ROLE OF RIGHT VENTRICULAR–PULMONARY ARTERY COUPLING IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION

Vo Van Tinh[1], Do Van Chien[2]

ABSTRACT

Objectives*:** To describe the clinical characteristics, right ventricular pulmonary artery (RV-PA) coupling and assess the correlation between RV-PA coupling and six-minute walk distance (6-MWD) in patients with heart failure with reduced ejection fraction (HFrEF). ***Subjects and methods*:** A prospective study with 39 patients with heart failure with HFrEF was recruited at 108 Central Military Hospital from December 2022 to October 2023. ***Results: A total of 39 patients were enrolled to the study with a majority of male (76.9%), mean age 63.7±15.7 years. Based on univariate and multivariate analysis, there is no correlation between right ventricular pulmonary artery coupling and 6-MWD, as evidenced by parameters including TAPSE/PASP (r=0.111, β=37.09, p=0.499), FAC/RVSP (r=0.012, β=1.29, p=0.944), and S'/RVSP (r=0.216, β=105, p=0.186). Nevertheless, there is a negative correlation between FAC/RVSP and S'/RVSP with LAVi, with respective values of (r = -0.522, β = -11.97, p-value = 0.001) and (r= -0.487, β = -0.005, p-value = 0.002). ***Conclusion*:** RVPAc cannot be used to predict exercise in HFrEF. Among echocardiographic RVPAc ratios, FAC/RVSP and S'/RVSP are correlated with left atrial volume index.

***Keywords**: Heart failure with reduced ejection fraction, right ventricular artery pulmonary coupling, exercise intolerance, six-minute walk test.*

[1] *College of Health Sciences, VinUniversity*
[2] *Cardiovascular Intensive Care Unit, 108 Military Central Hospital*
Responsible person: Do Van Chien
Email: vmechiendo@gmail.com
Date of receipt: 26/2/2024
Date of scientific judgment: 18/3/2024
Reviewed date: 25/3/2024

I. INTRODUCTION

Heart failure (HF) has been characterized as a pervasive global pandemic, affecting an estimated 64.3 million individuals worldwide in 2017[1]. This prevalence is anticipated to escalate, primarily attributable to enhance survival rates subsequent to a HF diagnosis, facilitated by the accessibility of evidence-based treatment and the overall increased life expectancy within the general population.

Exercise capacity has also been used to determine prognosis of heart failure patients because it can be quantified objectively with a couple modalities such as the six-minute walk test or cardiopulmonary exercise test (CPET). The association between reduced exercise capacity in heart failure patients and poor outcomes has been well-documented. Indeed, in the study of Ikeda and colleagues in 2017 demonstrated HF patients with abnormal 6-MWD < 340m had a significantly higher risk of cardiac death than those with 6-MWD ≥ 340m[2]. Moreover, in the management of patients with heart failure, particularly those with reduced ejection fraction, the anticipation of exercise intolerance assumes a pivotal role. Ensuring patients have timely access to innovative or advanced therapies are crucial for positively

influencing prognosis and reducing medical costs.

It has been proposed as a straightforward, easily tolerated, cost-effective alternative to the 6-MWT. We do not regularly evaluate exercise capacity using the 6-MWT for all heart failure patients, and not everyone qualifies for this test. Echocardiography could potentially serve as an alternative potential modality to the 6-MWT due to its simplicity, reproducibility and less time consuming in the clinical practice. Right ventricular (RV) function and pulmonary arterial pressure have an inseparable relationship with left ventricular (LV) function impaired RV contractility and lower stroke volume lead to reduced LV preload[3]. Because of RV dysfunction may be derived from LV failure due to elevated pulmonary vascular resistance, reflecting the pivotal role of arterio-ventricular interaction. Therefore, right ventricular function parameters could potentially serve as a reasonable alternative to 6-MWT in predicting exercise intolerance in HF patients, particularly HFrEF patients. Legris and colleagues suggest that TAPSE/PASP coupling might serve as a possible substitute parameter for the six-minute walk test[4].

The TAPSE/PASP ratio represents to right ventricular-pulmonary artery coupling, reflecting the relationship between RV contractility and pulmonary vasculature resistance. RV coupled with RV when RV function and its afterload are appropriately matched, it is defined as the ratio of RV end-systolic elastance (Ees) to PA elastance (Ea). Several right ventricular parameters have been used as noninvasive measures serving as surrogates for Ees/Ea, including TAPSE/PASP, RVLS/RVSP, RVFAC/RVSP, RVEF/PASP, SV/ESV, and S'/RVSP[5]. We initiated this study in patients with heart failure with reduced ejection fraction with two objectives: Describe the clinical characteristics, assess right ventricular pulmonary artery (RV-PA) coupling through echocardiography, exercise capacity measured by the six-minute walk test (6-MWT) and assess the correlation between RV-PA coupling and six-minute walk distance (6-MWD) in HFrEF patients.

