diameter stenosis [17].

Evaluation of ischemic burden

Records of ^{15}O-H_2O positron emission tomography were reviewed to extract information about ischemic burden. The following variables in the CTO myocardial area were extracted: (1) Rest MBF, which was obtained from a dynamic emission scan at rest; (2) Hyperemic MBF, which was obtained from a dynamic emission scan during hyperaemia by administration of intravenous adenosine (140 μ/kg/min); (3) CFR, which was the ratio of hyperemic MBF to rest MBF; (4) Perfusion defect size, which was the number of myocardial segments that had a hyperemic MBF <2.3 mL/min/g and <75% compared to hyperemic MBF in a normal reference vascular territory. In addition, characteristics at baseline (before PCI CTO) including age, sex, smoking status, medical history about myocardial infarction and previous PCIs, and comorbidities were also collected.

Statistical analysis

Continuous data were presented as mean ± standard deviation or median (25th-75th percentiles) according to whether they were normally distributed, and categorical data were presented as number (frequency). Comparisons of continuous data between groups were analyzed by a paired sample t-test or one-way ANOVA, Wilcoxon signed-rank test, or Kruskal-Wallis test, which depended on distribution of the data. Comparisons of categorical data were analyzed by Chi-squared test or Fisher's exact test. A two-sided *P* value <0.05 was considered statistically significant. All the statistical analyses were performed using SPSS software (Version 23.0).

Results

Baseline characteristics of the study participants

A total of 74 eligible patients were included into the study (**Figure 1**). The average age of the study participants was 62.0±7.5 years, of which 86.49% were male. 62.16% of the patients were current smokers at baseline, 51.35% of them had prior myocardial infarction, and

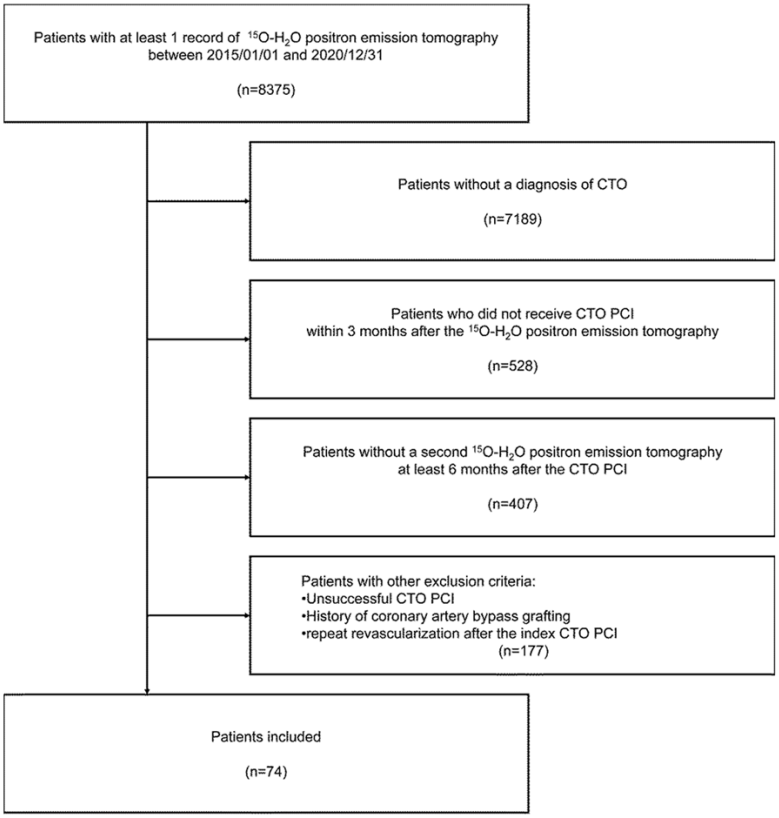

Figure 1. Inclusion of the study participants. CTO: Chronic coronary total occlusion; PCI: Percutaneous coronary intervention.

