Myocardial work is a predictor of exercise tolerance in patients with dilated cardiomyopathy and left ventricular dyssynchrony

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Short title: myocardial work and exercise tolerance in dilated cardiomyopathy

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ABSTRACT

Background: the assessment of myocardial work (MW) by pressure-strain loops is a recently introduced tool for the assessment of myocardial performance. Aim of the present study is to evaluate the relationship between myocardial work and exercise tolerance in patients with dilated cardiomyopathy (DCM).

Methods: 51 patients with DCM (mean age 57±13 years, left ventricular ejection fraction : 32±9%) underwent cardiopulmonary exercise test (CPET) to assess exercise performance. 22 patients (43%) had left or right bundle branch block with QRS duration > 120 ms. Trans-thoracic echocardiography (TTE) was performed before CPET. The following indices of myocardial work (MW) were measured regionally and globally: constructive work (CW), wasted work (WW), and work efficiency (WE). Left ventricular dyssynchrony (LV-DYS) was defined by the presence of septal flash or apical rocking at TTE.

Results: LV-DYS was observed in 16 (31%) patients and associated with lower LV ejection fraction (LVEF), lower global and septal WE, and higher global and septal WW. In patients with LV-DYS, septal WE was the only predictor of exercise capacity at multivariable analysis (β=0.68, p= 0.03), whereas LVEF (β=0.47, p=0.05) and age (β =-0.42, p=0.04) were predictors of exercise capacity in patients without LV-DYS.

Conclusions: In patients with DCM, LV-DYS is associated with an heterogeneous distribution of myocardial work. Septal WE is the best predictor of exercise performance in these patients.

Keywords: dilated cardiomyopathy, left ventricular dyssynchrony, myocardial work

Word count: 3811

Introduction

The relationship between myocardial performance and exercise tolerance in patients with LV dysfunction and mechanical dyssynchrony has not yet been well understood.

The non-invasive assessment of myocardial work (MW) by pressure-strain loop analysis allows the evaluation of global and regional myocardial function. In patients with LV dysfunction and mechanical dyssynchrony, global and regional alterations of myocardial performance and metabolism have been observed[1],[2],[3]. In these patients, myocardial constructive work has shown to be associated with LV remodeling[4] and survival[5] after cardiac resynchronisation therapy (CRT).

Previous studies have shown that myocardial constructive work correlates with exercise performance in patients with hypertrophic cardiomyopathy[6]. In patients with heart failure and preserved ejection fraction, myocardial constructive work is directly related to LV on exertion and exercise capacity[7]. Despite previous publications suggest an association between MW and LV contractility in CRT candidates[1],[2],[5], no specific study has been addressed at the assessment of the relationship between MW and exercise performance in patients with LV systolic dysfunction.

In this study we investigated the relationship between myocardial work and exercise tolerance in patients with dilated cardiomyopathy (DCM) according to the presence or absence of LV dyssynchrony (LV-DYS).

Methods

Population

51 patients with primary dilated cardiomyopathy from our Regional Competence Center of Genetic Disease were retrospectively included in this study. All the patients were in sinus rhythm and had a good acoustic window. Patients with cardiac resynchronisation therapy or pacemakers were excluded from the study. Clinical data, including age, gender, New York Heart Association (NYHA) functional class, systolic and diastolic blood pressure, lnNTproBNP, medical therapy were assessed for each patient. All patients underwent ECG enregistration, trans-thoracic echocardiography and cardiopulmonary exercice test (CPET). The study was conducted in accordance with the "Good Clinical Practice" Guidelines in the Declaration of Helsinki. All patients provided written informed consent for participation in the study.

