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ORIGINAL ARTICLE

Influence of collaterals on the left ventricular end-diastolic pressure and serum NT-proBNP levels in patients with coronary chronic total occlusion☆

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KEYWORDS

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Abstract *Objective:* Although numerous studies have shown the protective effects of the well-developed coronary collaterals on left ventricular functions, the relationship between collateral grade and left ventricular end diastolic pressure has not been studied in chronic total occlusion patients. Also, there are conflicting data on the effect of collaterals on NT-proBNP levels. The aim of our study was to evaluate the relationship between coronary collateral circulation and left ventricular end diastolic pressure and NT-proBNP levels in chronic total occlusion patients.
Methods: Study group was retrospectively selected from the patients who had undergone coronary angiography at our hospital between June 2011 and March 2013. Clinical, biochemical, angiographic and hemodynamic data of 199 consecutive patients having at least one totally occluded major epicardial coronary artery were evaluated. Coronary collateral circulation was graded according to Rentrop classification. While Rentrop grade 3 was defined as well-developed, all the remaining collateral grades were regarded as poor collaterals.
Results: Overall 87 patients were found to have good collaterals and 112 patients had poor collaterals. There was no significant difference between the patients with well- or poorly developed coronary collaterals with regard to left ventricular end diastolic pressure (16.84 ± 5.40 mmHg vs 16.10 ± 6.09, respectively, $p = 0{,}632$) and logNT-proBNP (2.46 ± 0.58 vs 2.59 ± 0.76, respectively, $p = 0{,}335$).

Abbreviations: CC, coronary collaterals; CCC, coronary collateral circulation; CTO, chronic total occlusion; Cx, circumflex artery; DM, diabetes mellitus; EDTA, ethylenediaminetetraacetic acid; HT, hypertension; LAD, left anterior descending artery; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; RCA, right coronary artery

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Conclusion: In patients with coronary chronic total occlusion even well-developed coronary collaterals are not capable of protecting the rise of left ventricular end diastolic pressure and NT-proBNP levels which are reliable markers of the left ventricular dysfunction.

1. Introduction

Coronary chronic total occlusion (CTO) is characterized by heavy atherosclerotic plaque burden within the artery, resulting in complete (or nearly complete) occlusion of the vessel for at least 3 months.[1] It is estimated that about 1/3 of patients undergoing coronary angiography have at least one CTO of the major epicardial arteries.[2] Different degrees of collateral vascularization are observed in almost all of these lesions. Well-developed collaterals have been shown to be capable to reduce myocardial ischemia and myocardial fibrosis and to preserve myocardial viability.[3,4] It was suggested that coronary collaterals are important in preserving left ventricular systolic and diastolic performance at least at rest.[5]

Numerous investigations have shown that well-developed coronary collaterals (CC) exert protective effect on left ventricular functions. Left ventricular end-diastolic pressure (LVEDP) is an important parameter of the left ventricular performance and can be used to identify patients at increased risk for heart failure. In addition, elevated LVEDP is an independent predictor of mortality in patients undergoing cardiac surgery.[6] In patients with normal left ventricular systolic function, well-developed coronary collaterals have been shown to exert a protective effect on LVEDP levels.[5] But, relationship between collateral grade and left ventricular end diastolic pressure has not been studied in chronic total occlusion patients.

N-terminal pro brain natriuretic peptide (NT-proBNP) – is a prohormone produced mainly from ventricular myocytes which has important diagnostic and prognostic utility in coronary heart disease and left ventricular dysfunction.[7] There are conflicting data regarding effect of collaterals on natriuretic peptide levels.[8–10]

In this study, we aimed to investigate the relationship between coronary collaterals and two important markers of the left ventricular functions – LVEDP, and NT-proBNP levels in patients with coronary CTOs which has not been studied previously.

2. Methods

2.1. Study population

Patients who had undergone coronary angiography at our center between June 2011 and March 2013 were evaluated. Only patients with a totally occluded major coronary artery and available clinical, hemodynamic and laboratory data were included.

Demographic, clinical and laboratory data were obtained from the patients' medical records. Diabetes mellitus (DM) was defined as a history of DM, the use of antidiabetic drugs, fasting plasma glucose levels of $\geqslant 7$ mmol/L or Hemoglobin A1C levels of $\geqslant 6.5\%$. Hypertension (HT) was defined as a history of HT or use of antihypertensive drugs, or a blood pressure $\geqslant 140/90$ mmHg. Smoking status was defined as current or former smoking.

