Right Ventricular Function and Beneficial Effects of Cardiac Rehabilitation in Patients with Systolic Chronic Heart Failure

Brief title: RV Function in Cardiac Rehabilitation

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Brief Summary: Cardiac rehabilitation had an important role in the management of heart failure. The predictors of exercise capacity improvement after cardiac rehabilitation are required in the management of heart failure. We demonstrated that patients with higher right ventricular strain during preload augmentation seem to have a benefit more from cardiac rehabilitation. The simple, but novel application of preload stress echocardiography is a noninvasive technique that can be used to find a beneficial group with cardiac rehabilitation.

Background: It has been recognized that a comprehensive cardiac rehabilitation (CR) program improves mortality in patients with chronic heart failure (HF). On the other hand, the magnitude of the improvement in exercise capacity after CR differs among individuals. The aim of this study was to assess the echocardiographic determinants of responders to CR using preload stress echocardiography.

Methods: We prospectively enrolled 58 chronic HF patients with reduced left ventricular ejection fraction (LVEF) (age 62±11 years; 69% male; LVEF 43±7 %) who had received optimized medical treatment in a CR program for 5 months. We performed preload echocardiographic studies using leg positive pressure (LPP) to assess the echocardiographic parameters during preload augmentation. We defined 41 patients as a development cohort to assess the predictive value of echocardiographic variables. Next, we validated results in the remaining 17 patients as a validation cohort.

Results: In the development cohort, significant improvement in peak VO_2 (>10%) after CR was observed in 58% patients. In a multivariable logistic regression model, the significant predictor of improvement in exercise capacity was right ventricular (RV) strain during LPP (odds ratio: 3.96 per 1 SD; p =0.01). A RV strain value of –16% during LPP had good sensitivity of 0.79 and specificity of 0.71 to identify patients with improvement in peak VO_2. In the validation cohort, an optimal cut off value of RV strain value was the same (AUC: 0.77, sensitivity: 0.78, specificity: 0.65).

Conclusion: RV strain during LPP may be an echocardiographic parameter for assessing beneficial effects of CR.

Key Words: preload stress; right ventricular function; cardiac rehabilitation; exercise capacity; chronic heart failure.

It has been recognized that a comprehensive cardiac rehabilitation (CR) program improves mortality in addition to functional cardiac capacity and symptoms in patients with chronic heart failure (HF).[1-4] On the other hand, previous reports showed that there were some patients with a lack of beneficial effect in exercise capacity after CR, and the lack of effect is an independent predictor of adverse cardiovascular events in the future.[5-8] The magnitude of the improvement in exercise capacity after CR may differ among individuals. Thus, the predictors of responders to CR are required in the management of chronic HF patients.

The determinants of exercise capacity improvement have not been well documented. In a previous study, patients with HF reduced ejection fraction who were able to increase cardiac output during an initial exercise test showed a significant improvement in exercise capacity with training.[9] This result suggested that the left ventricular (LV) functional reserve reflects an improvement after CR. However, functional reserve was consistent with an increase in both LV and right ventricular (RV) contractility.[10] Furthermore, RV function has been well established as functional and prognostic parameters in several cardiac diseases.[11-13] RV function may have an important role in improvement after CR.

Recently, our laboratory developed preload stress echocardiography using leg positive pressure (LPP) to assess echocardiographic variables during preload augmentation. In our previous studies, cardiac response (changes of stroke volume, E/e' or LV/RV strains) during preload augmentation is an important part of the phenomenon in the evaluation of prognosis and exercise capacity in various cardiovascular diseases.[14-16] In addition, we showed that impaired RV strain during preload augmentation was associated with decreased exercise capacity in chronic HF.[17] Therefore, we hypothesized that RV function during preload augmentation may provide an important information to predict responders to CR. This clinical research is planned as a proof of

concept study, and the aim of this study was to assess the echocardiographic determinants of responders to CR using preload stress echocardiography.

Methods

Study population. We prospectively enrolled 58 chronic HF patients who had received optimized medical treatment in a CR program for 5 months from October 2013 to October 2017. We performed preload echocardiographic studies (detail in the section of stress echocardiography) during LPP before the CR program. Cardiopulmonary exercise testing was performed to assess the exercise capacity before and after the CR program. To assure relatively homogenous study group, all patients fulfilled the following inclusion criteria: 1) HF defined according to the European Society of Cardiology guidelines[18]; 2) reduced LV ejection fraction (EF) (≤50%); 3) sinus rhythm; 4) stable clinical condition at the time of echocardiography with optimal medical treatment; 5) absence of chronic lung disease; 6) absence of unstable angina; 7) absence of severe valvular disease; 8) absence of anemia; 9) completion of CR; and 10) technically adequate 2-dimensional and Doppler echocardiograms. We have used the development cohort to determine the predictor of responder to CR. Next, we validated the predictor in the validation cohort. Because of the necessity of large number of development cohort, we defined 41 consecutive patients from October 2013 to September 2016 as a development cohort to assess predictors of improvement in peak VO_2 and to determine optimal cut-off value of echo variables. Next, we validated outcomes in 17 consecutive patients from October 2016 to October 2017 as a validation cohort. The Institutional Review Board of the Tokushima University Hospital approved the study protocol, and written informed consent was obtained from all subjects.

Standard echocardiography. Echocardiography was performed using a commercially available ultrasound machine (iE33; Philips Healthcare, Amsterdam, The Netherlands; Vivid E9; and GE Healthcare, Waukesha, WI). All echocardiographic measurements were obtained according to American Society of Echocardiography recommendations.[19] Peak systolic longitudinal strain (LS) measurements were obtained from gray-scale images recorded in the apical 4-chamber, 2-chamber, and long-axis views. The frame rate was maintained at a level >40 frame/s. LV strain was analyzed offline using speckle tracking vendor-independent software (EchoInsight, Epsilon Imaging, Ann Arbor, MI). Global LS (GLS) was obtained by averaging all segmental strain values from the apical 4-chamber, 2-chamber, and long-axis views. Peak strain for the 3 right ventricular (RV) free wall segments was averaged to produce global RV longitudinal free wall strain, with exclusion of the interventricular septum to avoid LV interaction (**Figure 1**). These offline analyses were independently performed in a blinded manner by 2 observers who were not involved in the image acquisition and had no knowledge of examination dates and other echocardiographic or clinical data.

