

High Coronary Collateral Circulation Increases Left Ventricular Reverse Remodeling Event in Patients with Chronic Ischaemic Heart Disease Underwent Coronary Artery Bypass Surgery

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High Coronary Collateral Circulation Increases Left Ventricular Reverse Remodeling Event in Patients with Chronic Ischaemic Heart Disease Underwent Coronary Artery Bypass Surgery

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Abstract

Background: Coronary collateral circulation (CCC) is linked to myocardial remodeling severity in patients with chronic ischaemic heart disease (IHD). However its effect on left ventricular reverse remodeling (LVRR) in patients with chronic IHD underwent coronary artery bypass surgery (CABG) has never been reported. Purpose of this study was to investigate the effect of CCC grade on the LVRR event in patients with chronic IHD underwent CABG.

Methods: This prospective cohort study was performed in patients with chronic IHD underwent CABG. The CCC was classified using Rentrop collateral score, i.e low CCC grade (Rentrop score 0 and 1) and high CCC grade (Rentrop score 2 and 3). LVRR event was defined as a reduction in left ventricular end systolic volume (LVESV) of 10% or more, measured by a 3D echocardiography at 1.5 months post CABG compared to the baseline before CABG.

Results: A total of 22 patients (81.8% male) with mean of age 58.6 years old were enrolled. LVRR occurred in 50% patients. LVRR event was significantly higher in the patients with high CCC grade than the low CCC grade patients ($p=0.009$). The high CCC grade increased LVRR event independently (odds ratio=26.67; relative risk=6.93).

Conclusion: High coronary collateral circulation may increase left ventricular reverse remodeling event in patients with chronic ischemic heart disease underwent coronary artery bypass surgery.

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Keywords: coronary collateral circulation; left ventricular reverse remodeling; chronic ischaemic heart disease; coronary artery bypass surgery; 3D echocardiography

Introduction

Left ventricular reverse remodeling (LVRR) is a reduction in left ventricular end systolic volume (LVESV) of 10% or more compared to the baseline. It is observed in diverse clinical settings including in patients with chronic ischaemic heart disease (IHD) underwent coronary revascularization.¹ Either LVESV or left ventricular ejection fraction (LVEF) can be used as parameter for measuring left ventricular function, however LVESV is less preload dependent compared to the LVEF.²

Coronary artery bypass grafting (CABG) is effective in improving symptoms and survival rate in patients with chronic IHD by promoting LVRR.³ Coronary collateral circulation (CCC) is alternative source of blood supply for myocardium at risk of ischaemia caused by a reduced coronary blood flow through native coronary arteries. Evidence shows protective role of CCC in chronic IHD patients.^{4,5,6} Higher CCC supply is associated with increased myocardial viability and improvement of regional and global cardiac systolic and diastolic function in patients with chronic IHD.^{7,8,9}

Several methods are used for assessing CCC grade, including collateral flow index, collateral connection score, washout calorimetry, and perfusion imaging. The visual collateral connection method using Rentrop score is the most common used method.¹⁰ It is simple, could be implemented clinically and has been validated.¹¹

Cardiac magnetic resonance imaging is the gold standard method to assess ventricular volume but it has shortcoming related with its availability, affordability and usability. In comparison to the gold standard, real time 3D Echocardiography (RT3DE) has higher accuracy and reproducibility, cost effective, safe and applicable for patients, and thus it is becoming the first choice method in assessing left ventricular volume.^{12,13} However, there is no study reporting the effect of CCC on the LVRR event in patients with chronic IHD underwent CABG, measured by RT3DE method. This study investigated the effect of CCC grade on the LVRR event in patients with chronic IHD underwent CABG using full volume RT3DE.