Exclusion criteria were as follows:

- Acute coronary syndrome within the last 3 months,
- acute decompensated heart failure,
- history of coronary artery bypass surgery,
- severe aortic or mitral valvular disease,
- acute or chronic renal failure,
- technically inadequate coronary angiography.

The study protocol was approved by the local ethics committee.

2.2. Cardiac catheterization, coronary angiography and coronary collateral scoring

Coronary angiography was performed through the femoral artery for all patients using the Judkins technique. Each angiogram was interpreted by two experienced cardiologists who were blinded to the clinical details and results of the other investigations of the patients.

Collaterals were graded from 0 to 3 according to the Rentrop scoring system: 0 – no filling of any collateral vessel; 1 – filling of the side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment; 2 – partial filling of the distal epicardial segment by collateral vessels; and 3 – complete filling of the distal epicardial segment by collateral vessels.[11] If there were multiple collaterals to the occluded vessel, the collateral with the highest Rentrop grade was used for analysis. If more than one CTO were present, the vessel that had the collateral with the highest Rentrop grade was analyzed. The study population was divided into two groups according to the Rentrop collateral grade: patients with grade 0–2 collateral development were classified as the poorly developed collateral group, and patients with Rentrop grade 3 collateral development were classified as the well-developed collateral group.

Invasive measurement of LVEDP was obtained with a 5 or 6 French fluid-filled pigtail catheter. The fluid-filled pressure was balanced and calibrated with the external pressure transducer positioned at the mid axillary level. End diastole was identified by R-wave peaks on ECG and LVEDP was obtained as an average value from 5 consecutive beats.

2.3. Blood samples and laboratory assay

Blood samples were collected in EDTA tubes and NT-proBNP concentration was analyzed with a chemiluminescence enzyme-linked immunosorbent assay (Roche Diagnostics) on a 2010 analyzer. The physicians involved in the study were unaware of the values obtained for NT-proBNP concentration.

2.4. Statistical analysis

All analyses were performed using SPSS version 15.0 (IBM Corporation, USA) for Windows (Microsoft Corporation, USA). Continuous variables are presented as mean ± SD and categorical variables are presented as percentages. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of variables was normal. For continuous variables the independent samples *t* test (parametric distribution) and "Mann-Whitney *U*" test (nonparametric distribution) were used and for categorical variables, the χ^2 test was used. Analysis of variance (ANOVA) was applied for multiple comparisons and the Bonferroni test was used for post hoc analysis. Correlation analysis was performed using Pearson's model. $p < 0.05$ was considered to be statistically significant.

3. Results

Among the patients who had undergone coronary angiography and cardiac catheterization between June 2011 and March 2013, we could identify 310 patients with CTO and available hemodynamic data. After applying exclusion criteria (40 patients with recent acute coronary syndrome, 10 patients with acute decompensated heart failure, 13 patients with severe valvular disease, 6 patients with renal failure and 42 patients without available NT-proBNP levels), data of total number of 199 patients were analyzed.

The prevalence of various demographic, clinical, angiographic and echocardiographic characteristics of the patients is summarized in Table 1. Baseline characteristics were not significantly different.

None of the patients had Rentrop grade 0. Sixteen patients (8%) had Rentrop grade 1, and 97 patients (49%) had Rentrop grade 2. All of the remaining 86 patients had Rentrop grade 3 collaterals. Unlike previous similar studies used to define well-developed collaterals as Rentrop grade 2 and 3, we included to well-developed collateral group only patients with Rentrop grade 3. So, well-developed collateral group consisted of 86 patients, and poorly developed collateral group consisted of 113 patients.

The location of CTO was in 54.8% of cases right coronary artery (RCA), in 31.2% left anterior descending (LAD), and in 15.1% left circumflex (Cx). Fig. 1 shows distribution of occluded arteries among groups. Poorly developed coronary collaterals were more frequently observed in patients with LAD and Cx occlusions.