Table 1. Baseline clinical characteristics of the study participants [n (%)]

Baseline clinical characteristics	Overall patients (n=74)
Age (years old)	62.0±7.5
Sex	
Male	64 (86.49%)
Female	10 (13.51%)
Current smoking	46 (62.16%)
Medical history	
Prior myocardial infarction	38 (51.35%)
Prior myocardial infarction in CTO territory	20 (27.03%)
Prior percutaneous coronary intervention	55 (74.32%)
Prior percutaneous coronary intervention in CTO territory	11 (14.86%)
Comorbidity	
Hypertension	47 (63.51%)
Hypercholesterolemia	35 (47.30%)
Diabetes	16 (21.62%)

Abbreviation: CTO, chronic coronary total occlusion.

74.32% had received PCI before. Hypertension (63.51%) was the most frequent comorbidities, and about half of the patients had hypercholesterolemia (**Table 1**).

Changes in ischemic burden after CTO PCI

When compared with ischemic burden at baseline (**Table 2**), significant improvements in rest MBF (0.76± 0.17 versus 0.94±0.19 mL/min/g, P<0.001), hyperemic MBF (1.32±0.39 versus 2.27±0.52 mL/min/g, P< 0.001) and CFR (1.72±0.47 versus 2.73±0.73, P<0.001) were observed after CTO PCI, while perfusion defect size was significantly decreased (3 (2-4) versus 1 (0-2) segments, P<0.001).

Changes in ischemic burden after CTO PCI according to baseline perfusion defect size

When stratifying the patients by baseline perfusion defect size (i.e., limited (0-1 segments), moderate (2-3 segments), and large (≥4 segments)) (**Table 3**), there were no significant differences among groups in changes of rest MBF (0.10 (0.09-0.32), 0.09 (-0.01-0.31), and 0.22 (0.13-0.32) mL/min/g, P=0.053, **Figure 2**), hyperemic MBF (0.93 (0.85-1.26), 1.16 (0.70-1.62), and 0.83 (0.66-1.13) mL/min/g, P=0.301, **Figure 3**), and CFR (1.20 (1.10-1.59), 1.18 (0.20-1.85), and 1.12 (0.76-1.46), P=0.850, **Figure 4**), but patients with larger perfusion defect size exhibited greater reduction in perfusion defect size (1 (1-1), 1.5 (0-2), and 3 (3-4) segments, P<0.001, **Figure 5**).

Table 2. Changes in ischemic burden after chronic total occlusion percutaneous coronary intervention

Ischemic burden	At baseline	After PCI	Changes	*P*-value
Rest MBF (mL/min/g)	0.76±0.17	0.94±0.19	0.14 (0.04-0.31)	<0.001
Hyperemic MBF (mL/min/g)	1.32±0.39	2.27±0.52	0.97 (0.69-1.47)	<0.001
Coronary flow reserve	1.72±0.47	2.73±0.73	1.18 (0.28-1.77)	<0.001
Perfusion defect size (segments)	3 (2-4)	1 (0-2)	2 (0-3)	<0.001

Abbreviation: PCI, percutaneous coronary intervention.

Table 3. Changes in ischemic burden after chronic total occlusion percutaneous coronary intervention according to perfusion defect size at baseline

Ischemic burden	At baseline	After PCI	Changes	*P*-value
Limited perfusion defect size at baseline (n=3)				
Rest MBF (mL/min/g)	0.80±0.23	1.05±0.06	0.10 (0.09-0.32)	0.145
Hyperemic MBF (mL/min/g)	1.30±0.21	2.40±0.64	0.93 (0.85-1.26)	0.049
Coronary flow reserve	1.43±0.59	2.83±0.61	1.20 (1.10-1.59)	0.046
Perfusion defect size (segments)	1 (1-1)	0 (0-0)	1 (1-1)	0.025
Moderate perfusion defect size at baseline (n=48)				
Rest MBF (mL/min/g)	0.79±0.17	0.93±0.20	0.09 (-0.01-0.31)	<0.001
Hyperemic MBF (mL/min/g)	1.33±0.46	2.30±0.56	1.16 (0.70-1.62)	<0.001
Coronary flow reserve	1.83±0.47	2.77±0.80	1.18 (0.20-1.85)	<0.001
Perfusion defect size (segments)	3 (2-3)	1 (0-3)	1.5 (0-2)	<0.001
Large perfusion defect size at baseline (n=23)				
Rest MBF (mL/min/g)	0.69±0.14	0.94±0.16	0.22 (0.13-0.32)	<0.001
Hyperemic MBF (mL/min/g)	1.30±0.25	2.21±0.42	0.83 (0.66-1.13)	<0.001
Coronary flow reserve	1.51±0.37	2.64±0.58	1.12 (0.76-1.46)	<0.001
Perfusion defect size (segments)	5 (4-5.5)	1 (1-2)	3 (3-4)	<0.001

