의학석사 학위논문

Role of phase parameters on gated myocardial perfusion SPECT 3 months after coronary bypass graft surgery (CABG) for the prediction of delayed reverse remodeling in patients with patent grafts and perfusion improvement after CABG

관상동맥 우회로 이식술 1년 후 이식 혈관 개통성이 있고 관류가 개선된 환자들의 지연된 역재형성 예측에 있어서 관상동맥 우회로 이식술 3개월 뒤 게이트 심근 관류 SPECT를 이용한 phase parameter들의 역할

2015년 8 월

서울대학교 대학원

의학과 핵의학 전공

박 소 현

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지도교수 천 기 정

이 논문을 의학석사 학위 논문으로 제출함

2015년 6 월

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박소현의 의학 석사 학위논문을 인준함

2015년 8월

위원장 김 용 진 (인)

부위원장 천 기 정 (인)

위 원 이 원 우 (인)

Contents

Abstract

Role of phase parameters on gated myocardial perfusion SPECT 3 months after coronary bypass graft surgery (CABG) for the prediction of delayed reverse remodeling in patients with patent grafts and perfusion improvement after CABG

Sohyun Park

College of Medicine, Department of Nuclear medicine

The Graduate School

Seoul National University

Purpose:

Phase analysis using gated myocardial perfusion single photon emission computed tomography (GMPS) is a tool used to assess left ventricular (LV) dyssynchrony. We attempted to investigate the role of LV dyssynchrony assessed by GMPS using phase analysis for the prediction of LV function after coronary artery bypass surgery (CABG).

Methods:

A total of 40 patients who received off pump CABG with patent graft 1 yr after CABG were enrolled retrospectively. All patients underwent GMPS before and 3 mo and 1 yr after CABG. Using the Emori Cardiac Toolbox, both phase histogram bandwidth (PBW) and phase standard deviation (PSD) derived by phase analysis were used for the analysis, in addition to the conventional parameter. For the evaluation of heart function, transthoracic echocardiography was also performed.

Results:

One year after CABG, 16 out of 40 patients exhibited reverse remodeling. All of these patients showed significant improvement in perfusion (paired t-test, $p<0.05$) 3 mo after CABG. Using stepwise logistic regression with forward selection, PBW 3 mo after CABG was able to predict reverse remodeling 1 yr after CABG (odds ratio [OR] 1.03, $p<0.05$). Using receiver operating characteristic curve analysis, PBW 3 mo after CABG had the largest area under the curve to detect reverse remodeling with a cutoff value of 82 (sensitivity 0.94, specificity 0.58, $p<0.001$).

Conclusion:

In the prediction of reverse remodeling, early postoperative LV dyssynchrony had predictive value.

Keywords: Phase analysis, LV dyssynchrony, Coronary artery bypass surgery,

Reverse remodeling

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Introduction

Coronary artery bypass surgery (CABG) is a treatment method for the revascularization and management of coronary artery disease (CAD). The presence of viable myocardium has traditionally been the standard determinant of revascularization, and it is associated with good prognosis (1-7). The majority of patients who receive CABG recover after perfusion of the heart, and have favorable prognosis eventually. But functional impairment can also occur, and negative outcomes include major adverse coronary events (MACE) (8).

So the outcomes after CABG are variable due to aggravation or different recovery conditions. Given this, perfusion of the heart after revascularization is critical factor, but underlying recovery mechanism is not fully known (9).

LV dyssynchrony is defined as an inharmonic LV contraction, and this results in different contraction of myocardium (10). This condition is a predictive factor for the response to cardiac resynchronized therapy (CRT), and a prognostic factor for heart failure patient, and myocardial infarction (MI) (11-15). In ischemic heart disease patients, even after revascularization, LV dyssynchrony at initial measurement is associated with poor prognosis (10, 16, 17).

Multiple attempts have been made to assess LV dyssynchrony using gated myocardial perfusion single photon emission computed tomography (GMPS), and these attempts have been well-correlated with tissue Doppler imaging assessments

(18, 19). It also has shown an excellent ability to predict the response to CRT and to predict functional outcomes in patients with systolic heart failure and end stage renal disease (20-24).

Based on these results, we presumed accordant LV contraction could be related to heart function recovery after CABG. But in our knowledge, no precise physiology is established how heart recovers in the patient with patent grafts and perfusion improvement and eventually exhibits heart function recovery.