Echocardiography

All patients underwent standard transthoracic echocardiography using a Vivid 7 or Vivid E9 and E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 3S or M5S 3.5-mHz transducer. Two-dimensional, color Doppler, pulsed-wave and continuous-wave Doppler data were stored on a dedicated workstation for the offline analysis (EchoPAC, GEHealthcare, Horten, Norway). Leaft atrial (LA) and LV volumes and function were measured by the biplane method, as recommended[8]. Peak early diastolic flow velocity (E), were measured from the apical four chamber view by pulsed-wave Doppler with the sample volume placed between the tips of the mitral leaflets. Pulsed-wave tissue Doppler was used to assess peak early diastolic tissue velocity (e'). The ratio of mitral inflow early diastolic velocity to the average e' velocity obtained from the septal and lateral portions of the mitral annulus (E/e') was calculated to estimate LV filling pressure. Tricuspid annular plane systolic

excursion (TAPSE) was measured by M-mode echocardiography with the curson aligned along the direction of the lateral tricuspid annulus in apical 4-chamber view. In patients with detactable tricuspid regurgitation, pulmonary artery pressure (PAPs) was estimated using the maximal velocity of the tricuspid regurgitation jet (TRV_{max}) and an estimation of the right atrial pressure (RAP) based on the inferion vena cava size and collapsibility according to the following formula: PAPs= 4x $(TRV^{max})^2$ + RAP[8].

LV global longitudinal strain (GLS) assessment

Two-dimensional greyscale images were acquired in the apical 4-, 3-, and 2-chamber views at a frame rate ≥60 frames/s. The recordings were processed using an acoustic-tracking dedicated software (EchoPAC version 112.99, Research Release, GE Healthcare, Horten Norway), to estimate LV global longitudinal strain (GLS).

Myocardial work evaluation.

Myocardial work (MW) and related indices were estimated using a vendor-specific module (EchoPAC Version 202, GE Vingmed Ultrasound, Norway), by the combination of LV strain data and the non-invasive estimation of the LV pressure curve as previously described[1]. The main steps for the estimation of MW are described above.

Briefly, peak systolic LV pressure is assumed to be equal to the peak arterial pressure recorded from the brachial cuff systolic pressure prior to the echocardiographic study. A patient-specific LV pressure curve is then constructed, adjusting LV pressure curve to the duration of the isovolumic and ejection phases, defined by valvular timing events.

Strain and pressure data are synchronized using the R wave on ECG as a common time reference. The area within the PSL provided an index of MW for each myocardial segment. Constructive work (CW) was defined as MW during segmental shortening in systole, and

segmental lenghtening during the isovolumic relaxation time. Wasted work (WW) was defined as the work performed during lengthening in systole and shortening in isovolumic relaxation, associated with energy loss. Work efficiency was defined as the ratio between myocardial CW and the sum of CW and WW. By averaging segmental work data for each segment, global constructive work (GCW), wasted work (GWW) , WE (GWE), and work index were estimated for the entire LV. An example of the estimation of myocardial work efficiency in a patient with and without left ventricular dyssynchrony is depicted in Figure 1.

Assessment of left ventricular dyssynchrony.

Left ventricular dyssynchrony (LV-DYS) was defined by the presence of a septal flash (SF) and or an apical rocking (AR) in different transthoracic echocardiography views. SF was defined by the presence of early septal thickening/thinning detected by M-mode within the isovolumetric contraction period or by the presence of a rapid change of colour in tissue Doppler imaging related to the early and fast contraction of the septum occurring during the isovolumetric period[9]. AR was defined as an apical transverse motion , with short initial septal contraction followed by delayed later wall activation [10].

Cardio-pulmonary exercise testing (CPET).

All subjects underwent a progressive exercise test on an ergocycle (ERG 900; Jaeger, Hochberg, Germany) according to the recommendations[11]. The initial workload of 30 Watts was progressively increased by 15–25 W every 2-minutes until symptoms' onset or maximal exertion was reached. Breath-by-breath gas exchanges were analyzed using an Oxycon device (Jaeger), and the electrocardiogram (CardioSys; Marquette-Hellige, Freiburg, Germany) was continuously monitored to detect eventual arrhythmias and/or repolarization alterations. The maximal oxygen uptake ($VO2_{peak}$) was expressed as mL/min/kg.

