Early Improvement of Left Ventricular Dyssynchrony After Percutaneous Coronary Intervention in Patients with Single Chronic Total Occlusion Vessel

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Abstract

Background

The effect of percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) on left ventricular dyssynchrony was unclear.

Methods

Patients with one CTO vessel were included. Tissue Doppler imaging was used to assess the left ventricular dyssynchrony index (DI) in twelve segments before and after successful CTO PCI. Multiple regression was used to identify independent correlates of DI reduction.

Results

41 patients were included with the mean age of 65.88 years. 39(95.12%) had left ventricular DI more than 33. It decreased significantly from 67.48 ± 28.73 to 44.69 ± 23.90 (P < 0.01) after successful CTO PCI. PCI of infarct-relative CTO was associated with less percentage of DI reduction (Coefficient [Coef.], 25.60; 95% confidence interval [CI], 8.13–43.08; P < 0.01). Higher initial DI was associated with more percentage of DI reduction (Coef., -0.35; 95% CI, -0.67– -0.03; P = 0.03). Percentage of DI reduction was associated with ejection fraction (EF) improvement (Coef., -5.09; 95% CI, -7.45– -2.72; P < 0.01) with linear relationship (P < 0.01).

Conclusion

Left ventricular dyssynchrony was reduced early after successful CTO PCI, which predicted EF improvement. The association between dyssynchrony reduction and long-term benefits of CTO PCI are expected.

Background

Several studies and clinical trials have examined the effect of successful percutaneous coronary intervention (PCI) of coronary chronic total occlusion (CTO) on clinical outcomes. Some studies have suggested that successful CTO PCI is associated with improvement in survival[1, 2] and quality of life[3, 4]. However, this conclusion is not consistent.[5] Further, in the clinical trials of EXPLORE and REVASC, CTO PCI has not shown the benefits of improvement in left ventricular ejection fraction and segmental wall thickening in the CTO territory.[6, 7]

Left ventricular regional dyssynchrony with single-vessel non-CTO coronary artery disease had been reported by radionuclide angiography.[8] Revascularization by PCI or coronary artery surgery resulted in
recovery of coronary blood flow and thus might alleviate the dyssynchrony and improve the function of left ventricular.[9, 10]

This study aimed to investigate 1) the early impact of CTO PCI on improvement of left ventricular dyssynchrony; 2) the factors associated with dyssynchrony reduction post CTO PCI; 3) the association between dyssynchrony reduction and ejection fraction (EF) improvement.

**Methods**

**Patient selection and definition**

Patients who had one CTO vessel and attempted PCI at Beijing Anzhen Hospital between June 1st 2018 and October 30th 2019 were screened for inclusion in this study. CTO was defined as completely occluded coronary arteries without antegrade coronary flow and an estimated duration of at least 3 months.[11] Only CTO in major epicardial arteries were included in this study. One CTO vessel meant no significant coronary luminal stenosis (≥ 50% diameter stenosis) in the other two major epicardial vessels and branches (luminal diameters > 1.5 mm). Successful CTO PCI was defined as final residual stenosis < 20% by visual angiographic estimation, TIMI flow grade 3 after CTO recanalization and no significant side branch (luminal diameters > 1.5 mm) occlusion. PCI and stent implantation were performed in a standard manner. Drug-eluting stents were used in all of the PCI procedures. Modern CTO PCI techniques were used including antegrade, retrograde and hybrid approaches. Dual antiplatelet therapy was used with aspirin plus clopidogrel or ticagrelor. Infarct-relative CTO (IRA-CTO) was determined by history of myocardial infarction in the territory of the coronary artery.[12] Myocardial infarction had to be documented by pathologic Q waves in relevant leads of electrocardiography and/or clear wall motion abnormalities at echocardiography.

Patients who met the following criteria were excluded: 1) no symptomatic angina; 2) non sinus rhythm determined by 12-lead electrocardiography; 3) left or right bundle branch block; 4) left ventricular aneurysm determined by echocardiography; 5) moderate or severe pulmonary hypertension determined by echocardiography; 6) History of coronary artery bypass graft.