Stress echocardiography. All patients underwent preload stress echocardiography. The LPP maneuver is useful for pre-load stress echocardiography because it allows noninvasive pre-load augmentation during an echocardiographic examination (**Supplement 1**). We customized a commercially available leg massage machine (Dr. Medomer DM5000EX, Medo Industries Co., Ltd., Tokyo, Japan) and used a setting of 90 mm Hg, because this pressure did not significantly increase either heart rate or systolic blood pressure, based on findings from our studies.[14, 15] All echocardiographic variables were obtained at baseline and during LPP. All patients tolerated 90 mm Hg LPP without any complications.

Exercise training program. The exercise training program was supervised by a nurse and/or a physiotherapist specialized in CR based on the guideline of Japanese Circulation Society.[20] The duration of the CR program is 5 months. All patients were admitted to the hospital in order to start the CR program 5 days per week. Each supervised session consisted of warm-up for 5 minutes, 30 minutes of pedaling on a bicycle ergometer, and calisthenics for 10 minutes followed by cooling down for 5 minutes. After hospitalization, patients continued the designed, supervised exercise training program 2-3 times a week and home exercise training at least twice a week for 5 months. Home exercise training included warm-up for 5 minutes, walking for 30-40 minutes, and calisthenics for 10 minutes, followed by cooling down for 5 minutes. The exercise intensity of the ergometer portion of the supervised session was performed at a watt strength equivalent to the work level 1 minute before the anaerobic threshold during the patients' maximal symptom-limited cardiopulmonary exercise tests.[21] After hospitalization, patients continued to perform the supervised exercise training program one to three times per week, as well as home exercise training at least twice a week for 5 months. Home exercise training consisted of 5 minutes of warm-up, 30-40 minutes of walking, 10 minutes of calisthenics, and 5 minutes of cool-down exercises. Cardiopulmonary exercise testing (CPX) is a reliable method of estimation of exercise capacity, especially in patients with HF.[22] Peak VO_2 was measured from a maximal symptom-limited CPX in all patients before and after the CR programs.[21] Exercise testing was performed on an upright bicycle ergometer (STB-3200, CATEYE Co. Ltd. Osaka, Japan). The test started with 2 min of rest and 2 min of warmup at 10 Watts followed by a 10-Watt ramp. The test ended when symptoms of exhaustion were exhibited. VO_2, carbon dioxide production, and ventilation were measured and calculated by the gas analysis system (CPEX-1, Inter Reha Co. Ltd., Tokyo, Japan). We defined peak VO_2 as the highest VO_2 obtained during and adequately performed

test.[22] The primary endpoint was a significant improvement of Peak Vo_2 after CR (responders to CR), defined as improvement of Peak VO_2 >10% after CR.

Statistical analysis. Data are presented as mean±SD if the Kolmogorov–Smirnov test showed a normal distribution. Otherwise, the median and interquartile ranges were used. Comparison of baseline characteristics between groups was performed using t tests or the Mann–Whitney U test for continuous variables as appropriate and $\chi 2$ tests for categorical variables. Between-group differences before and after CR were examined using an analysis of covariance (ANCOVA) adjusted for baseline measures. There is no interaction between baseline measures and group (improved or non-improved). Within-group differences before and after CR were examined using paired t tests or Wilcoxon signed-rank tests, as appropriate. Linear regression analysis was used to evaluate the associations between several variables and change of peak VO_2. Logistic regression analysis was used to evaluate the associations between several potential variables and improvement in peak VO_2. Identified variables ($p < 0.20$ in the univariate model) were considered to enter in a stepwise manner into a multivariable logistic regression model. Logistic regression was used to calculate. Receiver-operating characteristic (ROC) curve analysis was used to identify parameters that were best to predict improvement in peak VO_2. In the development cohort, the best cutoff value was defined as the upper limit of the CI of the Youden index. The DeLong method was used to compare the C-statistic.[23] The improvement in predictive accuracy was evaluated by calculating the net reclassification improvement using the R package PredictABEL. In the validation cohort, this optimal cut-off value was used to validate the prediction of improvement in peak VO_2. Statistical analysis was performed using standard statistical software packages (SPSS software 21.0; SPSS Inc, Chicago, IL, USA, and MedCalc Software 17; Mariakerke, Belgium). Statistical significance was defined by $p<0.05$.

Results

Patient characteristics. In the development cohort, baseline characteristics of the study group are presented in **Table 1**. The patient population consisted of 88% patients with ischemic cardiomyopathy. All patients with ischemic cardiomyopathy were completely revascularized. There were no difference of exercise capacity and echocardiographic variables between patients with stenosis of left coronary artery and patients with stenosis of right coronary artery. No patients dropped out of the study or changed the medical therapies due to the worsening of HF during the study period. No significant differences were observed with regard to clinical background between the development cohort and the validation cohort.

CPX parameters at baseline and 5 months. Overall, the CR program significantly increased peak VO_2 from 14.5±4.6 mL/kg/min to 17.3±6.6 mL/kg/min ($p < 0.01$). There were 15 patients with New York Heart Association (NYHA) functional class (FC) II and 26 patients with NYHA FC III. After CR, there were 34 patients with NYHA FC II and only 7 patients with NYHA FC III. Significant improvement in peak VO_2 (>10%) after CR was observed in 58% patients (responders to CR), and peak VO_2 did not significant improve in 42% patients (non-responders to CR). There were no differences of clinical backgrounds between responders to CR and non-responders to CR. In responders to CR, peak exercise was increased and VE-VCO_2 slope was decreased significantly after CR. On the other hand, in non-responders to CR, there is no significant difference of CPX parameters between at baseline and after CR (**Table 2**).

Echocardiographic parameters at baseline and during preload augmentation.

Echocardiographic data before LPP and during LPP are shown in **Table 1**. In this cohort, LVEF (43±7 %) and LVGLS (-14±5 %) were reduced. Measures of RV function were also below

normal reference values. Before LPP, responders to CR had significantly higher SVi, higher RVFAC, higher TAPSE, and higher RV free wall strain profiles than non-responders to CR. During LPP, responders to CR also had more significantly higher SVi (34±9 ml/m^2 vs. 25±8 ml/m^2, p =0.004), lower E/e' (10.9±4.0 vs. 15.0±6.0 %, p =0.011), higher RVFAC (42±12 % vs. 33±12 %, p =0.03), and higher RV free wall strain (-19±3 % vs. -14±4 %, p <0.001) profiles than non-responders to CR.