Mean LVEDP level was 16.84 ± 5.40 mmHg and 16.10 ± 6.09 mmHg in patients with well- and poorly developed collaterals respectively and there was no significant difference among the groups with regard to LVEDP levels ($p = 0.632$) (Fig. 2). Comparison of LVEDP levels between Rentrop grades revealed statistically significant difference only between grades 1 and 2 ($F = 4.813$, $p = 0.012$, Bonferroni's post hoc $p = 0.019$). Subgroup analyses did not reveal any influence of the number of vessels diseased on LVEDP levels (ANOVA $p = 0.155$). Also CTO location did not influence neither LVEDP levels, nor LVEDP-collateral status relationship (ANOVA $p = 0.661$). We did not find statistically significant correlation between Rentrop grades and LVEDP levels ($p = 0.788$, $r = -0.037$).

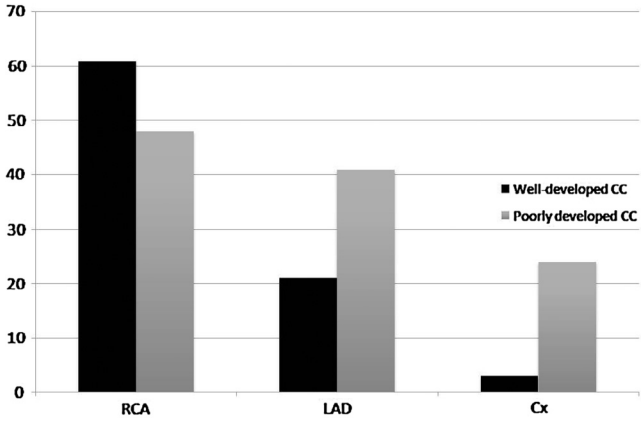

Figure 1 Bar chart showing the number of cases with RCA (right coronary artery), LAD (left anterior descending artery) and Cx (circumflex artery) chronic total occlusions with well-developed collaterals (black) and poorly developed collaterals (gray).

Table 1 Baseline characteristics of the study population.

Variables	Well-developed CC	Poorly developed CC	*p* value
Age (years)	62.6 ± 9.9	62.1 ± 9.6	0.709
Gender, male (*n*, %)	74 (85.1)	90 (80.4)	0.390
Diabetes mellitus (*n*, %)	27 (31)	40 (35.7)	0.491
Hypertension (*n*, %)	61 (70.1)	80 (71.4)	0.841
Smoking (*n*, %)	66 (75.9)	80 (71.4)	0.485
Statin use (*n*, %)	14 (16.1)	28 (25)	0.128
Number of diseased vessels. mean	2.0 ± 0.8	2.0 ± 0.8	0.595
LVEF, %	56.0 ± 10.3	54.8 ± 12.1	0.162
Hemoglobin, g/dL	13.56 ± 1.42	13.49 ± 1.86	0.756
Baseline creatinine, mg/dL	0.95 ± 0.28	1.04 ± 0.38	0.089
Total cholesterol, mg/dL	212.18 ± 53.14	205.73 ± 56.63	0.449
LDL cholesterol, mg/dL	130.15 ± 53.14	125.86 ± 48.64	0.563
HDL cholesterol, mg/dL	43.47 ± 14.46	41.17 ± 11.26	0.244
Triglyceride, mg/dL	196.90 ± 158.38	205.11 ± 157.40	0.737
Hs-CRP, mg/dL	10.33 ± 13.87	8.98 ± 10.53	0.560

Data are shown as the mean value ± SD or number and percentage of patients. CC: coronary collaterals, HDL: high density lipoprotein, Hs-CRP: high sensitive C-reactive protein, LVEF: left ventricular ejection fraction, LDL: low density lipoprotein, SD: standard deviation.