The aims of the present study were to evaluate the ability of GMPS-assessed phase parameter to predict the state of the heart 1 yr after CABG, which is not fully investigated in the aspect of recovery process after CABG.

Methods and materials

Subjects

A total of 51 patients with three-vessel coronary artery disease (3VD) who underwent CABG between March 2013 and February 2014 were enrolled retrospectively in this study. Among the enrolled patients, those who exhibited a patent CABG graft (n=40) 1 yr after CABG were selected for analysis. Patient characteristics are described in Table 1. None of the patients had a MACE, which was defined as death or post-CABG MI. All patients underwent GMPS and echocardiography before CABG (within 1 mo of the operation) and 1 yr after CABG, and GMPS alone was performed 3 mo after surgery (Figure 1).

SPECT protocols

A rest protocol, using only ^{201}Tl, or a stress-rest protocol, using ^{201}Tl and ^{99m}Tc–sestamethoxyisobutylisonitrile (^{99m}Tc–sestamibi), were performed before CABG. For the follow up analyses, GMPS stress-rest protocols were performed 3 mo and 1 yr after CABG. Pharmacological stress was induced by adenosine injection (0.14 mg/kg/min for 6 min). Ten minutes after an injection of 74 MBq of ^{201}Tl, rest images were acquired using a fixed 90˚ dual-head gamma camera (CardioMd, Philips, Cleveland, Ohio, USA) and a low-energy, high resolution collimator. Three minutes after beginning of the stress procedure, 555 MBq ^{99m}Tc-sestamibi was injected. After eating a fatty meal, post–stress images were taken after 90 minutes using the same camera and collimator. Rest ^{201}Tl SPECT images were reconstructed using a hanning filter with Astonish reconstruction.

To assess LV dyssynchrony using GMPS, phase analysis was performed using the Emory Cardiac Toolbox (Emory University, Atlanta, GA). Regional maximum counts were derived in three dimensions, and these counts were related to myocardial wall thickening, based on the partial-volume effect. Count-based wall thickening curves were generated by first Fourier harmonics function approximation and displayed on a histogram plot. After image processing, phase distribution was extracted, and five variables for assessing LV dyssynchrony were obtained (Figure 2): (1) phase standard deviation (PSD), i.e., the SD of the phase histogram; (2) phase histogram bandwidth (PBW), which includes 95% of the elements of the phase distribution; (3) peak phase (PP), the most frequent phase; (4) phase histogram skewness (Sk), i.e., symmetry of the histogram; (5) phase histogram kurtosis (Kur), i.e., the degree of the histogram peak (19).

Endpoint

Reverse remodeling was defined as a ≥15% reduction in the LV end-systolic volume (ESV) 1 yr after CABG, as assessed by GMPS; this was the endpoint of this study. To assess heart function, transthoracic echocardiography was performed with the patients in a supine position using the VIVID 7 or VIVID E9 echocardiograph (GE Medical Systems, Princeton, NJ, USA).

Statistical Analysis

Pearson’s correlation was used to assess the reproducibility of the phase analysis. Stepwise logistic regression analysis with forward selection was performed to determine the relationship between reverse remodeling and PSD, PBW, gender, age, BSA, LV EF and enlarged LV cavity. A paired t-test was performed to evaluate perfusion improvement in 16 patients with reverse remodeling. Student’s t-test was performed to determine the differences in investigated parameters between patients with and without reverse remodeling. Receiver operating characteristic (ROC) curves were obtained to determine the phase parameter cutoff values to predict reverse remodeling. ROC curves were obtained using MedCalc 14.10.2 (Broekostraat, Mariakerke, Belgium), and the other analyses were conducted using SPSS 22.0 (IBM, Armonk, NY, USA). Continuous data are given as means ± SD. A p value < 0.05 was considered statistically significant.

Result

Patient characteristics

A total of 40 patients who exhibited a patent graft after 1 yr CABG were enrolled retrospectively. None of the patient experienced MACE, defined as either death or post-CABG MI. Patient characteristics are summarized in Table 1.

Investigation of phase analysis reproducibility

To investigate the reproducibility of the study, phase analysis was replicated in the same study and the results compared. Excellent correlations were found between the parameters derived from each phase analysis (Figure 3).