Correlates of changes in exercise capacity after CR. Parameters of myocardial systolic and diastolic function correlated to improvement in peak VO_2. To determine the responders to CR, we performed multivariate analysis of the association between clinical/echocardiographic variables and responders to CR. The uni- and multivariate analysis for responders to CR was presented in **Table 3**. In stepwise multivariable logistic regression analysis, SVi during LPP (odds ratio: 2.42, 95% CI: 1.01-5.88, p =0.04) and RV free wall strain during LPP (odds ratio: 3.96, 95% CI: 1.31-11.8, p =0.01) were associated with responders to CR. During LPP, the relationships between echocardiographic variables and % change of peak VO_2 were significant (E/e': r= -0.30, p =0.05, SVi: r = 0.31, p =0.04, and RV free wall strain: r =0.46, p =0.002) (**Figure 2A-C**).

Results of the ROC curve analysis used to identify the optimal cutoff point for predicting responders to CR were shown in **Figure 3**. ROC analyses revealed that RV free wall strain during LPP had significantly better ability to detect the responders to CR compared with the other variables. This RV free wall strain during LPP had the highest AUC (0.81; p <0.001) among echocardiographic variables. A RV free wall strain value of –16% during LPP had good sensitivity of 0.79 and specificity of 0.71 to identify responders to CR. By incorporating RV free

wall strain into age, gender, BMI and SVi, net reclassification index (continuous) for the primary endpoint was 0.96 (95% CI, 0.42–1.50; p <0.001).

In the validation cohort, the RV free wall strain during LPP had the highest AUC (0.77; p =0.018) among echocardiographic variables. An optimal cut off value of RV free wall strain value was the same. A RV free wall strain value of –16% during LPP had good sensitivity of 0.78 and specificity of 0.65 to identify responders to CR. Therefore, the RV free wall strain during preload augmentation was one marker of responders to CR in patients with systolic chronic HF among echocardiographic variables.

Discussion

The prognosis of HF patients mainly depends on the exercise capacity.[24] CR can improve exercise capacity, and had an important role in the management of HF. However, not all the patients have improvement in exercise capacity after completion of CR. We demonstrated that patients with higher RV free wall strain during LPP seem to have a benefit more from CR. RV free wall strain during LPP can be a useful echocardiographic parameter for predicting beneficial effects of CR. The simple, but novel application of preload stress echocardiography is a noninvasive technique that can be used to find a beneficial group from systolic chronic HF with CR.

LV function in the efficacy of CR. As is well known, not all the patients who undergo CR achieve an improvement in exercise capability.[5-7] The variable clinical effect of CR is due to complex physiological mechanism. It was well established that exercise capacity was determined by peripheral factors such as skeletal muscle function, muscle bulk, and endothelial vasodilatory capacity rather than the cardiac factors.[25] On the other hand, the determinants of an improvement

in exercise capacity after CR have not been fully explained. Increased age, severity of disease, and poor cardiac function might be expected to influence the ability to benefit from CR. Several investigators showed that LV systolic function at rest was not significantly associated with the improvement in exercise capacity after CR.[26, 27] The resting echocardiographic parameters are limited to predict the effectiveness in CR. In a previous study, patients with HF who were able to increase cardiac output during an initial exercise test showed a significant improvement in exercise capacity with exercise training.[9] According to these results, we thought that patients with a greater LV functional reserve appear to have the greater potential for improving exercise capacity with training. In our study, the stroke volume index during preload augmentation was also associated with the improvement in peak VO_2. The results of this study are consistent with the previous work linking cardiac output during stress with the improvement of exercise capacity in HF. Thus, the level of cardiac output during stress was a good predictor of exercise capacity after CR in patients with HF.

RV function in the Efficacy of CR. There is an increasing recognition of the prognostic information provided by RV function in cardiovascular disorders such as HF. However, there is no knowledge about the relationship between RV function and improvement in exercise capacity after CR. In the present study, RV function during preload augmentation was a predictor of improvement in peak VO_2 after CR. Interestingly, conventional measures of RV function (RVFAC and TAPSE) were not significant predictors. The RV free wall strain had the highest AUC among echocardiographic variables. In addition, our laboratory also showed that the RV function during preload augmentation was associated with exercise capacity in systolic chronic HF.[17] The results of this study are consistent with our previous work linking RV strain with

exercise capacity. RV strain has a good reproducibility and it may be more sensitive than conventional measurements in the presence of heart failure.

The cause of RV dysfunction during pre-load augmentation in patients without improvement of exercise capacity is not fully explained given the complex interaction between left and right sides of the heart. In normal subjects, responses to pre-load augmentation is an increase in SV according to Frank-Starling's law.[28] If there is a sub-clinical RV failure in patients, the RV systolic function could not appropriately increase during pre-load augmentation according to RV Frank-Starling's law. Therefore, a lack of improvement in exercise capacity occurs in patients with impaired RV strain during preload augmentation due to the sub-clinical myocardial dysfunction. Importantly, the LV and RV are connected in series and may influence one another in parallel. This ventricular interaction may explain the strong association between LV/RV functional reserve and improvement of exercise capacity after CR. In the assessment of efficacy after CR, speckle tracking imaging can be used for detailed RV analysis during pre-load augmentation.

Limitations. The sample size was relatively small, and the study population was relatively heterogeneous. We could not enter some clinical variables (e.g., weight of skeletal muscle) into the model because of the relatively small number of outcomes, which poses a potential risk of model overfit. All patients completed CR, and no patient had severe frailty in our cohort. Thus, the impact of individual motivation and skeletal muscle volume seem to be small. However, exercise capacity is influenced by some unadjusted physiological parameters such as respiratory factors.[29-31] Although we used a setting of 90 mmHg LPP based on findings from our previous studies, we could not completely excluded some metaboreflex activation in this cohort. There are physiological differences with another type of stress echocardiography (e.g., supine bicycle or

treadmill test). These findings may not be interchangeable with another stress protocol type. In our study based on the guideline in Japan, the result may not be directly exploited to the other country.[20] According to these limitations, the present study should be considered as a proof of concept, and we believe that larger prospective multicenter studies are warranted.