Methods

Subject of study

This observational, prospective cohort study was performed in 24 patients with chronic IHD underwent CABG at the Dr. Kariadi General Hospital, Semarang, Indonesia from April to September 2018. We included patient with LVEF < 50% and end diastolic wall thickness more than 6 mm with sinus rhythm. Patient with left bundle branch block (LBBB), acute coronary syndrome (ACS) < 1.5 months prior to CABG, concomitant congenital heart disease, prior history of CABG, concomitant valve surgery, or poor echo window were excluded; and those with periprocedural infarction, having acute coronary syndrome, or death during 1.5 months follow-up were dropped out. A consecutive sampling method was used. The University and Hospital Ethical Committee approved the study, and written informed consent was obtained from all of the patients. Investigational procedures were in accordance with institutional guidelines.

Assessment of coronary collateral circulation and left ventricular reverse remodeling

Demographic, clinical and echocardiographic data were collected from all subjects. CCC grade of the coronary angiogram before CABG was assessed using the Rentrop collateral score,¹⁴ while the occurrence of LVRR was assessed with the 3D echocardiography study prior and 1.5 months post CABG.

The Rentrop collateral score was as follow: score 0 = no filling from collateral, 1 = filling of side branches of the artery via collateral channels without visualization of the epicardial segment, 2 = partial filling of the epicardial segment via collateral channels, 3 = complete filling of the epicardial segment of the artery via collateral channels.¹⁴ In patients with more than 1 coronary collaterals, the highest collateral score was used. Patients were classified as having low CCC grade (Rentrop score 0 and 1) or high CCC grade (Rentrop score 2 and 3). Collateral grade was assessed by two senior interventional cardiologists with blinding to the clinical data of the patients. When there was a disagreement between them, the collateral grade was decided by the third observer.

Table 1. Baseline clinical and echocardiographic characteristic of patients with (+) and without (-) left ventricular reverse remodeling

Parameter	LVRR (-) (n= 11)	LVRR (+) (n= 11)	P
Clinical Characteristic			
CCC grade (n(%))			
• Low	8 (88.9)	1 (11.1)	0.008b
• High	3 (23.1)	10 (76.9)	
Age (years)	61.72 ± 8.93; 62.42(48.42-79.83)	55.54 ± 8.76; 55.92(42.58-69.92)	0.117a
Sex (n(%))			
• Male	8 (44.4)	10 (55.6)	0.586b
• Female	3 (75)	1 (25)	
Diabetes Mellitus (n(%))	5 (83.3)	1 (16.7)	0.149b
Hypertension (n(%))	8 (53.3)	7 (46.7)	1.000b
Chronic kidney disease (n(%))	-	-	*
LVR severity before CABG (ml/m2)	72.27 ± 36.1; 61.13(35.09-128.07)	62.70 ± 22.67; 55.84(36.45-116.78)	0.467a
History of ACS (n(%))	7 (50)	7 (50)	1.000b
Anti-remodeling drugs (n(%))	11 (50)	11 (50)	*
• β-blocker	8 (44.4)	10 (55.6)	0.586b
• ACE-inhibitor/ARBs	10 (50)	10 (50)	1.000b
• MRA	5 (55.6)	4 (44.4)	1.000b
Baseline Echocardiographic Characteristic			
LVESV 3D full-volume (ml)	80.92 ± 48.71; 58.1 (33-168.2)	67.95 ± 32.48; 62.1 (37.6-148)	0.974c
	48.64 ± 28.27;	38.72 ± 17.47;	0.718c
LVESV 3D full-volume (ml)	36.31 (17.74-92.93)	31.87 (21.86-80.87)	
	121.95 ± 59.36;	112.45 ± 43.81;	0.674a
LVEDV 3D full-volume (ml)	97.8 (65-231.8)	103.3 (62.7-231.7)	
	73.55 ± 34.77;	64.08 ± 23.1;	0.462a
LVEDVi 3D full-volume (ml/ m2)	61.13 (35.11-128.07)	55.84 (36.45-116.78)	
	37.32 ± 9.64;	40.89 ± 6.48;	0.323a
	40.6 (24.6-49.4)	42.3 (30.8-49.9)	
LVEF 3D full-volume (%)	1.61 ± 0.44; 1.44 (1.06-2.13)	1.42 ± 0.28; 1.31 (1.13-2)	0.373c
WMSI			