Predictive factors of reverse LV remodeling 1 yr after CABG

Sixteen patients showed reverse remodeling 1 yr after CABG, all of whom had improved perfusion after 3 mo compared with their preoperative states (paired t-test of SRS, $p<0.05$). To identify predictive factors for reverse remodeling, stepwise logistic regression with forward selection was performed. In the univariate analysis, initial EF abnormality (defined as < 45%), PSD and PBW 3 mo after CABG were significant predictive factors for reverse remodeling. However, in the multivariate analysis, only PBW was found to be significant 3 mo post-CABG (Table 2). Student's t-test was used to assess differences between patients with and without reverse remodeling. Only PSD and PBW were significantly different 3 mo post-CABG (Table 3).

Subgroup analysis classified by perfusion state

To minimize the effect of perfusion on the prediction of reverse remodeling, an additional analysis was performed comparing the normal and reverse remodeling groups 3 mo after CABG. Patients in the normal group had no or mild reversibility, and this was defined as a summed stress score (SSS) < 4 (n=8). The demographics of the patient subgroups are summarized in Supplemental Table 1 (Suppl. Table 1). In the reverse remodeling group, PSD and PBW were significantly different 3 mo after CABG ($p < 0.05$).

ROC analysis for PBW 3 mo after CABG for the prediction of reverse remodeling

Since the 3 mo post-CABG PBW values were predictive of reverse remodeling, ROC curves were obtained to determine the predictive cutoff value. The area under the curve (AUC) maximum (0.806) for PBW was found 3 mo post-CABG. The optimal cutoff value for PBW prediction of reverse remodeling 1 yr after CABG was 82, with a sensitivity and specificity of 0.94 and 0.58, respectively (Figure 4, $p<0.001$).

Table 1. Patient Characteristics

Number of Patients	N = 40
Gender (Female/Male)	5/35
Age (years) at initial diagnosis	67.8 (range 37 – 86)
BSA	1.73±0.16
Initial perfusion (initial)	
Reversible/Partially reversible	23/11
Persistent	5
Normal	1
SSS	9.23±6.89
SRS	3.73±5.04
EF	52.1±11.5
LVIDd	49.7±6.51
Phase parameter	
PSD	46.5±22.7
PBW	105±48.6

BSA; body surface area at initial measurement, SSS; Summed stress score at 3 mo after CABG, SRS; Summed rest score at 3 mo after CABG, EF; ejection fraction at initial measurement, LVIDd; Left ventricular internal diameter end diastole at initial measurement, PSD; phase SD at initial measurement, PBW; phase histogram bandwidth at initial measurement.