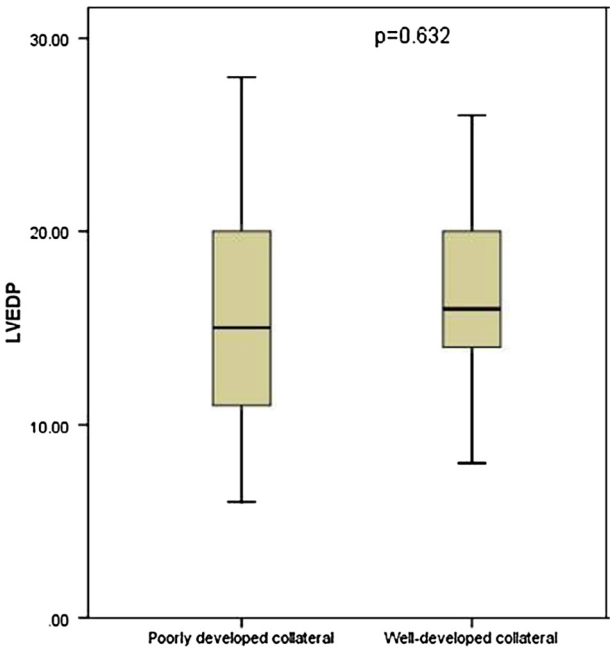

Figure 2 Comparison of LVEDP (left ventricular end-diastolic pressure) levels of the study groups.

Because NT-proBNP was not normally distributed, values were log-transformed to produce a normal distribution for statistical analysis. Mean of log-transformed NT-proBNP was 2.46 ± 0.58 and 2.59 ± 0.76 in patients with well- and poorly developed collaterals respectively and these levels were not statistically different ($p = 0.335$) (Fig. 3). Comparison of log NT-proBNP between Rentrop grades revealed no statistically significant difference (ANOVA $p = 0.202$). Subgroup analysis according to the number of vessels diseased showed that log NT-proBNP was statistically different between Rentrop 1 and 3 grade (ANOVA $p = 0.018$, Bonferroni's post hoc $p = 0.014$). CTO location did not affect neither log NT-proBNP, nor log NT-proBNP-collateral status relationship (ANOVA $p = 0.661$). We did not find statistically significant correlation between Rentrop grades and log NT-proBNP ($p = 0.160$, $r = -0.144$).

Only number of diseased vessels and hemoglobin level (negatively) were correlated with log NT-proBNP levels (Table 2) on univariate analysis. However, linear regression analysis revealed that none of these parameters were independently associated with log NT-proBNP levels. The statistical analyses showed a trend toward significance in the correlation of LVEDP levels and log NT-proBNP ($p = 0.08$, $r = 0.305$).

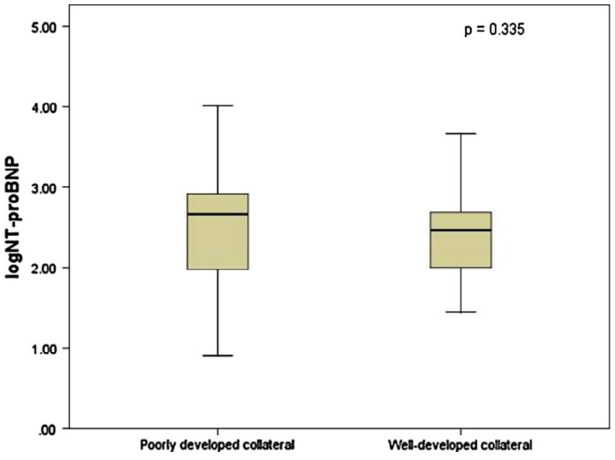

Figure 3 Comparison of log NT-proBNP in poorly developed collateral group vs well-developed collateral group.

4. Discussion

In this study we investigated relationship between the collateral circulation status and LVEDP and NT-proBNP levels in the patients with coronary CTO. As the presence of a CTO constitutes optimal conditions for the collateral development, we decided to investigate effects of the coronary collaterals on the left ventricular parameters in the patients with CTO.