Statistical analysis

Continuous variables are expressed by their mean and standard deviation and compared using the Student's *t*-test. Categorical data are expressed in terms of frequencies and percentage and compared by the χ^2 test. To identify correlates of $VO2_{peak}$, univariable linear regression analysis was carried out. After excluding variables showing collinearity (Pearson's coefficient ≥0.6), all the variables that were significant at univariable analysis were entered into a stepwise multivariate regression analysis. A p-value ≤0.05 indicated statistical significance. All statistical analysis was performed using a standard statistical software program (SPSS Version 20.0, IBM, Chicago - IL, USA).

Results.

Clinical, echocardiographic, and CPET data from the overall population and based on the presence of LV dyssynchrony are presented in Table 1.

In the overall population, mean age was 57±13 years, 32 (63%) patients were males and LV-DYS was observed in 16 (31%) patients. There were no significant differences between the groups in NYHA function class, therapy regimens and cardiovascular risk factors. Exercise tolerance was also similar in the two groups. LV volumes tended to be larger in patients with LV-DYS without reaching statistical significance. LVEF was significantly lower in patients with LV-DYS (28±7 vs 34±10 %, p=0.04), and GLS was much more altered in LV-DYS (-13±3 vs -10±3, p=0.001). In the LV-DYS group, GWW was significantly higher, and GWE was lower with respect to patients without LV-DYS. If we look at the regional distribution of MW, Septal CW (CW_{sept}), lateral CW (CW_{lat}) and septal WE ($WE_{sep}t$) were significantly impaired in patients with LV-DYS, whereas septal (WW_{sept}) and lateral WW ($WW_{lat)}$ were significantly increased (Table 1, Figure 2 A-F). LA volume, TAPSE and PAPs were not significantly different in patients with and without LV dyssynchrony.

Parameters related with $VO2_{peak}$

The main correlates of $VO2_{peak}$ at univariable linear regression analysis are listed in Table 1.

In patients with LV-DYS, LVEF, WE_{sept} and CW_{sept} were the only correlates of $VO2_{peak}$.

In patients without LV-DYS, LVEF, age, and lnNT-proBNP emerged as correlates of $VO2_{peak}$.

At the multivariable regression analysis, WE_{sept} (β=0.68, p=0.03) was the only correlate of $VO2_{peak}$ in patients with LV-DYSS, wheras no LV functional parameter was able to predict $VO2_{peak}$ in patients without LV dyssynchrony (Figure 3).

Discussion

The present study demonstrate that in patients with dilated cardiomyopathy, LV-DYS assessed by echocardiography is characterized by a significant increase of GWW and reduction in GWE, which are particularly altered in septum.

In these patients, the residual WE in the septum is the main correlate of exercise tolerance as assessed by the CPET.

Heart failure with reduced ejection fraction is a great therapeutic challenge. When the symptoms resist to first line medical therapy, with no or incomplete recovery of the systolic function, new therapeutics may be used, like CRT, in order to improve LV performance[6]. Recent studies have shown that the presence of LV-DYS in CRT-candidates is a predictor of LV contractile reserve[12] and is able to improve the prognostic value of guideline-based patients' selection for CRT[13]. Interestingly, the predictive role of LV-DYS is maintained also in patients with QRS duration <120 ms[13].

Several methods mostly based on the analysis of timing of longitudinal myocardial velocity peaks have been proposed in order to identify LV-DYS [14]. Nevertheless, the results of the

PROSPECT trial have raised serious doubts regarding the robustness of these parameters, which makes their application unsuitable in everyday clinical practice[15].

The visual identification of LV-DYS by the detection of SF and AR is a relatively recent tool, which have shown to be associated with the response to cardiac resynchronisation therapy (CRT) and survival in patients CRT-candidates [16].

In the present study conducted on patients DCM, LV-DYS was defined by the presence of septal flash and or apical rocking and was detected in 31% of patients.

Despite the great majority of patients with LV-DYS in our population had a widened QRS, a proportion of patient with LV-DYS (25%) did not have LV conduction disturbances.

These findings are in line with previous publications on this topic[13],[17], and support the concept that specific sign of mechanical dyssynchrony assessend by echocardiography can be present regardeless of QRS width.

In our population, LV-DYS was associated with a significant increase in GWW and reduction in GWE, which were paricularly pronounced in the septum.