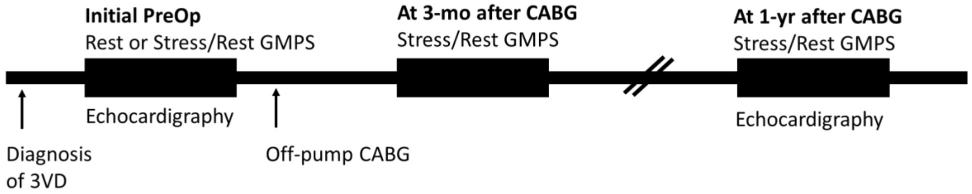
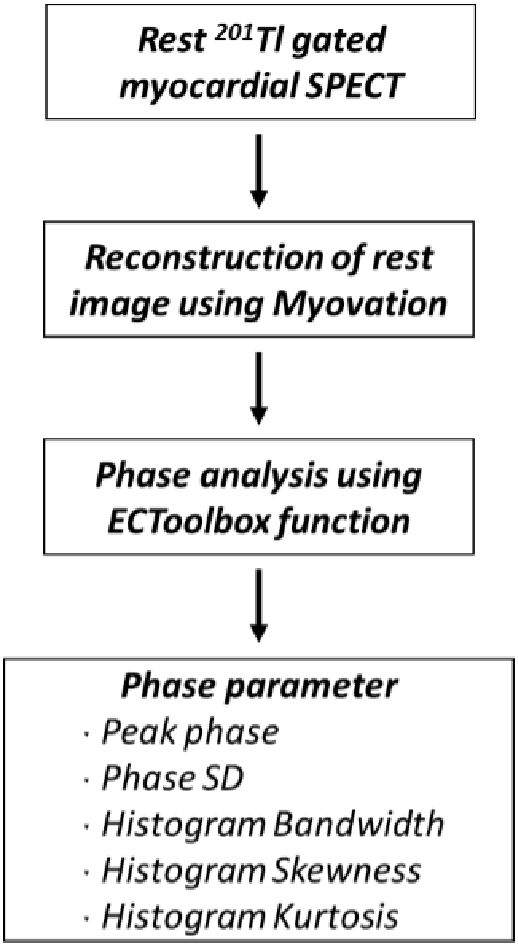
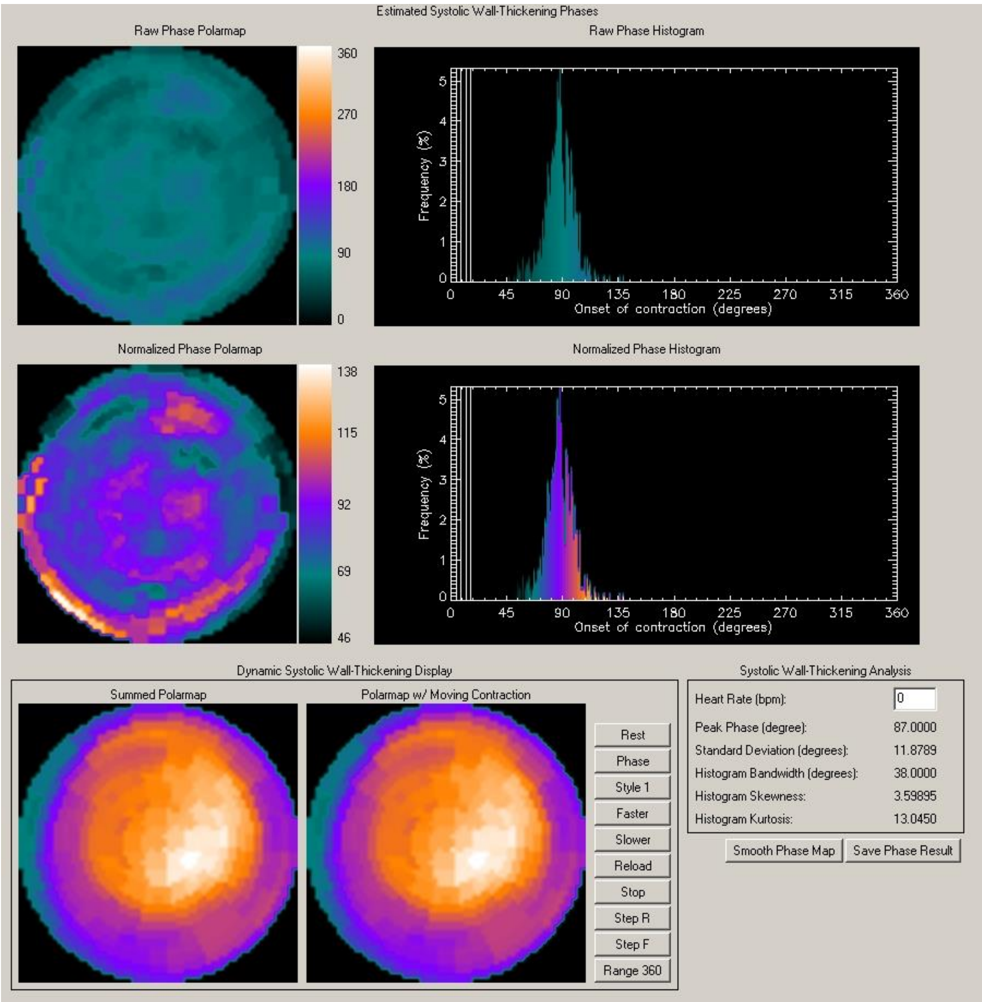


Figure 1. Study Protocol. Patients with 3VD who required surgical revascularization, as determined by a cardiologist, with subsequent CABG was enrolled retrospectively, with a patent graft 1 yr after CABG. Patients underwent GMPS, the rest only or stress/rest protocol and echocardiography as the initial preoperative study, within 1 mo of CABG. Three months after CABG, patients only underwent GMPS with the stress/rest protocol. One year after CABG, patients underwent GMPS with the stress/rest protocol and echocardiography.

A.