**Echocardiography**

All patients had echocardiography assessments before (< 7 days) and after (before discharge) index procedure. Standard echocardiography with Doppler studies was performed using a commercially available system (Vivid 5, Vingmed-General Electric, Holten, Norway). Left ventricular EF was calculated by using modified biplane Simpson rule. Tissue doppler imaging (TDI) data was stored digitally with at least three consecutive beats and analyzed off-line. The sampling volume was placed at the following segments (12 segments in total): left ventricular anterior, anteroseptal, inferoseptal, inferior, inferolateral and anterolateral segments at both basal and middle levels utilizing three apical views (apical four-chamber, apical two-chamber and apical long).[13] Both anterior and anteroseptal segments were
assigned to the territory of left anterior descending arteries (LAD). Both inferoseptal and inferior segments were assigned to the territory of right coronary arteries (RCA). Both inferolateral and anterolateral segments were assigned to the territory of left circumflex arteries (LCX). The interval from onset of R-wave to the maximum positive velocity during the ejection period was measured as time to peak systolic tissue velocity (Ts). For the assessment of systolic dyssynchrony index (DI), the standard deviation of Ts in all twelve segments was calculated. The percentage of DI reduction in each individual was calculated as follow: percentage of DI reduction (%) = (DI after CTO PCI - initial DI) / initial DI*100.

Intra- and inter-observer variability of echocardiography parameters raged from 4.8–9.4%.

Statistical Analysis

Continuous variables were expressed as mean (SD) and categorical variables as counts (percentages). Highly skewed continuous distributions were described by median (interquartile range). A student t test, rank sum test, or $\chi^2$ test was used as appropriate. Multiple regression was used to identify independent correlates of DI reduction. Baseline variables were included as predictor factors in the analysis. Simple linear regression was used to identify the linear relationship between percentage of DI reduction and initial DI / EF improvement.

All statistical analyses were based on 2-tailed tests. P < .05 was considered statistically significant. Statistical analyses were performed with Stata version 14.0 (StataCorp).

Results

Baseline Characteristics

A total of 48 patients with one CTO vessel were screened. 3(5.77%) patients had failure procedures. 2(3.85%) patients had TIMI flow grade < 3 and 2(3.85%) had side branch (luminal diameters > 1.5 mm) occlusion after CTO recanalization. Finally, a total of 41 patients were included in this study (Table 1). The mean (SD) age was 65.88 (8.30) years and 73.17% were men. The target CTO vessels included 16 (39.02%) LAD, 8 (19.51%) LCX and 17 (41.46%) RCA. Of these, 11 (26.83%) were IRA-CTO. The initial EF was 55.34 ± 6.97%.
| Table 1 | Baseline characteristics |
|---------|--------------------------|
| **Age (year)** | **65.88 ± 8.30** |
| Male sex, No. (%) | 30 (73.17%) |
| Hypertension, No. (%) | 28 (68.29%) |
| Diabetes, No. (%) | 18 (43.9%) |
| eGFR (ml/min/1.73 m$^2$) | 72.14 ± 20.61 |
| BNP (pg/ml) | 85.46 ± 29.92 |
| IRA-CTO, No. (%) | 11 (26.83) |
| CCS Angina Classification, No. (%) |  |
| I | 4 (9.76%) |
| II | 17 (41.46%) |
| III | 14 (34.15%) |
| IV | 6 (14.63%) |
| CTO Vessel, No. (%) |  |
| LAD | 16 (39.02%) |
| LCX | 8 (19.51%) |
| RCA | 17 (41.46%) |
| Collateral flow grade, No. (%) |  |
| Rentrop 0 | 2 (4.88%) |
| Rentrop 1 | 8 (19.51%) |
| Rentrop 2 | 13 (31.71%) |
| Rentrop 3 | 18 (43.90%) |
| Initial EF (%) | 55.34 ± 6.97 |
| Initial LVEDD (mm) | 47.26 ± 4.16 |
| Initial LVESD (mm) | 30.44 ± 4.09 |
| Initial DI | 67.48 ± 28.73 |