(+) with and (-) without left ventricular reverse remodeling, aIndependent t-test; bFisher's exact test; cMann-Whitney test; *statistical analysis could not be proceeded; LVRR: left ventricular reverse remodeling; CCC: coronary collateral circulation; LVR: left ventricular remodeling; CABG: coronary artery bypass surgery; ACS: acute coronary syndrome; ACE-inhibitor: Angiotensin Converting Enzym-inhibitor; ARBs: Angiotensin-Receptor Blockers; MRA: Mineralocorticoid/Aldosterone Receptor Antagonist; LVESV: left ventricular end systolic volume; LVESVi: left ventricular end systolic volume index; LVEDV: left ventricular end diastolic volume; LVEDVi: left ventricular end diastolic volume index; LVEF: Left ventricular ejection fraction; WMSI: wall motion score index

LVRR was defined as a reduction in LVESV of 10% or more at 1.5 months follow-up post CABG compared to the baseline before CABG. 3.15 LVESV was assessed by employing a 3D full volume method, using the Philip Epic-7 Netherlands device, with the IntelliSpace Cardiovascular, Cardiovascular Image and Information Management System version 1.2, 20-06-2016 software. Offline analysis was done using the commercial software

(Qlab, version 4.0, Philips) by two senior noninvasive cardiologists with blinding to the clinical data of the patients. Left ventricular remodeling (LVR) severity was defined as a baseline left ventricular end diastolic volume (LVEDV) indexed by the body surface area. LVEDV was assessed by employing a 3D full volume method using the same device and software applied to the LVESV.