Rest 201Tl gated myocardial SPECT
Reconstruction of rest image using Myovation
Phase analysis using ECToolbox function
Phase parameter
· Peak phase
· Phase SD
· Histogram Bandwidth
· Histogram Skewness
· Histogram Kurtosis

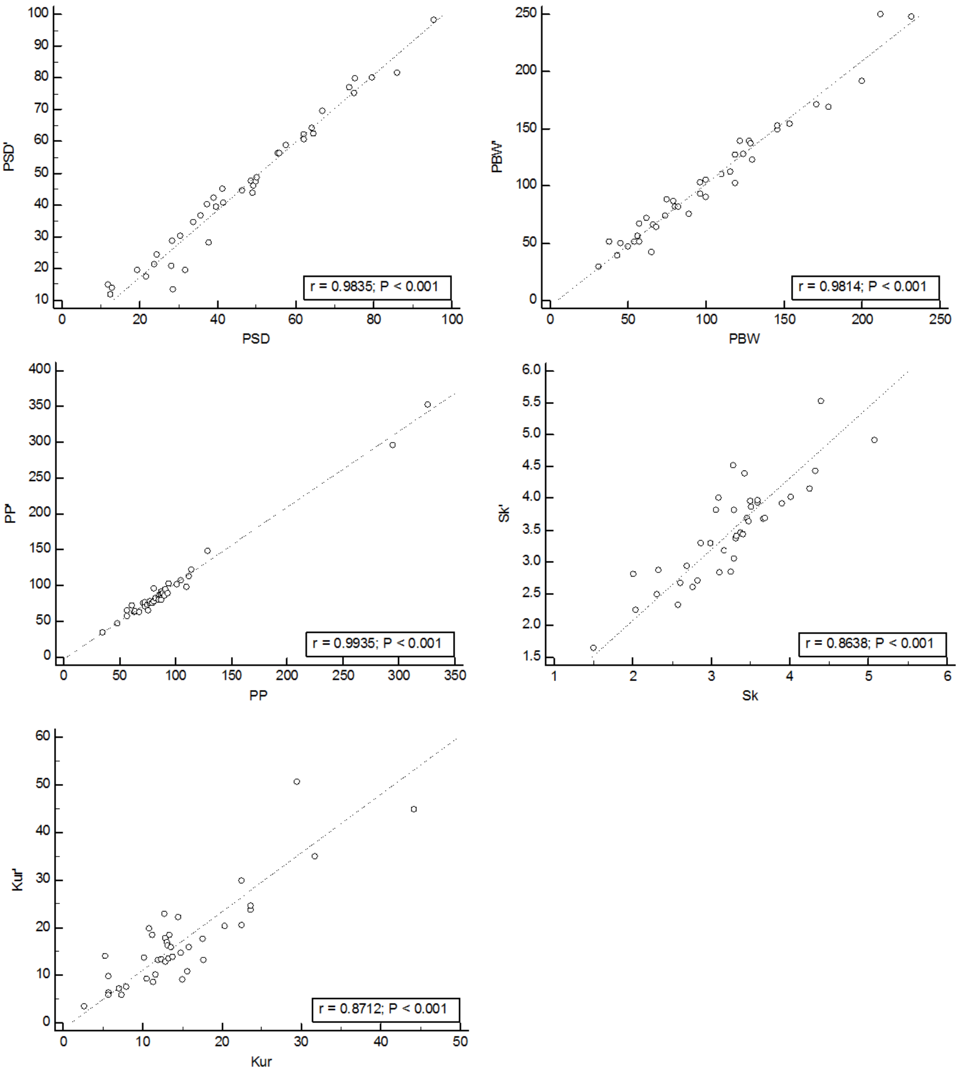
B.



Estimated Systolic Wall-Thickening Phases
Raw Phase Polarmap
Raw Phase Histogram
360
270
180
90
0
Frequency (%)
Onset of contraction (degrees)
Normalized Phase Polarmap
Normalized Phase Histogram
138
115
92
69
46
Dynamic Systolic Wall-Thickening Display
Summed Polarmap
Polarmap w/ Moving Contraction
Rest
Phase
Style 1
Faster
Slower
Reload
Stop
Step R
Step F
Range 360
Systolic Wall-Thickening Analysis
Heart Rate (bpm): 0
Peak Phase (degree): 87.0000
Standard Deviation (degrees): 11.8789
Histogram Bandwidth (degrees): 38.0000
Histogram Skewness: 3.59895
Histogram Kurtosis: 13.0450
Smooth Phase Map
Save Phase Result

Figure 2. Processing the flow of reconstruction and phase analysis for the assessment of LV dyssynchrony and image in a representative case. A. Processing flow of a rest image of GMPS. Using Myovation software, reconstruction was performed. Based on the reconstruction, the ECToolbox was used, and phase analysis was performed in the 'function' tab. B. A representative normal patient without LV dyssynchrony.