This redistribution of MW has already been observed[1],[2],[3] in patients with LV-DYS and is associated with a significant decrease of the metabolic activity of the septum with respect to the lateral LV wall[2],[3].

As a matter of fact, previous studies shown that typical LV-DYS is associated with a specific septal deformation pattern, which is caracterised by an early shortening followed by a rebound stretch. The entity of this rebound stretch, is an indirect measure of septal viability and is associated with CRT-reponse [18]and prognosis[19]. These alterations in septal mechanics are associated with local modifications in the metabolic activity and overall myocardial performance. Moreover, experimental studies have shown that LV dyssynchrony in failing hearts generates a “molecular polarization” between the septum and the lateral

wall, which may contribute to the heterogeneity of electromechanics observed in patients with LV-DYS[10].

As a matter of fact, patients with DCM without LV mechanical dyscoordination had a more homogenous distribution of MW-derived parameters.

In patients with HF and reduced LVEF, $VO2_{peak}$ assessed by CPET has shown to be associated with LV contractile reserve during exercise[20] and with prognosis[11].

In current study, LVEF and age were predictors of $VO2_{peak}$ only in patients without LV-DYS. On the contrary, WE_{sept} emerged as the only predictor of exercise performance in patients with LV-DY, irrespective of the fact that LVEF and GLS were significantly more impaired in these patients. Despite the indeniable relationship between LVEF and prognosis in cardiac patients, decreased LVEF is a late and insensitive finding in the natural history of DCM. This might be particularly evident in patients with LV mechanical discoordination, who have significant alteration in regional LV mechanics and local metabolic activity[1],[2],[3].

Aalen et al. have shown that the dyssynchronous ventricle is particularly sensitive to increase in LV afterload. This is particularly evident in the septum with respect to the lateral wall[21], and might explain the relationship between septal work efficiency and exercise performance in patients with LV-DYS. In a small cohort of patients undergoing CRT, Zweerink et al. have shown that the contribution of the septum to LV work varies widely in CRT candidates and that the lower is the septal contribution to myocardial work at baseline, the higher is the acute pump function improvement that can be achieved with CRT[22].

Myocardial work efficiency represents the portion of myocardial energy which is correctly used for the stroke work during LV ejection. This support the hypothesis that exercice impairement in patients with LV-DYS is directly linked to the suboptimal use of energy due to heterogenous electromechanical activation and metabolical distribution. This

interpretation can explain why patients who have higher septal work efficiency have better exercise performances.

Limitations

Our survey have several limitations.1) This is a monocentric, retrospective study conducted on a very limited number of patients. 2) Brachial cuff pressure was used as a non-invasive LV pressure derivative to calculate MW. This might impact the accuracy of the estimation of myocardial work. Nevertheless, the non-invasive method for the estimation of myocardial work has been validated by previous studies and in different hemodynamics condictions[1],[23]. 3) Patients with atrial fibrillation and myocardial ischemia were excluded from the study. This has the merit of making our population quite homogenoeous, but limits the external validity of our study.

Conclusions

In patients with dilated cardiomyopathy, the presence of LV-DYS assessed by echocardiography is associated with a significant increase of GWW, a decrease in GWE, and an heterogeneous distribution of MW. Septal WE was the best predictor of exercise performance in patients with LV-DYS. Further studies should explore whether the relationship between MW, exercise performance and LV contractility has any utility in predicting CRT response in patients with LV-DYS.

Conflict of Interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Disclosures

All authors made substantial contributions to the study.

FL.S., participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article ; E.G. participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval of the version to be submitted. F.S, E.D participated in the critical revision of the article for important intellectual content, and final approval of the version to be submitted

Etichal standars

This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients included in the study gave their informed consent prior to their inclusion in the study. All details that might disclose the identity of the subjects have been omitted.