Conclusions. The magnitude of the improvement in exercise capacity after CR differs among individuals. Some reports showed that a lack of beneficial effect in exercise capacity after CR is the independent predictor of adverse cardiovascular events in the future. Thus, the predictors of the improvement in exercise capacity after CR are required in the management of chronic HF patients. To the best of our knowledge, this is the first investigation of RV function during preload augmentation to predict the responders to CR in systolic chronic HF. RV assessment during preload augmentation may have an important role to manage chronic systolic HF.

Disclosures: None.

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Figure legends:

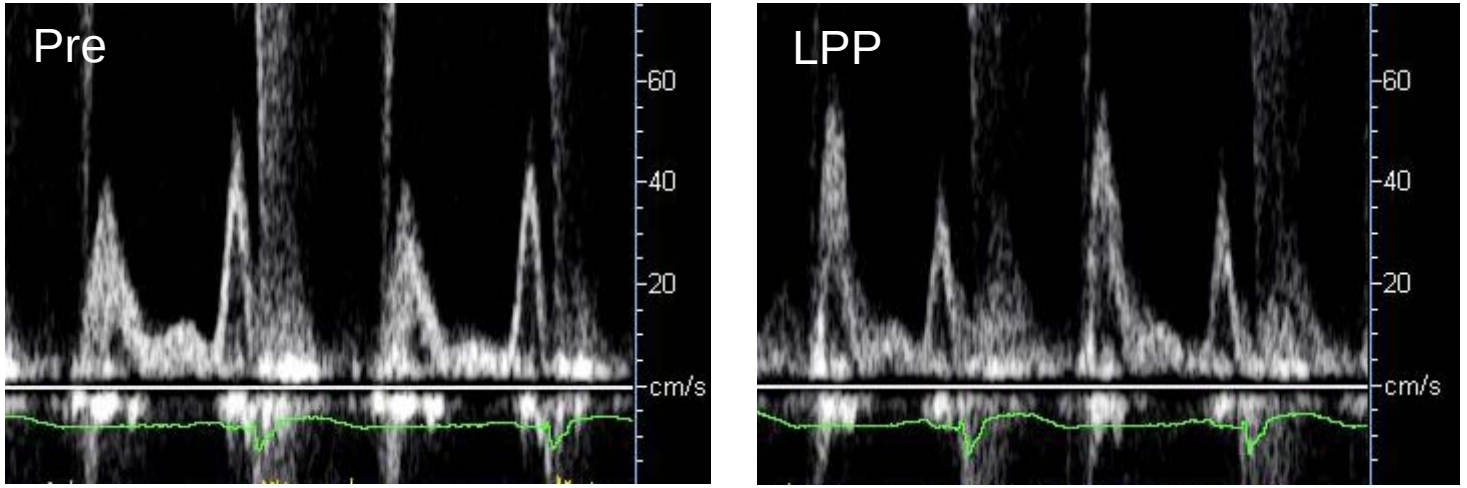
Figure 1: Representative Recordings of Doppler and B-mode Echocardiography at Baseline and during Leg Positive Pressure (LPP).

Figure 2: Correlations between Change of peak VO_2 and Echocardiographic Variables.

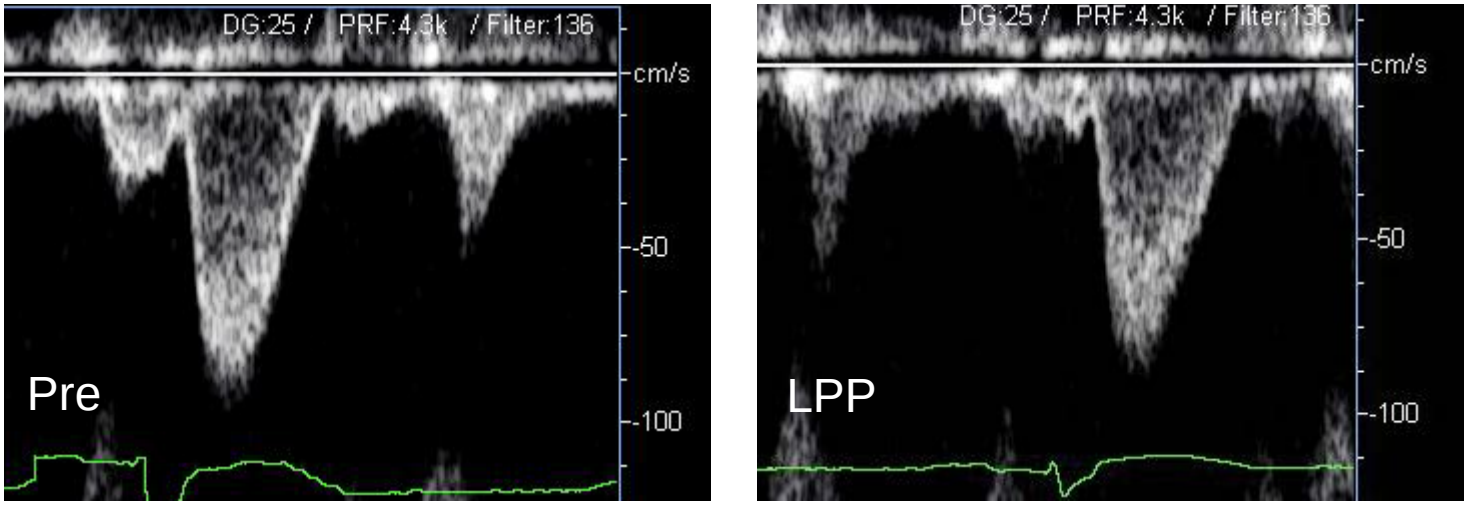
Figure 3: ROC Curve Analysis of Echocardiographic Variables for Predicting Improvement in VO_2 before (A) or during (B) Pre-Load Augmentation. The RV free wall strain during LPP had the highest AUC (AUC: 0.81) among echocardiographic variables. AUC = area under the curve; ROC = receiver-operating characteristic.

Video legend: The leg positive pressure (LPP) maneuver is useful for pre-load stress echocardiography because it allows noninvasive pre-load augmentation during an echocardiographic examination. LPP stress echocardiography was performed 20 seconds after the inflation of the airbags. If the data acquisition time was over 3 minutes, airbags were temporarily deflated and then inflated for the analysis.