Abbreviations: eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; IRA-CTO, infarct-related chronic total occlusion artery; CCS, Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; DI, dyssynchrony index.
Reduction Of Dyssynchrony

Average Ts of each four segments assigned to the territory of LAD, RCA or LCX where CTO located was calculated and compared before and after CTO PCI (Table 2). After CTO PCI, Ts was increased significantly compared to the initial Ts. Further, the left ventricular DI was reduced significantly after PCI regardless of the location of CTO vessel (Table 2). Of all 41 patients, 39(95.12%) had left ventricular DI more than 33. It decreased significantly from 67.48 ± 28.73 to 44.69 ± 23.90 (P < 0.01) after successful CTO PCI (Fig. 1).

|              | Ts (ms) | DI     |
|--------------|---------|--------|
|              | Before PCI | After PCI | P value | Before PCI | After PCI | P value |
| LAD (N = 16) | 218.08 ± 61.45 | 142.75 ± 20.35 | < 0.01 | 61.02 ± 29.19 | 36.35 ± 15.69 | < 0.01 |
| LCX (N = 8)  | 209.72 ± 72.37 | 150.88 ± 33.91 | 0.04 | 60.06 ± 21.95 | 37.97 ± 13.74 | 0.04 |
| RCA (N = 17) | 238.40 ± 69.76 | 184.22 ± 63.57 | < 0.01 | 77.04 ± 29.80 | 55.70 ± 29.89 | < 0.01 |

Correlates Of Dyssynchrony Reduction

For all patients, percentage of DI reduction was − 40.91 ± 25.36%. 19(46.34%) patients fully recovered the DI to less than 33 after CTO PCI. PCI of IRA-CTO was associated with less percentage of DI reduction (Coefficient [Coeff.], 25.60; 95% confidence interval [CI], 8.13–43.08; P < 0.01) (Table 3, Fig. 2). Higher initial DI was associated with more percentage of DI reduction (Coeff., -0.35; 95% CI, -0.67-- -0.03; P = 0.03) (Table 3). There was a statistically significant linear relationship between initial DI and percentage of DI reduction (P < 0.01) (Fig. 3). However, collateral flow grade assessed by rentrop classification was not associated with percentage of DI reduction (Fig. 4).
**Table 3**
Baseline Factors Correlated with dyssynchrony index reduction

|                | Coefficient | 95% CI       | P value |
|----------------|-------------|--------------|---------|
| Age            | 0.12        | -1.05–1.28   | 0.84    |
| Male sex       | -10.58      | -29.17 8.01 | 0.25    |
| Hypertension   | -3.92       | -22.40–14.55 | 0.67    |
| Diabetes       | 4.66        | -14.30–23.62 | 0.62    |
| eGFR           | -0.24       | -0.65–0.17   | 0.23    |
| BNP            | 0.16        | -0.12–0.45   | 0.25    |
| IRA-CTO        | 25.60       | 8.13–43.08   | < 0.01  |
| **CTO Vessel** |             |              |         |
| LAD            | Reference   |              |         |
| LCX            | -3.42       | -24.64–17.79 | 0.74    |
| RCA            | 13.12       | -7.22–33.47  | 0.20    |
| **Collateral flow grade** |     |              |         |
| Rentrop 0/1    | Reference   |              |         |
| Rentrop 2      | 2.47        | -18.17–23.10 | 0.81    |
| Rentrop 3      | 0.79        | -20.79–22.37 | 0.94    |
| Initial EF     | -0.88       | -2.42–0.65   | 0.25    |
| Initial LVEDD  | 0.14        | -2.44–2.72   | 0.91    |
| Initial LVESD  | -1.25       | -3.53–1.03   | 0.27    |
| Initial DI     | -0.35       | -0.67–0.03   | 0.03    |

Abbreviations: eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; IRA-CTO, infarct-related chronic total occlusion artery; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; DI, dyssynchrony index.