II. SUBJECTS AND METHODS

2.1. Subjects

39 patients diagnosed with heart failure with reduced ejection fraction sought care in both outpatient and inpatient settings at 108 Military Central Hospital from December 2022 to October 2023.

***2.1.1. Inclusion criteria*:** Heart failure (NYHA I-III), LVEF < 40%, able to walk on a flat floor; agree to participate in the study.

2.1.2. Exclusion criteria: Previous cardiac surgery, major cardiovascular surgery, planned coronary revascularization, place implantable cardioverter-defibrillator, cardiac resynchronization therapy, unstable angina/myocardial infarction (MI) and/or cardiac intervention within previous 6 weeks, patients who underdent major organ transplant or intent to transplant, anemia with hemoglobin (Hgb) <10 g/dL, acute heart failure, participants are unable to walk on the flat floor.

2.2. Methods

2.2.1. Study design: Cross-sectional, prospective study

2.2.2. Recruitment process and data collection: a certified echocardiography was trained to obtain adequate image quality, will be responsible for the quality. The investigator will assist technician in

conducting the six-minute walk test in the general cardiology ward.

2.2.3. Statistical analysis

SPSS (IBM coop, USA) Statistics software version 25.0 will analyze all data. Descriptive statistics for normally distributed quantitative variables will include mean and standard deviation (mean ± SD); Correlation analysis will use Pearson correlation for normally distributed quantitative variables and Spearman. A p-value < 0.05 will determine a statistically significant.

III. RESULTS

3.1. Characteristics of the study population

A total of 39 patients were enrolled to the study. The characteristics of the overall population are shown in **Table 1**, with a majority of male (76.9%), mean age 63.7±15.7 years, the body mass index (BMI) of group 6-MWD < 340 m and 6-MWD ≥ 340 m are homogenous (22 ± 2.9 and 22.5 ± 3.2), and New York Heart Association (NYHA) class I (43.6%), II–III (56.4%).

Table 1. ***Baseline characteristics***

Dermographics	**Overall population (n=39)**	**6-MWD < 340m (n=14)**	**6-MWD ≥ 340 m (n=25)**	**p**
Age, years (mean ± SD)	63.7±15.7	73.8 ± 11.2	57.5 ± 14.9	0.001
Male (n, %)	30(76.9)	7(50)	23(92)	0.003
BMI (kg/m^2)	22.3±3	22 ± 2.9	22.5 ± 3.2	0.636
SBP (mmHg)	118.9±10.5	117.5 ± 11.9	119.6 ± 9.9	0.558
DBP (mmHg)	76.2±7.9	75.2 ± 9.9	76.8 ± 6.8	0.555
HR (beats/minute)	76.9±7.6	77.9 ± 9.8	76.2 ± 6.2	0.514
NYHA (n, %)				
1	17(43.6)	2(14.3)	15(60)	0.016
2	15(38.5)	9(64.3)	6(24)	
3	7(17.9)	3(21.4)	4(16)	
Medical history (n, %)				
Hypertension	17(43.6)	8(57.1)	9(36)	0.201
Prior HF hospitalization within 12 months	8(20.5)	4(28.6)	4(16)	0.351
CABG/ PCI	11(28.2)	5(35.7)	6(24)	0.435
Prior ICD/pacemaker	3(7.7)	2(14.3)	1(4)	0.248
Afib/flutter	5(12.8)	3(21.4)	2(8)	0.229
Chronic coronary disease	14(35.9)	6(42.9)	8(32)	0.498
Diabetes	9(23.1)	4(28.6)	5(20)	0.542
Stroke/TIA	3(7.7)	0(0)	3(12)	0.177
Chronic kidney disease	7(17.9)	3(21.4)	4(16)	0.672

3.2. Echocardiographic characteristics

A significant difference exists between 6-MWD < 340 m and 6-MWD ≥ 340 m groups (35.5 and 26.5, p=0.006). LV diastolic parameters (lateral e', septal e', E/e', LAVi, peak TR velocity) are similar. No difference in right ventricular systolic function is observed between two groups. Right ventricular pulmonary artery coupling, assessed by TAPSE/PASP (0.59 ± 0.16 and 0.66 ± 0.24, p=0.294), FAC/RVSP (1.56 ± 0.52 and 1.64 ± 0.7, p=0.715), S'/RVSP (0.395 and 0.45, p=0.057), is also not different between two groups, 6-MWD < 340 m and 6-MWD ≥ 340 **(Table 2).**