Figure 1: A case without improvement of Peak VO_2（63 y.o. female)

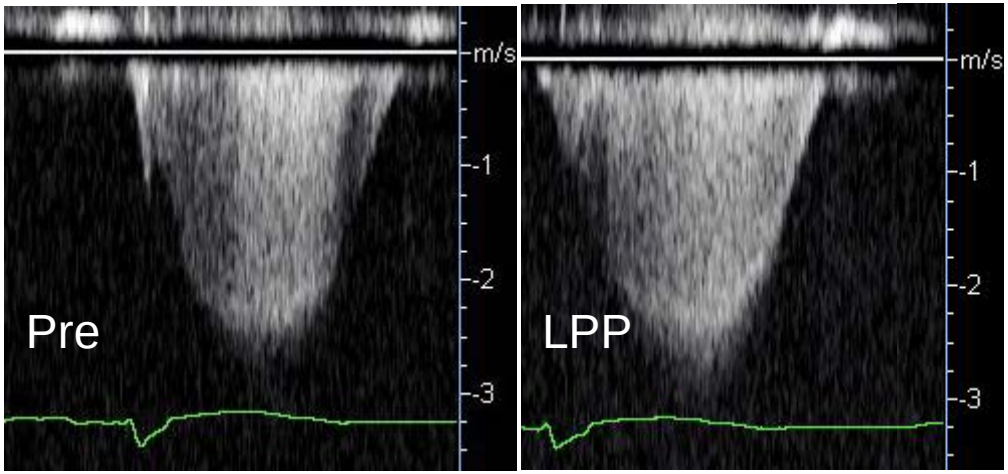


Transmitral flow
(E/e': pre: 11, LPP: 14.5)

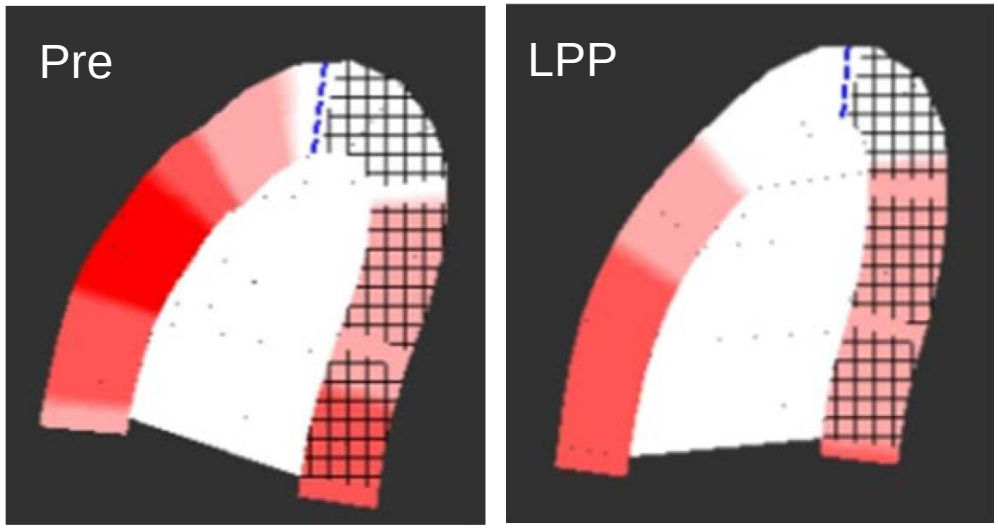


Left ventricular outflow
(SVi: pre: 40 ml/m^2, LPP: 38 ml/m^2)

Figure 1: A case without improvement of Peak VO_2（63 y.o. female)



Tricuspid regurgitant velocity
(PASP: pre: 28 mmHg, LPP: 36 mmHg)



Strain imaging analysis
(RV free wall strain: 16 %, LPP: 14 %)

Figure 2A: Correlation between change of peak VO_2 and E/e'