Abbreviation: PCI, percutaneous coronary intervention.

Discussion

In the study, we compared the changes in ischemic burden among CTO patients who had received PCI. The main findings are: (1) At least 6 months after successful CTO PCI, improved ischemic burden could be observed from the evaluation of hyperemic MBF, CFR, and perfusion defect size; (2) there were no significant differences in the changes of hyperemic MBF and CFR after CTO PCI among patients with different baseline perfusion defect size, but patients with larger perfusion defect size at baseline displayed a greater change in perfusion defect size after CTO PCI. Considering that evidence about the effects of CTO PCI remains limited, especially for patients with different levels of ischemic burden at baseline, and that CTO PCI now is mainly recommended for patients with a large perfusion defect at baseline, our study provides support for the benefit from CTO PCI in patients with limited or moderate perfusion defect size, although patients who had a larger baseline perfusion defect may benefit more from the procedure.

There is limited evidence of high quality that suggests CTO PCI can improve survival, and therefore the principal indication is to improve symptoms [22]. A recent study reported that the status of recanalization or revascularization for total occlusions was not associated with 10-year mortality risk [23], but a significant improvement in the health status was observed in CTO patients who received PCI [24]. Considering that reduction in ischemic burden may benefit the survival of CTO patients [18], investigations on changes in ischemic burden after CTO PCI are necessary to further identify indications for CTO PCI. A recent study investigated the changes in ischemic burden after CTO PCI, and found major reductions in ischemic burden after CTO PCI [21].