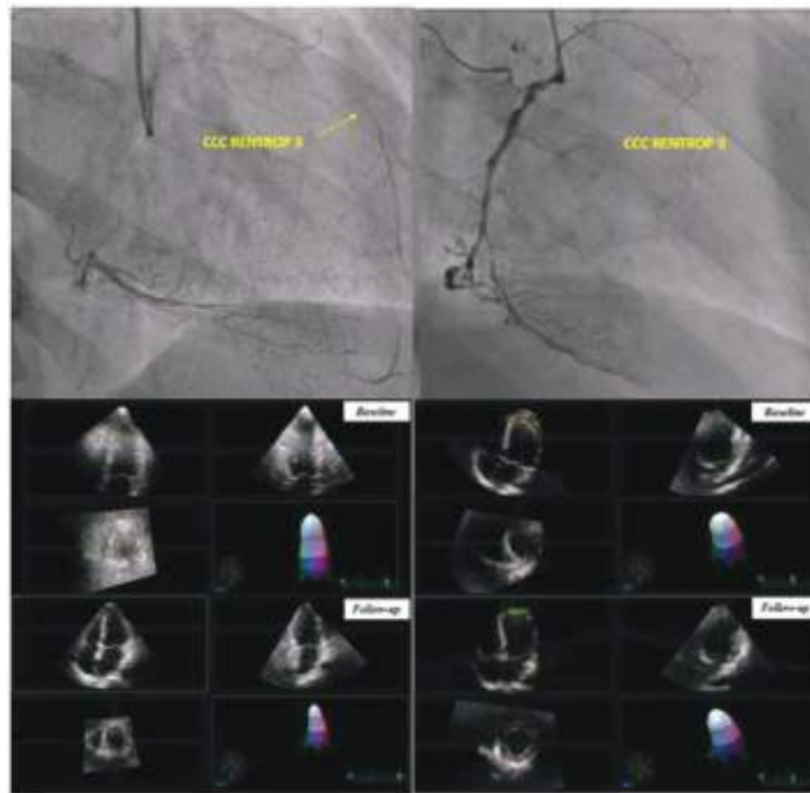


Figure 1. Representative cases of coronary collateral circulation (CCC) and left ventricular reverse remodeling (LVRR). (A) High CCC supply (Rentrop 3) from distal RCA to the CTO lesion at mid LAD. (B) LVRR event in patient with Rentrop 3 CCC supply obtained 1.5 months post CABG (baseline LVESV = 38.3 ml; follow up LVESV = 30.9 ml). (C) Patient underwent CABG without CCC supply (Rentrop 0). (D) Patient without CCC supply (Rentrop 0) did not experience LVRR event at 1.5 months follow up post CABG (baseline LVESV = 122.1 ml; follow-up LVESV = 118.6 ml) although having LVEF increment (baseline LVEF = 33.5%; follow-up LVEF = 34.3%).

Statistical analysis

Statistical analysis was done using software SPSS 25.0 (SPSS, Inc., Chicago, IL, USA). Intra-/inter-observer reliability in CCC grade and LVESV were assessed using Kappa and Bland-Altman analysis, respectively. Parametric hypothesis testing were done using either Chi-Square, independent t-test or dependent t-test. Non-parametric hypothesis testing were done using either Fisher's exact, Mann-whitney or Wilcoxon test. Logistic regression multivariate analysis was used to control the effect of other variables on LVRR in order to get adjusted odds ratio (OR), 95% confident interval (C.I.) and relative risk. A $p < 0.05$ was considered statistically significant.

Results

Twenty seven patients were scheduled to have CABG in April to September 2018. Two patients did not meet inclusion criteria with $LVEF \geq 50\%$ and one patient was excluded because poor echo window. During 1.5 months follow-up, two patients were dropped out, one patient died and the other did not present at the follow-up echocardiography. Therefore 22 patients completed the study and having data before and 1.5 months after CABG. Table 1 shows the baseline clinical and echocardiographic characteristic comparison between patients with and without LVRR. Of 22 patients, 50% (11 patients) had LVRR. There was no

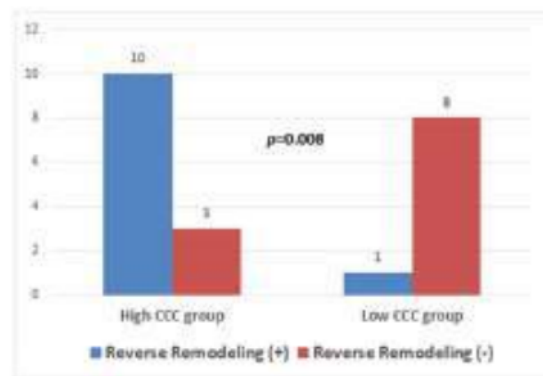
Table 2. Improvement of echocardiographic parameters in the high CCC grade group

Parameter	High CCC group (n= 13)	Low CCC group (n=9)	P
Δ Baseline - follow-up LVESV 3D full-volume (ml)	-13.43 ± 8.18; -12.3 (-35.1-(-5.3))	-2.86 ± 3.23; -1,5 (-10.9-(-0.4))	<0.001a
Δ Baseline - follow-up LVESVi 3D full-volume (ml/m2)	-7.63 ± 4.2; -6.59 (-18.37-(-3))	-1.66 ± 1.68; -0.86 (-5.65-(-0.24))	<0.001a
Δ Baseline - follow-up LVEDV 3D full-volume (ml)	-14.63 ± 9.96; -12.4 (-32.9-(-0.1))	-2.88 ± 3.82; -1.7 (-12.6-(-0.2))	0.004a
Δ Baseline - follow-up LVEDVi 3D full-volume (ml/m2)	-8.3 ± 5.29; -7.98(-17.23-(-0.05))	-1.65 ± 1.97; -1.02(-6.52-(-0.13))	0.003a
Δ Baseline - follow-up LVEF 3D full-volume (%)	4.44 ± 3.93; 4.6 (-2.1-14.3)	1.29 ± 1.52 0.7 (-0.4-4.8)	0.018a
Δ Baseline - follow-up WMSI	-0.32 ± 0.28; -0.25 (-0.87-0)	-0.12 ± 0.12; -0.07 (-0.38-0.06)	0.037b