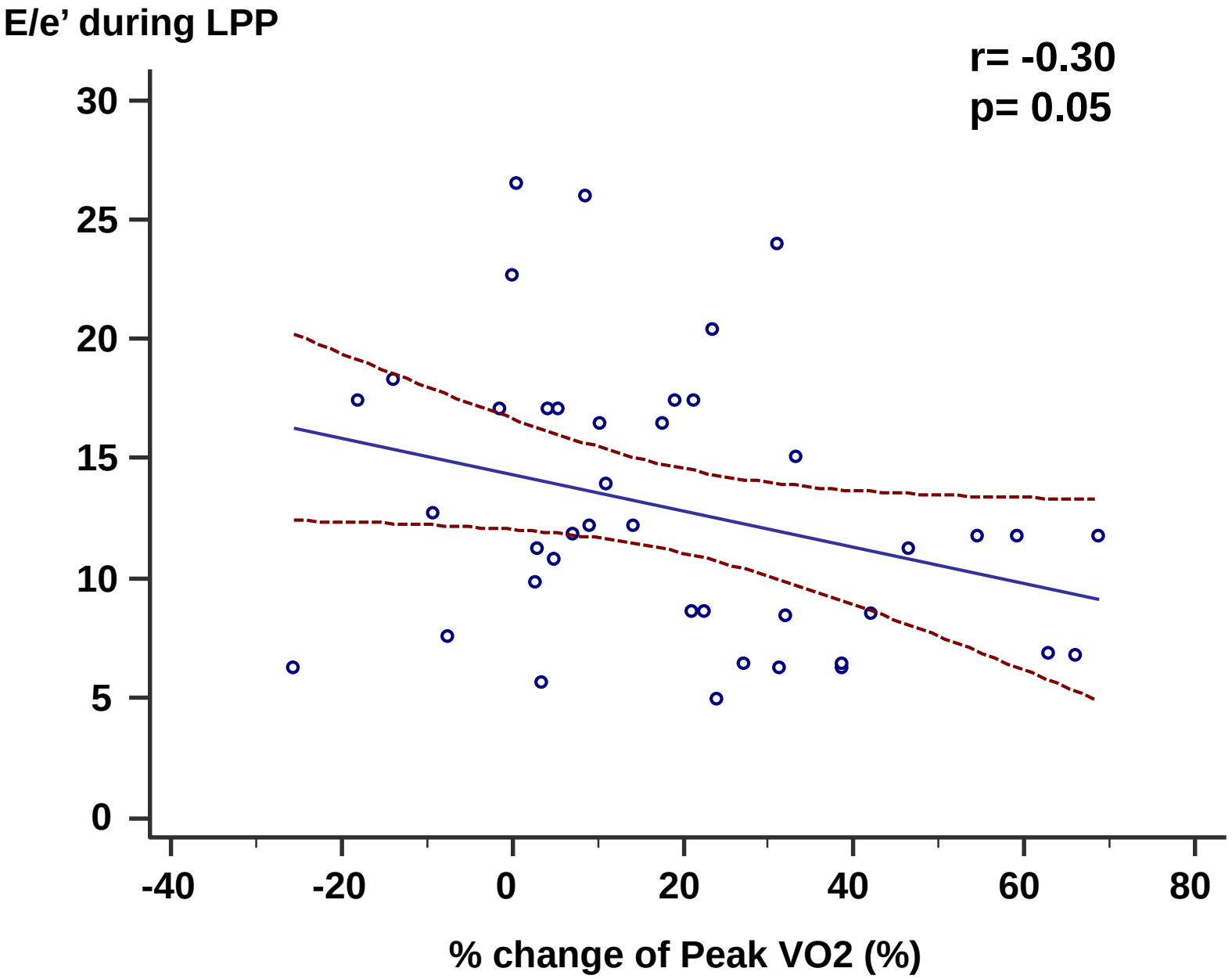


Figure 2B: Correlation between change of peak VO_2 and SVi

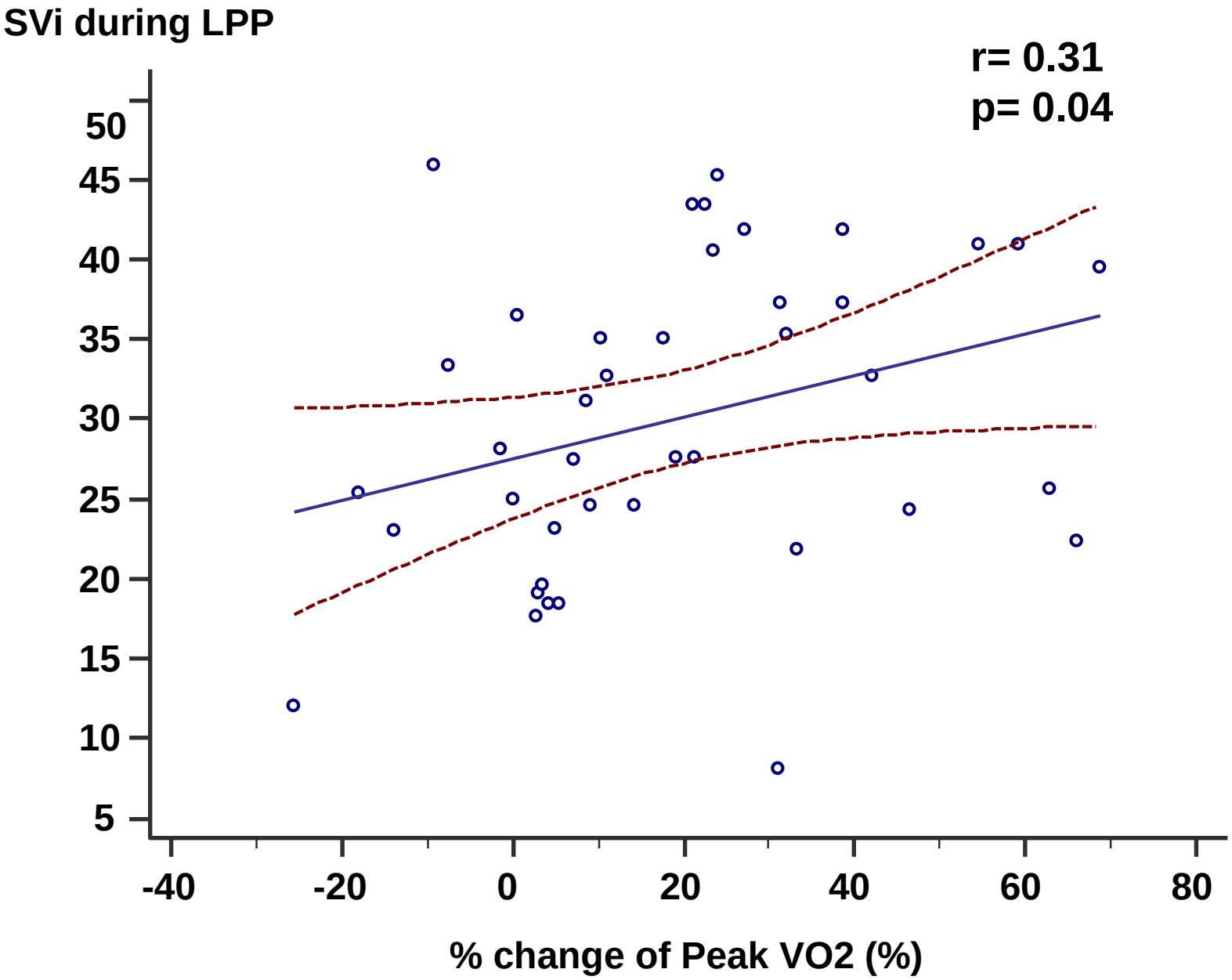


Figure 2C: Correlation between change of peak VO_2 and RV free wall strain

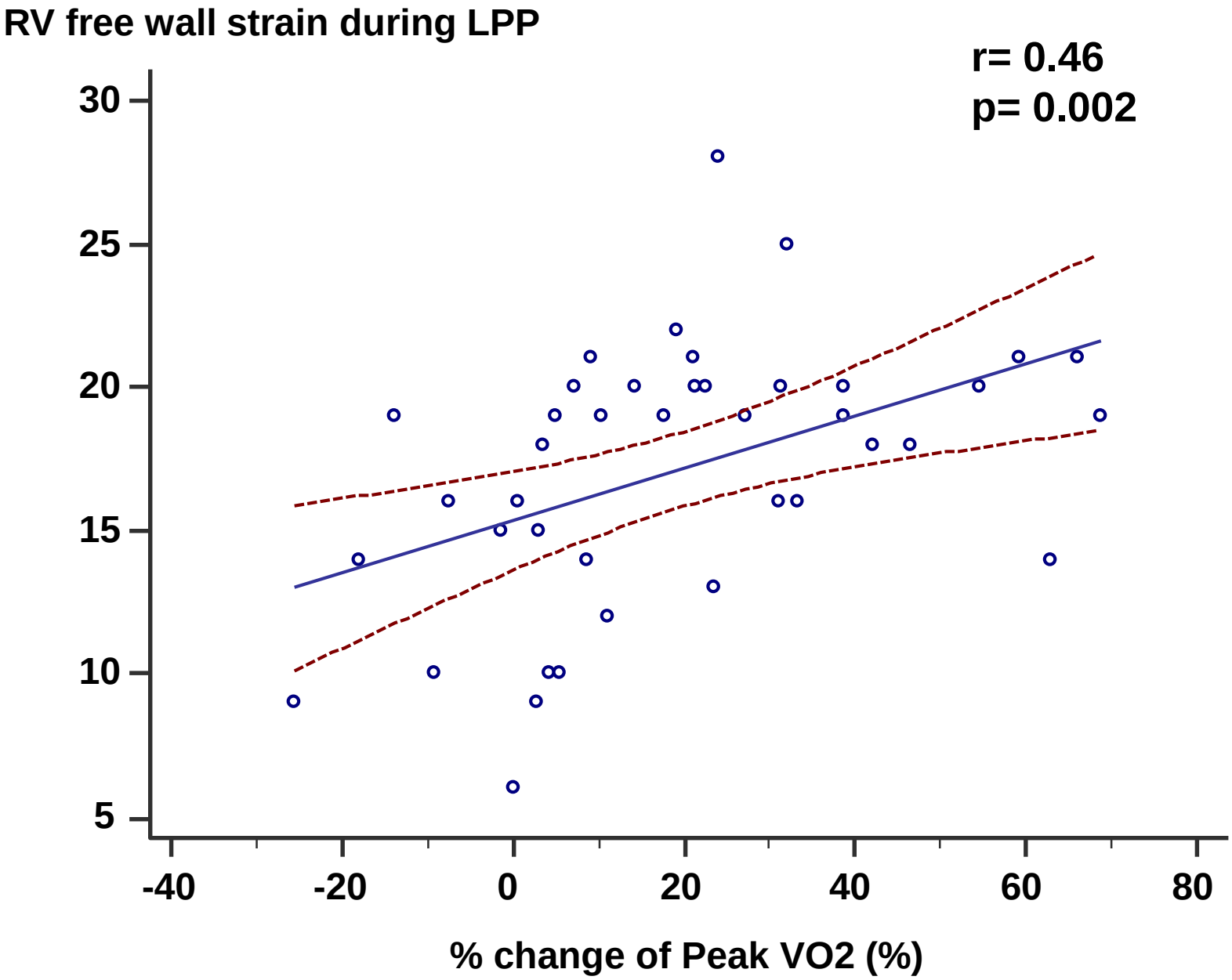


Figure 3: ROC curves

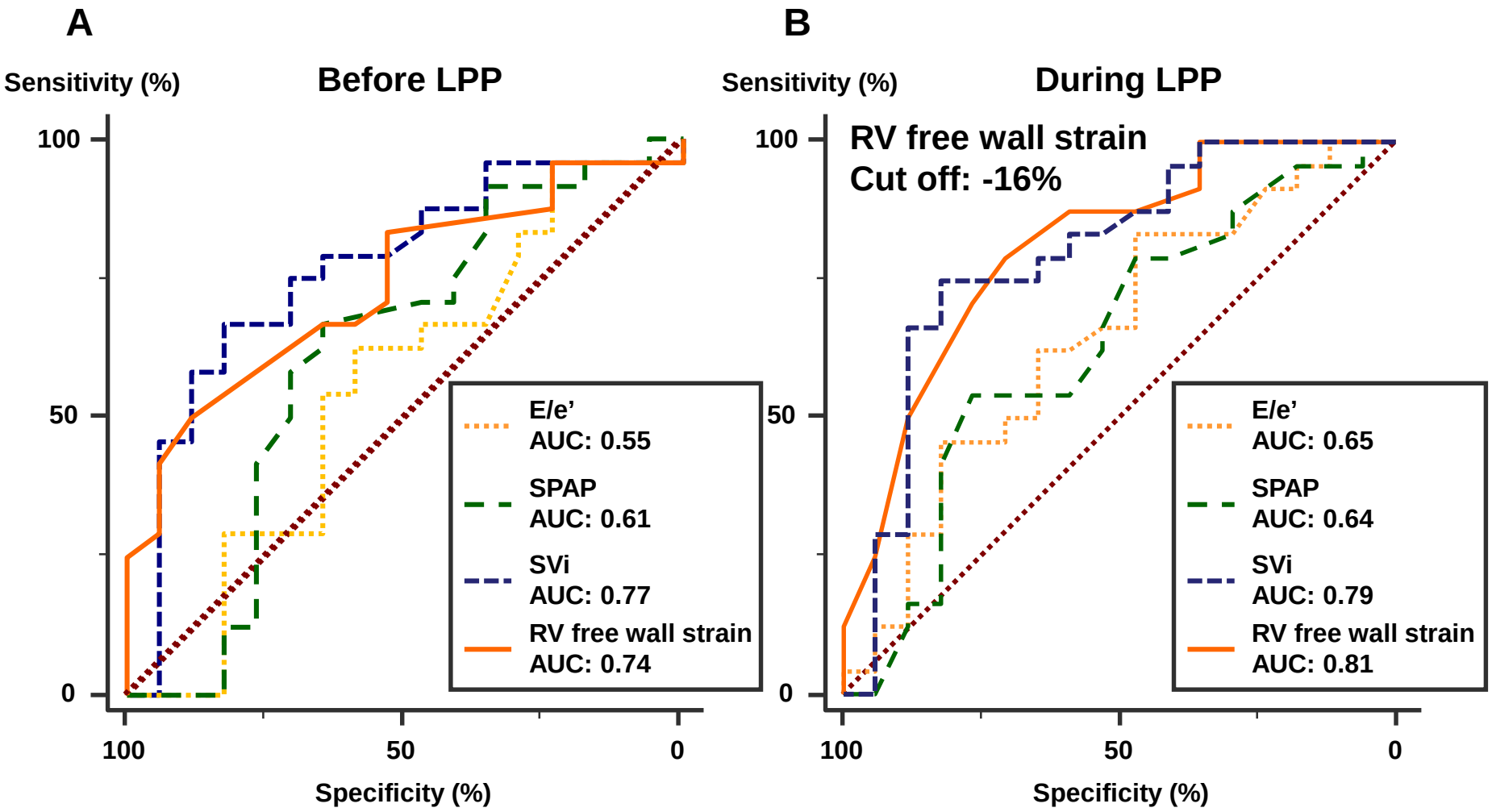


Table 1: Clinical characteristics

	All	Responders to CR	Non-responders to CR	p value
N, %	41	24 (58)	17 (42)	
Age	62±11	63±10	61±13	0.56
Male, %	28 (68)	18 (75)	10 (59)	0.28
HR, bpm	76±19	74±13	80±27	0.28
SBP, mmHg	116±18	117±15	115±21	0.7
DBP, mmHg	69±17	70±17	67±17	0.57
Body mass index, kg/m2	24 (23-28)	23 (22-25)	24 (23-28)	0.09
Diabetes, %	9 (22)	3 (13)	6 (35)	0.09
Hypertension, %	31 (76)	16 (67)	15 (88)	0.12
Etiology				
Ischemic cardiomyopathy, %	36 (88)	22 (92)	14 (82)	0.38
Drugs				
ACEI/ARB, %	39 (95)	22 (92)	17 (100)	0.22
β-blocker, %	24 (59)	16 (67)	8 (47)	0.23
Loop diuretics, %	18 (44)	11 (46)	7 (41)	0.77
CPX				
Peak exercise, Watt	96±37	98±37	94±38	0.74
HR at peak exercise, bpm	129±30	127±37	131±18	0.69
SBP at peak exercise, mmHg	160±30	159±27	163±35	0.66
Peak VO_2, ml/kg/min	14.5±4.6	14.8±5.4	14.1±3.3	0.67
$\Delta VO_2/\Delta WR$, mL/min/W	6.8±2.7	7.2±2.8	5.8±2.3	0.17
VE-VCO_2 slope	33±7	33±7	32±8	0.76
Echocardiography				
Before LPP				
LVEDVi, ml/m^2	65±28	70±28	58±27	0.17
LVEF, %	43±7	45±8	40±5	0.21
SVi, ml/m^2	27±8	30±7	23±8	0.002
LVGLS, %	-14±5	-14±6	-13±6	0.64
E/e'	10.9±4.9	10.5±4.4	11.6±5.6	0.49