**Improvement Of EF**

EF post CTO PCI was improved significantly in comparison with initial EF (55.34 ± 6.97 vs 56.41 ± 7.01, P = 0.02). Percentage of DI reduction was associated with EF improvement significantly (Coef., -5.09; 95% CI, -7.45–-2.72; P < 0.01) with linear relationship (Fig. 5). The time of EF reassessment was 2.37 ± 0.86 days after CTO PCI.
**Discussion**

In the present study of patients with single CTO vessel, we found that 1) About 95% patients had left ventricular dyssynchrony detected by TDI; 2) Left ventricular DI was improved early after CTO PCI, which correlated to IRA-CTO and initial DI; 3) The percentage of DI reduction was associated with EF improvement.

Left ventricular dyssynchrony has been recognized as an independent risk factor for ventricular arrhythmias[14–16] and all-cause mortality[17–19] in patients with myocardial infarction and/or heart failure. In this study of patients with single CTO vessel, we demonstrated about 95% had left ventricular dyssynchrony. However, the relationship between left ventricular dyssynchrony and higher risk of ventricular tachycardial/ventricular fibrillation and mortality in patients with CTO[20] was still unclear.

The extent of dyssynchrony was reduced significantly early after successful CTO PCI in our study. This was similar to previous report which demonstrated the reduction of the tree-dimensional systolic dyssynchrony index one month after CTO PCI[21]. Patients with IRA-CTO had less DI reduction may indicate the clinical significance of viable myocardial in cardiac intervention. The benefit of CTO PCI may be underestimated by the inclusion of patients with less amount of viable myocardium in patients with history of myocardial infarction. Interestingly, collateral circulation did not predict the percentage of reduction of left ventricular DI. This may be due to the presence of collateral circulation was a sensitive (89%) but not a specific (31%) sign of myocardial viability.[22]

Our study has some limitations. First, it was an observational study with small patient sample. Especially, it may affect the analysis of correlation between location of CTO vessel and reduction of DI. Second, the echocardiography assessment at initial or post CTO PCI was not fully blind to the technicians. Third, the long-term follow-up data beyond the hospital stay was missing.

**Conclusion**

The present study showed that left ventricular dyssynchrony was reduced early after successful CTO PCI, which predicted EF improvement. The association between dyssynchrony reduction and long-term benefits of CTO PCI need to be further investigated.

**Abbreviations**

CTO
Chronic Total Occlusion
Coef.
Coefficient
CI
Confidence interval
DI
Dyssynchrony index
EF
Ejection Fraction
IRA
Infarct-relative artery
LAD
Left anterior descending arteries
LCX
Left circumflex arteries
PCI
Percutaneous coronary intervention
RCA
Right coronary arteries
TDI
Tissue Doppler imaging
Ts
Peak systolic tissue velocity

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethics committee at Beijing Anzhen Hospital, and all of the patients provided written informed consent.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: This study was conceived and designed by Shaoping Wang, Shiyiing Li and Jinghua Liu. Shaoping Wang, Yijia Li, Yejing Zhao, Tong Liu, Shujuan Cheng, Hongyu Peng, Zheng Wu, Donghui Zhao, Bin Zheng, and Wei Dong were responsible for collection of data or analysis. Shaoping Wang and Shiyiing Li drafted the manuscript. Jinghua Liu checked it and revised critically. All authors read and approved the final manuscript.

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Figures

Figure 1

The comparison of left ventricular dyssynchrony index between before and after successful CTO PCI.
Figure 2

The comparison of dyssynchrony index reduction between PCI of infarct-relative CTO and non-infarct-relative CTO.
Figure 3

The linear relationship between dyssynchrony index reduction and initial dyssynchrony index.
Figure 4

The comparison of dyssynchrony index reduction in patients with different collateral flow Rentrop grade classifications.
Figure 5

The linear relationship between dyssynchrony index reduction and ejection fraction (EF) improvement.