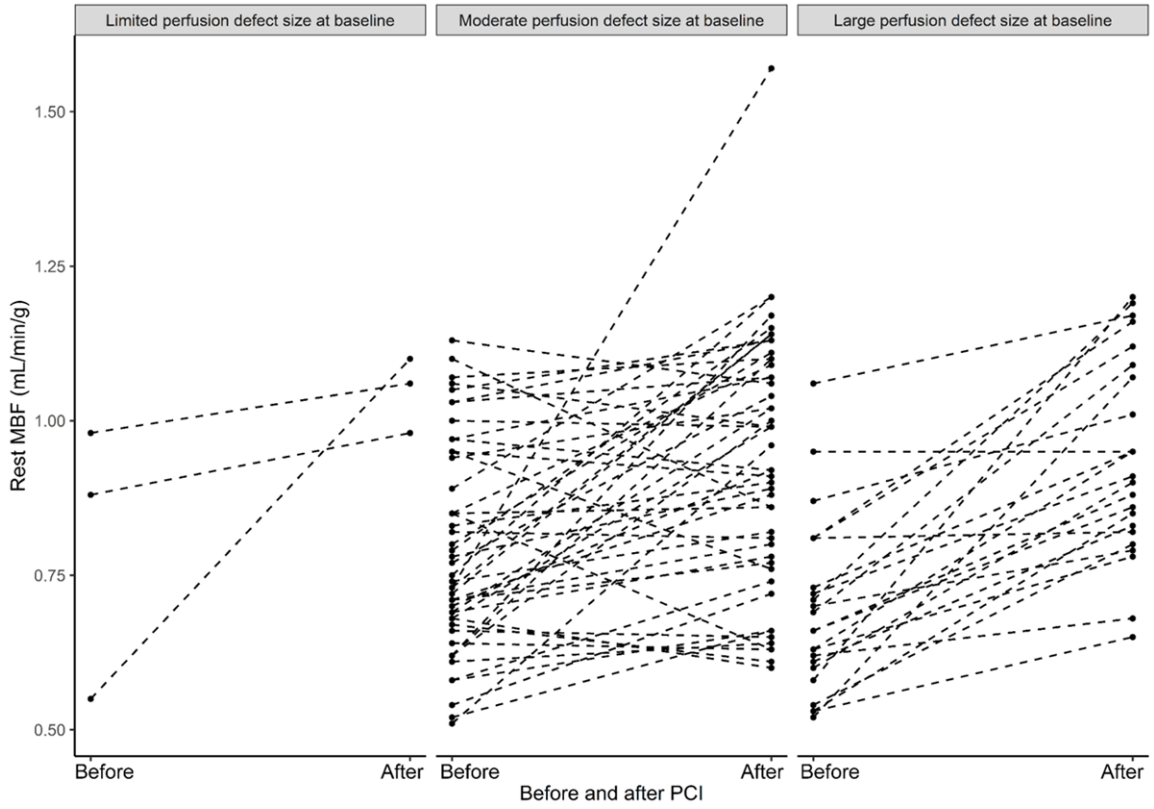

Figure 2. Changes in rest MBF after chronic total occlusion percutaneous coronary intervention. MBF: Myocardial blood flow; PCI: Percutaneous coronary intervention.

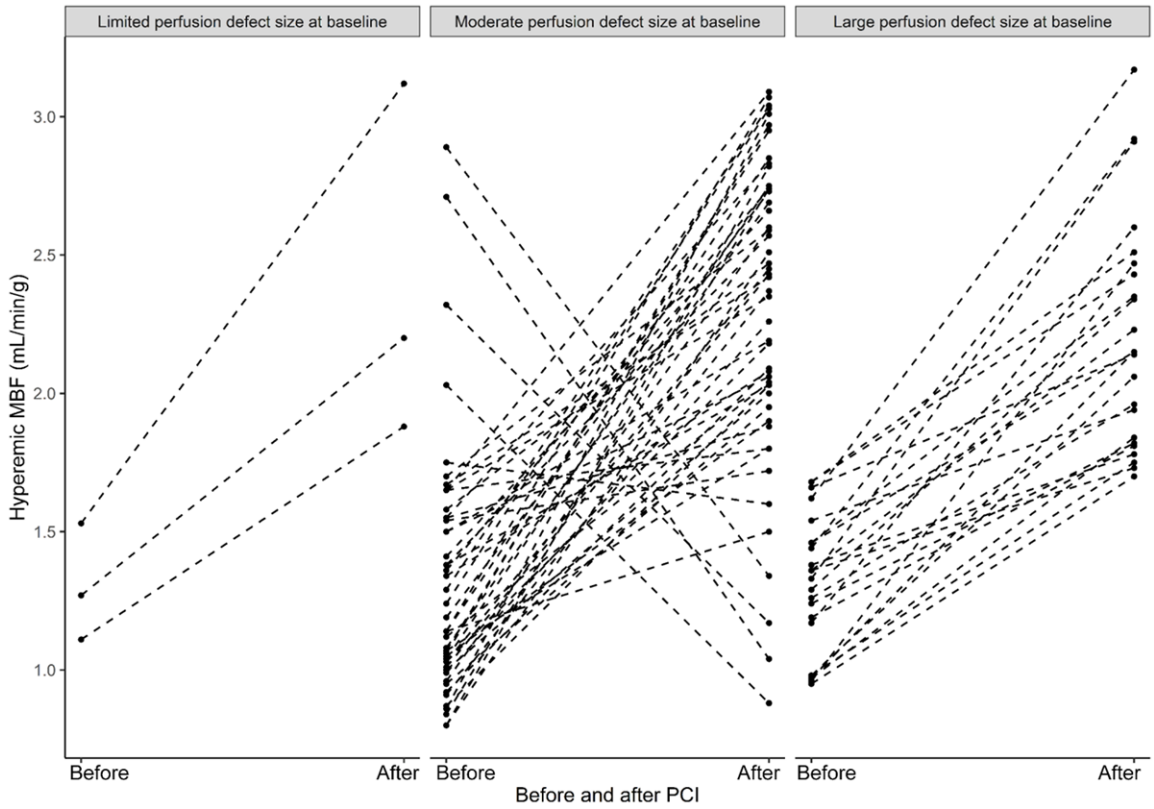

Figure 3. Changes in hyperemic MBF after chronic total occlusion percutaneous coronary intervention. MBF: Myocardial blood flow; PCI: Percutaneous coronary intervention.