significant difference of age ($p=0.117$), sex category ($p=0.586$), diabetes mellitus ($p=0.149$), hypertension ($p=1.000$), and history of ACS ($p=1.000$) between both groups. No one had chronic kidney disease and all patients were received antiremodeling drugs therapy. The CCC grade was significantly higher in patients with LVRR than that of patients without LVRR ($p=0.008$). Patients experienced LVRR tends to have better LVR severity before CABG compared to the patients without LVRR (baseline LVEDVi 64.08 ± 23.1 ml/m2 and 73.55 ± 34.77 ml/m2 respectively).

Figure 1A and 1B show example of a case of patient with high CCC (Rentrop 3) from the distal of right coronary artery (RCA) to the distal of left anterior descending coronary artery (LAD) with chronic total occlusion (CTO) lesion at its mid segment. Patient had a critical left main (LM) stenosis with bifurcation lesion at LM-LAD-left circumflex coronary artery (LCX); CTO lesion at mid LAD; significant ($>50\%$) stenosis at the first diagonal artery and proximal-mid RCA. Three-D echocardiography obtained at 1.5 months follow-up post CABG showed a LVRR event. Figure 1C and 1D show example of a case of patient with multiple significant stenosis at proximal, mid and distal RCA, a significant stenosis at LCX, significant stenosis at proximal and distal LAD without CCC supply (Rentrop 0). This patient did not show LVRR event at 1.5 months follow up post CABG.

Table 2 shows comparison of delta baseline–follow-up echocardiographic parameters between the high CCC and low CCC groups. The delta baseline–follow-up for LVESV 3D full-volume, LVESVi 3D full-volume,

**Figure 2.** Left ventricular reverse remodeling event in high and low coronary collateral circulation (CCC) groups.

LVEDV 3D full-volume, LVEDVi 3D full-volume, LVEF 3D full-volume and WMSI were significantly higher in patients with high CCC group than that of low CCC group ($p<0.001$, <0.001 , 0.004 , 0.003 , 0.018 and 0.037 , respectively).

^aMann-Whitney test; bindependent t-test; LVESV : left ventricular end systolic volume; LVESVi : left ventricular end systolic volume index; LVEDV : left ventricular end diastolic volume; LVEDVi : left ventricular end diastolic volume index; LVEF : left ventricular ejection fraction; WMSI : wall motion score index.

Figure 2 shows bivariate analysis of variables affecting LVRR. There was a statistically significant difference in CCC grade between patients with and without LVRR event ($p=0.008$) whereas there was no significant differences for other variables including

Table 3. Bivariate analysis of variables affecting left ventricular reverse remodeling event post CABG

Parameter		LVRR (-)		LVRR (+)		P	Relative risk	95% C.I.	
		n	%	n	%			min	max
• CCC grade	Low	8	88.9	1	11.1	0.008a	3.85	1.39	10.67
	High	3	23.1	10	76.9				
• Diabetes Mellitus	Yes	5	83.3	1	16.7	0.149a	2.22	1.07	4.6
	No	6	37.5	10	62.5				
• Hypertension	Yes	8	53.3	7	46.7	1.000a	1.24	0.47	3.31
	No	3	42.9	4	57.1				
• Chronic kidney disease	Yes	-	-	-	-	a			
	No	11	100	11	100				
• LVR before CABG (ml/m2)	≥75.26	5	71.4	2	28.6	0.361a	1.79	0.82	3.88
	≤75.26	6	40	9	60				
• History of ACS	Yes	7	50	7	50	1.000a	1.00	0.42	2.38
	No	4	50	4	50				
• Antiremodeling drugs therapy	Yes	11	100	11	100	a			
	No	-	-	-	-				

aFisher's exact test; *statistical analysis could not be proceeded; LVRR : left ventricular reverse remodeling; CCC : coronary collateral circulation; LVR : left ventricular remodeling; CABG : coronary artery bypass surgery; ACS : acute coronary syndrome