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Table 1. Main characteristics of the overall population and according to the presence of intraventricular dyssynchrony

	All n=51	No-dyssynchrony n=35 (69%)	LV-Dyssynchrony n=16 (31%)	*p-value*
Clinical data				
Age	57±13	57±13	57±15	0.91
Males	32 (63)	24 (69)	8 (50)	0.17
NYHA	1.7±0.5	1.7±0.5	1.7±0.5	0.85
lnNT-proBNP, pg/ml	6.2±1.2	6.1±1.1	6.4±1.5	0.51
Hypertension, n(%)	9 (18)	4 (11)	5 (31)	0.09
Diabetes, n(%)	6 (12)	5 (14)	1 (6)	0.38
Dyslipidemia, n(%)	11 (22)	9 (26)	2 (13)	0.25
Beta-blockers, n(%)	51 (100)	35 (100)	16 (100)	-
Antialdosteronics, n(%)	15 (29)	11 (31)	4 (27)	0.51
ACEI/ARB, n(%)	45 (88)	31 (89)	14 (88)	0.62
LBBB/RBBB, n(%)	22 (43)	10 (29)	12 (75)	0.002
Echocardiographic data				
LVEDV, ml	190±75	178±66	216±86	0.92
LVESV, ml	129±56	122±53	144±62	0.19
LVEF, %	32±9	34±10	28±7	0.04
E/e'	12±6	12±6	12±5	0.60
LAV_i, ml/m^2	42±15	42±15	41±17	0.84
TAPSE, mm	20±4	20±4	22±5	0.18
PAPs, mmHg*	32±10	30±9	34±11	0.43
GLS, %	-12±3	-13±3	-10±3	0.001
GCW, mmHg%	1325±398	1342±354	1287±491	0.65
GWW, mmHg%	201±147	154±95	304 ±191	<0.0001
GWE, %	85±9	88±7	78 ±10	<0.0001
CW_{sept}, mmHg%	1172±459	1274±398	949±516	0.017
CW_{lat}, mmHg%	1518 471	1472±386	1620±622	0.30
WW_{sept}, mmHg%	283±275	174±98	522 ±376	<0.0001
WW_{lat}, mmHg%	135±88	117±81	176±92	0.02
WE_{sept}, %	78±16	84±9	62± 18*	<0.0001
WE_{lat}, %	90±7	91±7	88±7	0.16
VO2 data				
Maximal workload, Watt	112±43	114±45	107±41	0.58
$VO2_{peak}$, ml/min/Kg	21±6	22±6	21±7	0.79
HR_{max}, bpm	138±24	139±26	135±23	0.85

ACEi, angiotensin conversion enzym inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CW_{lat}, constructive work lateral wall; CW_{sept}, constructive work septal wall; GCW, global constructive work; GWE, global work efficiency; GWW, global wasted work; HR, heart rate; LAV_i, indexed left atrial volume; LBBB, left bundle branch bloch; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF : left ventricular ejection fraction; NYHA, New York heart association funtional class; PAPs, estimated pulmonary artery pressure; RBBB, right buldle branch block; TAPSE,

tricuspid annular plane systolic excursion; VO2 peak, maximal oxygen uptake; WE_{lat}, work efficiency lateral wall; WE_{sept}, work efficiency septal wall; WW_{lat}, wasted work lateral wall, WW_{sept}, wasted work septal wall.

*Tricuspid regurgitation jet was detactable in 24 (47%) patients, 16 (45%) without LV dyssyncrhony and 8 (50%) with LV dyssynchrony.

Table 2. Univariable and multivariable association of exercise capacity (peakVO2) according to left ventricular dyssynchrony.

Variables		**LV dyssynchrony**					**No LV dyssynchrony**			
		Univariable		**Multivariable**			**Univariable**		**Multivariable**	
				Model R^2= 0.55, *p=0.02*					**Model R^2= 0.36, *p=0.01***	
	β	**R^2**	***p-value***	**β**	***p-value***	**β**	**R^2**	***p-value***		***p-value***
Age	-0.34	0.11	0.20			-0.40	0.16	0.02	-0.42	0.04
LnNTproBNP	-0.31	0.09	0.30			-0.43	0.18	0.02	0.12	0.64
LVESV	-0.27	0.08	0.44			-0.29	0.08	0.09		
LVEDV	-0.21	0.04	0.31			-0.18	0.03	0.10		
LVEF	0.52	0.27	0.04	0.23	0.48	0.47	0.20	0.005	0.47	0.05
GLS	-0.36	0.13	0.17			-0.26	0.07	0.13		
GCW	0.25	0.06	0.36			0.11	0.01	0.52		
GWW	-0.34	0.11	0.20			-0.16	0.03	0.35		
GWE*	0.60	0.37	0.01			0.27	0.07	0.11		
CW_{sept}	0.53	0.29	0.03	0.02	0.94	0.11	0.01	0.51		
CW_{lat}	-0.01	0.00	0.97			0.09	0.01	0.62		
WW_{sept}	-0.42	0.17	0.11			-0.09	0.01	0.58		
WW_{lat}	-0.14	0.02	0.60			-0.13	0.02	0.45		
WE_{sept}	0.71	0.50	0.002	0.68	0.03	0.20	0.04	0.25		
WE_{lat}	0.17	0.03	0.53			0.21	0.04	0.24		