We could not find a significant relationship between the CC grade and LVEDP levels. To our knowledge, this study is the first to investigate the relationship between the CC grade and LVEDP levels in the patients with coronary CTO. However, our results are compatible with results obtained from the studies investigating this issue in the patients without CTO (mainly, patients with acute coronary occlusion). In patients with previous Q wave myocardial infarction, there was no significant difference between groups with well- and poor-developed coronary collaterals with regard to having LVEDP more than 12 mmHg.[3] Ilia et al., have demonstrated that coronary collaterals did not affect LVEDP levels in patients without left ventricular systolic dysfunction.[5] In another study by the aforementioned authors including patients only with well-developed coronary collaterals, LVEDP levels were significantly higher in patients with left ventricular systolic dysfunction.[12] Our results may be explained by the existing bidirectional interaction between the coronary collateral status and LVEDP levels. The first direction is the influence of coronary collaterals on filling pressures. Poorly developed CC is not always sufficient to prevent myocardial ischemia which in turn causes elevated LVEDP levels. In case of well-developed CC, elevated LVEDP levels could be explained with two different mechanisms – CC, albeit well-developed is not capable to substitute native coronary vessels and studies utilizing myocardial perfusion scintigraphy showed that even well-developed collaterals could not prevent stress myocardial ischemia. The second mechanism is that well-developed coronary collaterals can reduce left ventricular compliance and so elevate LVEDP levels. This effect is known as Salisbury effect.[13] As the collateral circulation can affect the filling pressures, there is also reciprocal interaction between them. In case of elevated LVEDP levels, exceeding 25–30 mmHg limit coronary collaterals could be collapsed. This effect, demonstrates influence of left ventricular functions on the CC status and is known as Waterfall effect.[14]

There was not also significant difference between groups with regard to NT-proBNP levels. This result is somewhat conflicting with previous findings. Kadı et al., have found in a study including patients with totally occluded coronary arteries (however, if they are chronic is not emphasized) that well-developed CC could lower NT-proBNP levels via protecting from myocardial ischemia.[8] Another, more recent study

Table 2 Univariate correlations (r) of LVEDP and Log NT-proBNP levels with some clinical, angiographic and laboratory variables.

Variables	LVEDP		Log NT-proBNP	
	r	p Value	r	p Value
Age	0.199	0.138	0.192	0.061
Sex	0.219	0.101	0.070	0.496
Diabetes mellitus	0.087	0.580	−0.035	0.756
Hypertension	0.030	0.850	0.072	0.521
Smoking	0.112	0.474	−0.008	0.946
CTO vessel	−0.109	0.455	0.032	0.756
Number of diseased vessels	0.170	0.211	**0.294**	**0.004**
Rentrop group	−0.037	0.788	−0.109	0.292
log NT-proBNP	0.305	0.080		
Hb, g/dL	−0.175	0.193	**−0.291**	**0.004**
Creatinine, g/dL	−0.060	0.657	0.027	0.797
Hs-CRP, mg/L	0.173	0.788	0.215	0.110
LVEDP			0.305	0.080

CTO: chronic total occlusion, Hb: hemoglobin, Hs-CRP: high-sensitive C-reactive protein, LVEDP: left ventricular end diastolic pressure.

investigating only CTO patients, showed that poor CC was associated with significantly higher NT-proBNP levels when compared with well-developed CC.[9] This result was explained by two mechanisms – firstly, by protection against myocardial ischemia provided by well-developed collaterals, and secondly, elevated NT-proBNP levels might be only reflection of the required humoral status for the stimulation of angiogenesis in patients with poor CC. On the other hand, in another study BNP levels were found to be significantly higher in patients with well-developed coronary collaterals and this result was explained by the potential triggering effect of BNP on angiogenesis.[10] Inconsistency between the results could be explained by the difference between study populations and definitions used to describe CCC status. In our study well-developed CC group was composed of only Rentrop grade 3 collaterals. Elevated NT-proBNP levels in patients with Rentrop grade 3 collaterals could be explained by the aforementioned potential angiogenetic effect of the natriuretic peptide. It was demonstrated in an animal study that NT-proBNP molecules increased the number and functional capacity of the endothelial progenitor cells and so had vasculogenetic effect.[15] From this perspective, elevated NT-proBNP levels may also be interpreted as a stimulus for collateral development, not only as a consequence of insufficient coronary collaterals.

The major limitation of this study was the retrospective design. Secondly, the collaterals visualized by angiography may not accurately quantify collateral circulation. In addition, the Rentrop scale of collateral grading is semi quantitative and assessment of the collateral circulation using a qualitative method might be more precise. And finally, the absence of data with respect to the myocardial ischemia extent makes difficult the interpretation of the results.

5. Conclusion

Our results suggest that, even well-developed coronary collaterals may be incapable of protecting the rise of left ventricular end diastolic pressure and NT-proBNP levels which are reliable markers of the left ventricular dysfunction. Further well-designed studies using quantitative methods for collateral assessment are needed to make a firm conclusion.

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