Table 2. Improvement of echocardiographic parameters in the high CCC grade group

Parameter	Variable	P Value	OR	95%CI	
Step 1a	CCC grade (1)	0.016	23.13	1.81	296.03
	Diabetes Mellitus(1)	0.201	6.33	0.37	107.13
	Constant	0.038	0.033	NA	NA
Step 2a	CCC grade (1)	0.009	26.67	2.31	308
	Constant	0.05	0.125	NA	NA

diabetes mellitus, hypertension, chronic kidney disease, LVR severity before CABG, history of acute coronary syndrome and antiremodeling drugs therapy (table 3).

Logistic regression multivariate analysis to control the effect of other variables on LVRR after CABG showed a significant association between CCC grade and LVRR event post CABG, (p=0.009, adjusted OR=26.67 (95% C.I. 2.31–308)) (table 4)

Discussion

Clinical relevance of CCC in the cardiac remodeling remains unclear.⁶ Result of this study adds evidence of the protective role of CCC in patients with chronic IHD underwent CABG. To the best of our knowledge, there was no study addressing the effect of CCC on LVRR based on the improvement of LVESV assessed

by the RT3DE method. The important finding in this study was that the LVESV improvement rather than its LVEF was affected by degree of CCC. In addition, this study showed that 41% (9 of 22) patients with LVEF improvement did not experience LVRR event. Thus, this data support the idea that a less preload dependent parameter of left ventricular systolic function, LVESV, assessed by RT3DE is a useful parameter to assess LVRR.

Patients underwent CABG are representative samples of population with multivessel coronary artery disease and severe myocardial remodeling who have complete revascularization in one step procedure.¹⁶ These patients are considered to be the ideal population to assess LVRR event, from which we could expect not only regional but also global myocardial recovery of viable dysfunctional myocardium.¹ The global myocardial recovery is an important factor affecting

LVESV improvement.^{1,17,18}

Possible mechanisms of how the higher CCC affect LVRR event in chronic IHD patients underwent CABG have been proposed. Higher CCC grade increases myocardial viability^{7,8,9,19}, reduces ischaemic event,²⁰ myocardial infarction risk,⁸ and induces regional and global left ventricular myocardial function recovery after coronary revascularization.^{7,9,20} The reduction of ischaemic event as well as better myocardial viability and left ventricular function recovery are able to reduce the severity of LVR, reduce myocardial wall stress and secondary neurohormonal activation^{21,22} and increase the LVRR event post CABG.^{23,24}

Data of this study showed that delta baseline–follow-up value for LVESV, LVESVi, LVEDV, LVEDVi, LVEF and WMSI parameters are significantly higher in the high CCC group than that of the low CCC group. This means that myocardial viability is better in the high CCC group than in the low CCC group. Patients who experienced LVRR event at 1.5 months post CABG tend to have better LVR severity prior operation than those who did not have LVRR. Taken together, the better myocardial viability and LVR severity prior CABG may be the cause of LVRR event in the patients with high CCC.

There were several limitations of this study. This study was conducted in a relatively small sample and short follow-up period, the presence of any ipsilateral collateral including bridging collateral and the dose variability of antiremodeling drug therapy in each patient were not assessed

Study Limitation

We acknowledge the small number of study subjects in our study. This might explain the rather wide confidence intervals in some of the analysis results in this study. However, the fact remains that our analyses were statistically significant and the small number of study subject of this study does not diminish the significance and importance of our findings.

Conclusion

Our data suggest that high coronary collateral circulation may increase left ventricular reverse

remodeling event in patients with chronic ischaemic heart disease underwent coronary artery bypass surgery.

Publication Approval

All authors read and approved the final manuscript.

Conflict of Interest

None.

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Ethical Clearance

The Ethical Committee of Dr. Kariadi General Hospital, Semarang, Indonesia approved this study, with ethical code 91/EC/FK-RSDK/II/2018.

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