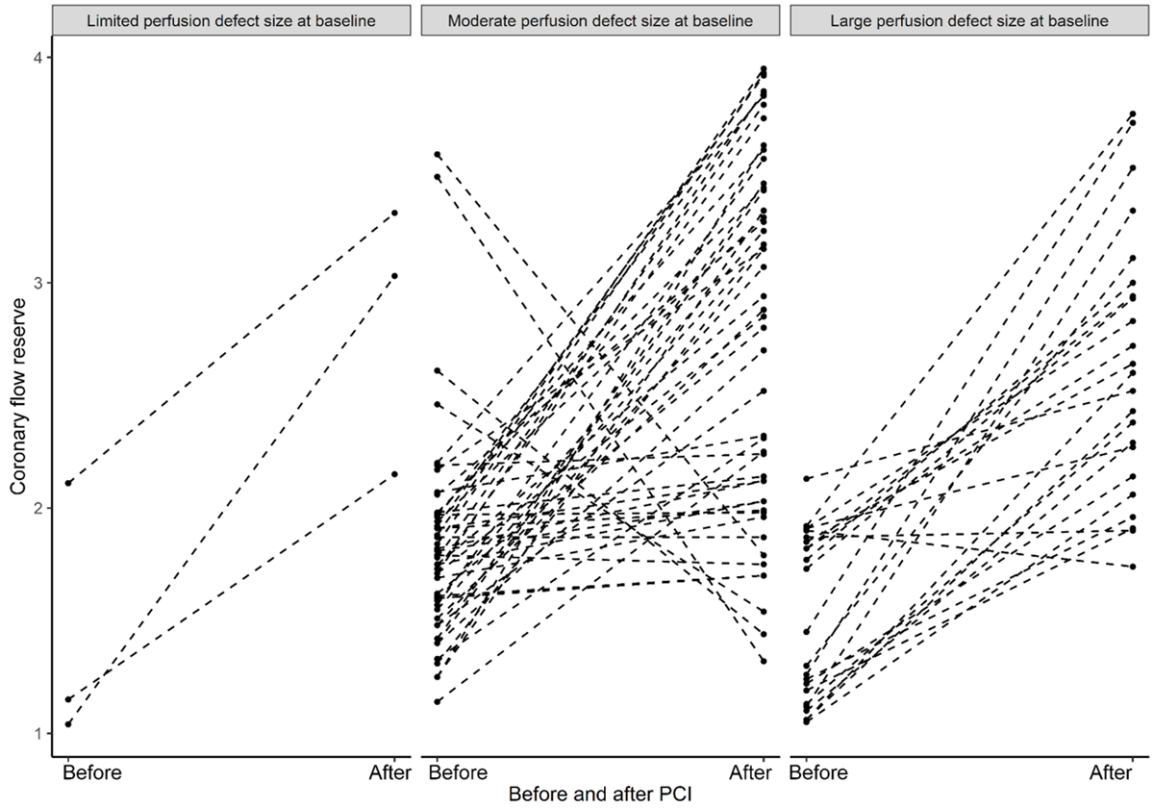

Figure 4. Changes in coronary flow reserve after chronic total occlusion percutaneous coronary intervention. PCI: Percutaneous coronary intervention.

Similar to our study, the study found that hyperemic MBF and CFR were both improved after CTO PCI irrespective of baseline perfusion defect size. A difference is that our study compared baseline ischemic burden with that at least 6 months after CTO PCI, while the study investigated changes in ischemic burden 3 months after CTO PCI. Compared to the absolute changes in hyperemic MBF and CFR between these two studies, our study observed higher absolute changes. This may be related to that the patients in our study had a 3-month longer follow-up, since myocardial perfusion would gradually increase after revascularization [25].