A.



PSD'
PSD
r = 0.9835; P < 0.001
PBW'
PBW
r = 0.9814; P < 0.001
PP'
PP
r = 0.9935; P < 0.001
Sk'
Sk
r = 0.8638; P < 0.001
Kur'
Kur
r = 0.8712; P < 0.001

Figure 3. Assessment reproducibility of phase parameters derived twice with same exam. Correlation plot of each parameter, phase standard deviation (PSD), phase bandwidth (PBW), peak phase (PP), histogram skewness (Sk), and histogram kurtosis (Kur). All exhibited significant correlation (PSD $r = 0.9835$, $p < 0.0001$; PBW $r = 0.9814$, $p < 0.0001$; PP $r = 0.9935$, $p < 0.0001$; Sk $r = 0.8638$, $p < 0.0001$, Kur $r = 0.8712$, $p < 0.0001$).

Table 2. Univariate and Multivariate analysis to Predict Reverse Remodeling

	Univariate analysis		Multivariate analysis	
	OR	p value	OR (95% CI)	p value
Gender	5.31	0.166		
Age	1.02	0.582		
BSA	7.12	0.369		
SSS	1.09	0.089		
SRS	1.02	0.727		
EF abnormality	6.60	0.036		
Enlarged LV cavity	2.54	0.341		
PSD initial	1.03	0.088		
after 3mo	1.07	0.011		
PBW initial	1.01	0.189		
after 3mo	1.03	0.005	1.03(1.01-1.05)	0.005

BSA; body surface area at initial measurement, SSS; summed stress score 3 mo after CABG, SRS; summed rest score 3 mo after CABG, EF; ejection fraction at initial measurement, LV cavity; left ventricular cavity at initial measurement, PSD; phase SD, PBW; phase histogram bandwidth

Table 3. Characteristics of Patients classified by reverse remodeling: A comparison

	Patients with reverse remodeling	Patients without reverse remodeling	p-value
Patient Number	16	24	
Clinical information			
Gender (Female/Male)	2/14	3/21	0.139
Age (range)	67.1(54-84)	68.9 (37-86)	0.584
BSA	1.76±0.18	1.72±0.14	0.400
Echocardigraphic parameters			
EF Initial	50.9±11.6	56.4±9.39	0.127
1 yr after	57.4±7.03	57.0±8.30	0.859
LVIDd Initial	51.4±6.72	48.5±6.23	0.179
1 yr after	46.9±4.90	48.0±5.98	0.519
Phase parameter			
PSD intial	54.1±22.6	41.4±21.7	0.087
after 3 mo	48.9±14.6	35.1±14.6	0.006
PBW initial	118±44.3	96.9±50.4	0.178
after 3 mo	130±39.7	85.6±36.1	0.001
SPECT parameter			
SSS	11.6±7.43	7.67±6.17	0.093
SRS	4.06±1.13	3.50±5.44	0.725
LV chamber size			
EDV initial	121±45.7	100±36.2	0.138
after 3 mo	97.6±30.3	106±32.8	0.464
1 yr after	90.5±23.4	106±32.6	0.122
ESV initial	67.5±42.6	47.3±32.0	0.118
after 3 mo	45.7±23.0	51.7±32.1	0.542

1 yr after	40.3±18.7	50.0±29.7	0.210

BSA; body surface area at initial measurement, EF; ejection fraction, LVIDd; left ventricular internal diameter end diastole, PSD; phase SD, PBW; phase histogram bandwidth, SSS; summed stress score 3 mo after CABG, SRS; summed rest score 3 mo after CABG, EDV; end diastolic volume measured using GMPS, ESV; end systolic volume measured using GMPS