Figure captions

Figure 1. Example of the estimation of myocardial work efficiency in a patient with left ventricular dyssynchrony (A) and in a patient without left ventricular dyssynchrony (B)

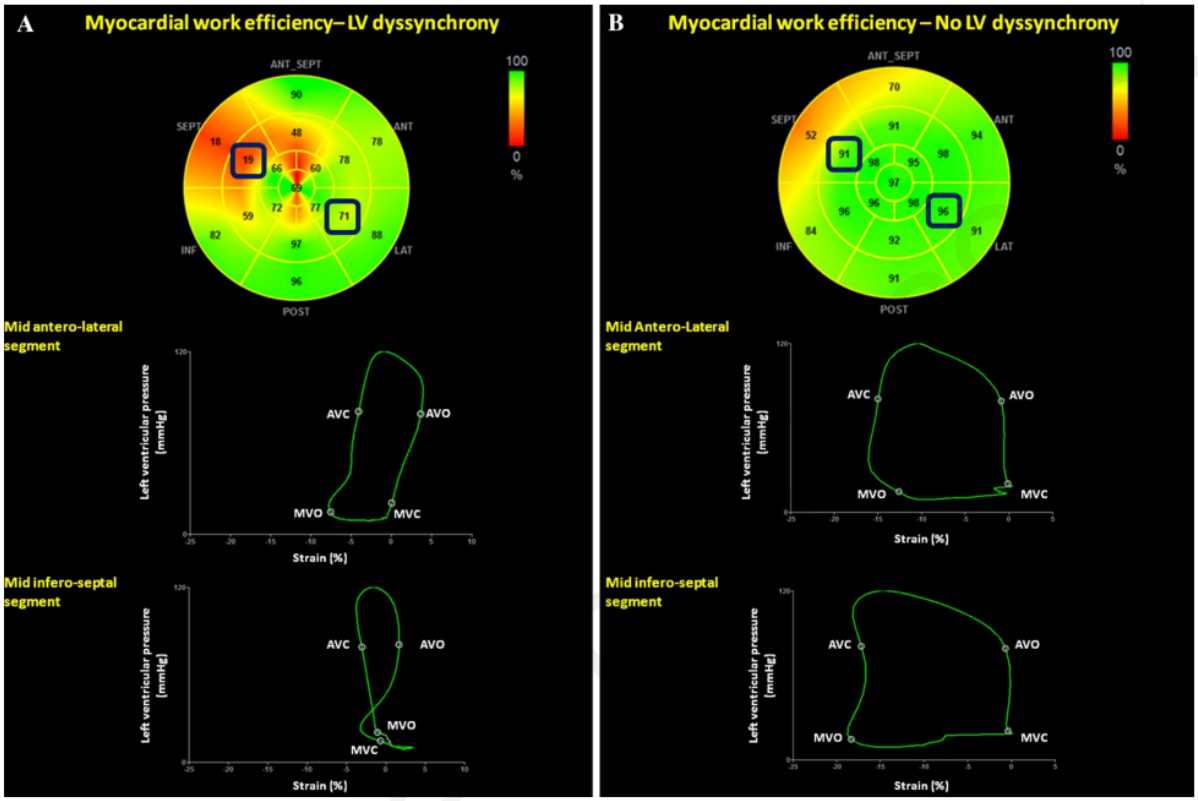

Figure 2 A-F. Myocardial Work parameters according to the presence or absence of LV-dyssynchrony