The study has some limitations that should be noticed. First, the study used a retrospective study design and therefore the identification of CTO patients and successful CTO PCI, and the evaluation of ischemic burden were all conducted in a retrospective way, which relied on review of recorded data without further validation. In addition, unlike a prospective design, indications and procedures of CTO PCI might differ between operators, which may have an impact on the outcomes of the procedure [26]. Second, since we only included patients who received successful CTO PCI, the study participants were highly selected. Given the relatively low success rate of CTO PCI [9-11], more researches are needed to evaluate the risk and benefit of CTO PCI especially in patients with limited or moderate perfusion defect size. Third, the study only included a limited sample size. Studies with larger sample sizes and improved methodology are warranted to confirm our findings.

In conclusion, CTO PCI can relief ischemic burden for at least 6 months, and patients with larger baseline perfusion defect size might ben-

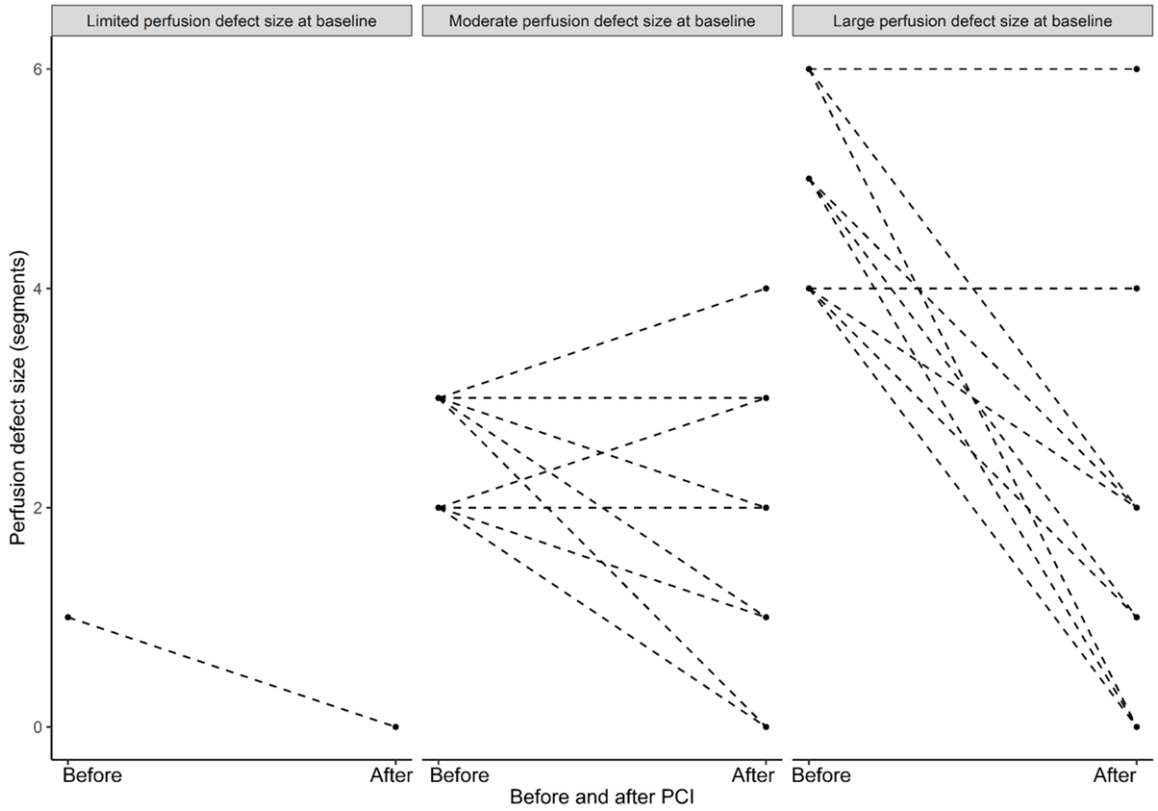

Figure 5. Changes in perfusion defect size after chronic total occlusion percutaneous coronary intervention. PCI: Percutaneous coronary intervention.

efit more from CTO PCI in terms of ischemic burden.

Disclosure of conflict of interest

None.

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