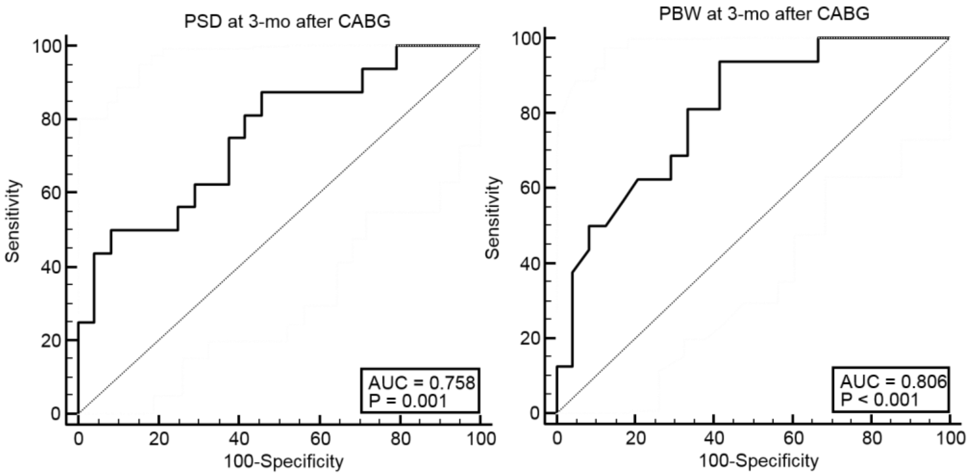


Figure 4. ROC curve for the prediction of reverse remodeling of phase parameter at 3 mo after CABG. ROC analysis was done about Phase SD (PSD) and Phase histogram bandwidth (PBW) at 3 mo after CABG. PBW at 3 mo after CABG showed largest AUC. Cutoff value was 82, with sensitivity 0.94 and specificity 0.58 ($p<0.05$).

Suppl. Table 1. Patients with Remained Reversibility classified by Reverse Remodeling

	Patient with reverse remodeling	Patient without reverse remodeling	P value
Patient Number (n=32)	15	17	
Clinical information			
Gender (Female/Male)	2/13	3/14	0.260
Age (range)	69.1 (range 54-84)	66.8 (range 54-80)	0.480
BSA	1.76±0.13	1.77±0.18	0.395
Echocardiographic Parameters			
EF Initial	40.7±11.2	55.9±9.07	0.246
After 1 yr	57.5±7.28	55.0±8.77	0.392
LVIDd Initial	50.5±11.9	55.2±10.6	0.250
After 1 yr	47.1±5.00	50.0±5.62	0.129
Phase parameter			
PSD initial	45.2±24.4	40.9±19.3	0.228
3 mo after	49.7±14.7	39.4±18.9	0.018
PBW initial	120±44.3	104±57.6	0.363
3 mo after	132±40.5	91.5±38.8	0.007
SPECT parameter			
SSS	11.8±7.74	8.94±5.76	0.252
SRS	3.60±4.73	3.59±5.30	0.995

BSA; body surface area at initial measurement, EF; ejection fraction, LVIDd; left ventricular internal diameter end diastole, PSD; phase SD, PBW; phase histogram bandwidth, SSS; summed stress score 3 mo after CABG, SRS; summed rest score 3 mo after CABG

Discussion

The present study aimed to evaluate the prediction of LV function using LV dyssynchrony derived by phase analysis using GMPS. First, excellent reproducibility was obtained by phase analysis, which is advantageous compared to tissue Doppler imaging (25). Among 40 patients, 16 showed reverse remodeling 1 yr after CABG. Among several parameters evaluated, an increase in phase parameter 3 mo after CABG had predictive value in the prediction of reverse remodeling. Furthermore, in these patients, additional functional recovery was also observed. Patients with low EF improved more than 8%.

Preoperative LV dyssynchrony is an independent poor prognostic factor after CABG in patients with stable LV dysfunction (16, 17). Poor prognosis is related to LCOS, which leads to multiple organ failure. LCOS can stimulate compensatory mechanisms, which promote LV remodeling (26). However, little is known about the impact of early postoperative LV dyssynchrony on further prognosis or the remodeling process.

There were 16 patients who exhibited reverse remodeling and showed perfusion improvements 3 mo after CABG compared with preoperative perfusion, which was read by experienced two nuclear physicians (paired t-test of SRS, $p<0.05$). Previous studies on the perfusion state of patients who underwent CABG reported that the perfusion state is related to reverse remodeling (27, 28). However, none of these previous studies investigated the early postoperative state, as done in the present study. The reason LV dyssynchrony showed predictive value in reverse remodeling at early postoperative time points could be explained as follows: functional recovery has not yet improved in the patients who exhibit reverse remodeling, even if perfusion was improved by revascularization 3 mo after CABG. In conclusion, at early postoperative time points, if perfusion improvement is presumed, there is a chance of reverse remodeling in patients with LV dyssynchrony.