Peak SPAP, mmHg	32±6	31±5	33±8	0.39
RVEDAi, cm^2/m^2	10±2	9±2	10±3	0.51
RVFAC, %	36±14	41±15	30±12	0.015
TAPSE, mm	17±5	18±4	15±4	0.022
RV free wall strain, %	-17±5	-19±4	-15±5	<0.001

LAVi, ml/m^2	31±14	29±15	33±13	0.36
During LPP				
LVEDVi, ml/m^2	69±30	75±26	60±34	0.11
LVEF, %	45±7	46±7	44±6	0.69
SVi, ml/m^2	30±10	34±9	25±8	0.004
LVGLS, %	-15±4	-16±5	-14±4	0.29
E/e'	12.6±5.3	10.9±4.0	15.0±6.0	0.011
Peak SPAP, mmHg	36±8	34±7	38±9	0.12
RVEDAi, cm^2/m^2	11±2	11±2	11±2	0.66
RVFAC, %	38±13	42±12	33±12	0.03
TAPSE, mm	18±3	19±3	17±3	0.09
RV free wall strain, %	-17±5	-20±3	-14±4	<0.001

Data are presented as number of patients (percentage), mean ± SD or median (interquartile range).

Abbreviations: HR, heart rate; BP, blood pressure; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; SVi, stoke volume index; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular motion; RVFAC, right ventricular functional area change; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; GLS, global longitudinal strain.

Table 2: CPX parameters at baseline and after CR

	Responders to CR			Non-responders to CR			
	Baseline	After CR	Within-group p value	Baseline	After CR	Within-group p value	Between-group p value
Peak exercise, Watt	98±37	113±42	<0.001	94±38	92±29	0.28	0.04
Resting HR, bpm	74±11	74±14	0.76	78±13	78±10	0.69	0.41
Peak HR, bpm	127±37	136±20	0.17	131±18	134±29	0.25	0.42
Resting BP, mmHg	109±33	102±30	0.15	99±20	90±17	0.08	0.53