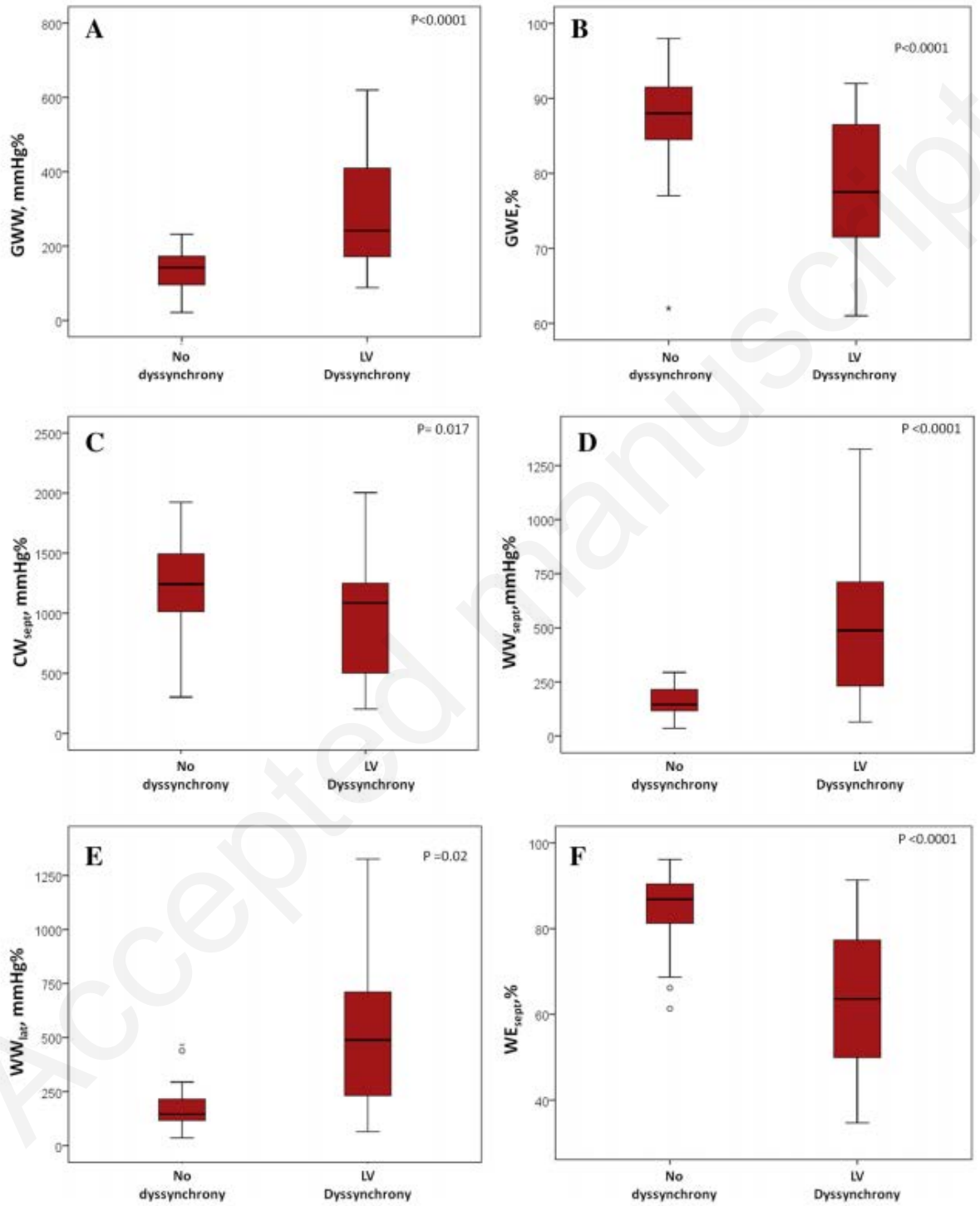

Figure 3 : Association between septal work efficiency (WE_{sept}) and VO2 Peak