Previously, the time point to investigate outcomes after CABG was related to preoperative assessment of various clinical factors. However, 3 mo after CABG is also an optimal time point to investigate functional outcomes. Three months after CABG, the reversibility score improved greatly in previous studies using GMPS (29, 30). This time point appears critical for functional recovery.

A limitation of our study is the relative short-term follow up after CABG used to investigate outcomes. The evaluation outcome after CABG was performed 1 yr after CABG. This could be the reason why none of the patients exhibited MACE. Also, all patients would have damage to myocardium because of significant stenosis at 3VD, but not all of patients had heart failure symptoms before CABG, which could be a limitation in the investigation of reverse remodeling.

Another possible limitation is the protocol used in the present study. Many of the studies that investigated LV dyssynchrony used ^{99m}Tc-sestamibi in GMPS. In contrast to previous studies, we used ^{201}Tl; yet, a previous study reported concordant results between ^{201}Tl and ^{99m}Tc-sestamibi (31). We expect no definite change compared with previous phase analysis study. After CABG, paradoxical septal motion is a well-known phenomenon exhibited in GMPS (32), which may influence phase parameters, but it was concluded as no impact was existed (33).

To summarize, LV dyssynchrony assessed by phase analysis using GMPS exhibited excellent reproducibility. Three months after CABG, PBW predicted reverse remodeling 1 yr after CABG. We could suggest phase parameters as early postoperative markers of functional recovery. However, large scale prospective studies are needed due to the limitations of this retrospective study.

Conclusion

LV dyssynchrony assessed by phase analysis using GMPS 3 months after CABG had predictive value for reverse remodeling 1 year after CABG.

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요약 (국문초록)

관상동맥 우회로 이식술 1년 후 이식 혈관 개통성이 있고 관류가 개선된 환자들의 지연된 역재형성 예측에 있어서 관상동맥 우회로 이식술 3개월 뒤 게이트 심근 관류 SPECT를 이용한 phase parameter들의 역할

목적:

게이트 심근관류 SPECT 를 이용한 phase analysis는 좌심실 비동기화를 평가하기 위한 도구이다. 본 연구에서 연구자들은 게이트 심근관류 SPECT를 이용한 phase analysis로 측정한 좌심실 비동기화가 관상동맥 우회로 이식술 후 1년이 된 환자들에게 심근 기능을 어떻게 예측하는지 알아보고자 하였다.

방법:

관상동맥 우회로 이식술 1년 후에 이식 혈관 개통성이 있는 환자 40명이 후향적으로 연구에 포함되었다. 모든 환자들이 게이트 심근관류 SPECT를 수술 전, 수술 후 3개월 및 수술 후 1년 뒤 시행하였고, 심에코는 수술 전 및 술 후 1년 뒤에 시행하였다. Emori Cardiac Toolbox를 사용하여 phase analysis를 실행하였고, phase bandwidth (PBW) 및 phase standard deviation (PSD)를 구하여 분석에 이용하였다. 또한 심기능을 평가하기 위해서 경흉부 심에코를 시

행하였다.

결과:

관상동맥 우회로 이식술 1년 뒤, 열여섯명의 환자들이 지속적인 역재형성을 보였다. 이 환자들은 수술전과 비교하여 모두 유의한 관류 계선을 보였다 (paired t-test, $p<0.05$). 단계적 전향적 로지스틱 회귀분석 결과, 수술 후 3개월째의 PBW가 수술 후 1년 뒤의 역재형성을 예측할 수 있었다 (OR 1.03, 각각, $p < 0.05$). ROC curve 분석을 통하여, 수술 후 3개월째의 PBW가 제일 큰 AUC를 보였으며, 절단값은 82 였다 (민감도 0.94, 특이도 0.58, $p < 0.001$).

결론:

이 연구에서, 게이트 심근관류 SPECT를 이용한 phase analysis를 통해 도출한 3개월째의 좌심실 비동기화가 심근의 관류 개선을 보였던 환자들 중에서 수술 후 1년뒤 역재형성을 예측할 수 있음을 관찰하였다.

keywords: Phase analysis, **좌심실 비동기화, 관상동맥 우회로 이식술, 역재형성**

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