Peak BP, mmHg	159±27	174±23	0.002	163±35	163±30	0.68	0.08
ΔVO2/ΔWR, mL/min/W	7.2±2.8	7.8±3.3	0.25	5.8±2.3	5.5±2.9	0.26	0.11
VE-VCO2 slope	33±7	30±7	0.04	32±8	35±14	0.43	0.02

Abbreviations: See Table 1.

Table 3: Uni- and multi- variable Associations of responders to CR

	Univariate logistic regression analysis			Stepwise multivariable logistic regression analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.02	0.96-1.08	0.14	†		
Male gender	2.10	0.55-7.99	0.28			
Body mass index	0.87	0.74-1.03	0.57			
Diabetes	0.27	0.05-1.25	0.09	†		
Ischemic cardiomyopathy	6.00	1.04-34.7	0.04	†		
CPX variables						
Peak exercise*	1.18	0.65-2.13	0.59			
HR at rest*	0.93	0.50-1.74	0.84			
Systolic BP at rest*	0.98	0.60-1.61	0.96			
HR at peak*	0.87	0.46-1.67	0.68			
Systolic BP at peak*	0.86	0.59-1.24	0.39			
Peak VO_2*	1.15	0.60-2.21	0.66			
Echocardiography						
Before LPP						
LVEF*	1.54	0.79-2.99	0.19	†		
SVi*	3.18	1.37-7.39	0.01	†		
LVGLS*	1.17	0.62-2.20	0.64			
E/e'*	0.79	0.42-1.50	0.48			
Peak SPAP*	0.76	0.40-1.43	0.39			
RV free wall strain*	2.40	1.12-5.18	0.03			
During LPP						
LVEF*	1.14	0.61-2.15	0.68			
SVi*	3.23	1.43-7.28	0.005	2.42	1.01-5.88	0.04
LVGLS*	1.52	0.74-2.73	0.29			
E/e'*	0.56	0.29-1.10	0.09	†		
Peak SPAP*	0.59	0.30-1.16	0.13	†		
RV free wall strain*	4.93	1.72-14.1	0.003	3.96	1.31-11.8	0.01

Abbreviations: See Table 1. OR, odds ratio. †Eliminated through the stepwise method. *Odds ratio was calculated per increase of 1 SD