Table 2. *Echocardiographic parameter characteristics*

Left ventricular parameters (median, IQR)	Overall population (n=39)	6-MWD < 340m (n=14)	6-MWD ≥ 340 m (n=25)	p
LVEDD (mm)	56.5(50-62.25)	50.5(46.5-66.75)	57(52.5-61)	0.303
LVESD (mm)	46(39-53)	39.5(36-56.5)	48(40.5-52.75)	0.289
EF Simpson (%)	32(25.8-37.3)	35.5(28.75-39)	26.5(22.25-35.75)	0.006
LAVi (ml/m^2)	32.5(27.5-42.3)	37(29-44)	31.5(26-42.75)	0.178
Right ventricular parameters (n ± SD)				
RV-FAC, %	37.3± 9.30	38.07 ± 9.0	36.8 ± 9.6	0.688
TAPSE, mm	18.75± 4.10	17.93 ± 3.47	19.22 ± 4.4	0.353
PASP, mmHg	31.5± 8.60	32.57 ± 10.7	30.84 ± 7.3	0.553
TAPSE/PASP	0.64 ± 0.21	0.59 ± 0.16	0.66 ± 0.24	0.294
FAC/RVSP	1.61 ±0.63	1.56 ± 0.52	1.64 ± 0.7	0.715
S'/RVSP (median, IQR)	0.43(0.38-0.55)	0.395(0.35-0.4525)	0.45(0.4-0.575)	0.057

3.3. Six-minute walk test

The mean 6-MWD in the entire study population was determined to be 356.4 ± 71.1. A notable statistical difference in the mean six-minute walk distance was observed between male and female participants, with a p-value of 0.004.

3.3. Predictors of six-minute walk test

Univariate analysis of predictors for 6-MWD are summarized in **Table 3**. No correlation exists between right ventricular pulmonary artery coupling and 6-MWD, seen in TAPSE/PASP (r=0.111, β=37.09, p=0.499), FAC/RVSP (r=0.012, β=1.29, p=0.944), and S'/RVSP (r=0.216, β=105, p=0.186). Multivariate analysis also shows no correlation **(Table 3).** ROC analysis indicates thresholds for 6-MWD ≥ 340m: TAPSE/PASP (cut off=0.59, sensitivity=64%, specificity=71.4%, p=0.242), FAC/RVSP (cut off=2.05, sensitivity=28%, specificity=92.9%, p=0.693), and S'/RVSP (cut off=0.42, sensitivity=72%, specificity=64.3%, p=0.057), all without statistical significance.

Table 3. *Correlation among RV-PA coupling parameters (TAPE/PASP, FAC/RVSP, S'/RVSP) and 6-MWD under univariate and multivariate analysis.*

Parameters	Univariate analysis			Multivariate analysis
	r	β	p	p
TAPSE/PASP ratio	0.111	37.09	0.499	0.448
FAC/RVSP	0.012	1.29	0.944	0.192
S'/RVSP	0.216	105	0.186	0.106

3.4. Left side parameters and right ventricular pulmonary artery coupling

The only parameter associated with RV-PA coupling was the left atrial volume index (LAVi), as summarized in **Table 4**. A weak correlation was observed between LAVi and FAC/RVSP (β=-11.97, R^2=0.272, p=0.001), as well as between LAVi and S'/RVSP (β=-48.31, R^2=0.237, p=0.002).

Table 4. ***Correlation between RV-PA coupling and LAVi***

Parameters	Univariate analysis			Multivariate analysis
	β(95%CI)	R^2	p	p
TAPSE/PASP ratio	-17.4(-39.36; 4.56)	0.065	0.117	0.223
FAC/RVSP	-11.97(-18.49; -5.45)	0.272	0.001	0.028
S'/RVSP	-48.31(-77.16; -19.46)	0.237	0.002	0.150

IV. DISCUSSION

The main findings of our study is that among echocardiographic RVPAc ratios, FAC/RVSP and S'/RVSP shown to be correlated with LAVi but not the other echo parameters and all RVPAc ratios are not able to predict exercise ability in HFrEF patients.

In our study, the lack of correlation between TAPSE/PASP and 6-MWD (r=0.111, β=37.09, p=0.499) **(Table 4)** contrasts with Legris' findings, where TAPSE/PASP correlated with 6MWD in a subgroup (β = 72.4; p = 0.04) with a larger sample size (100 patients)[4]. Our study, with 39 participants, featured less severe patients (76.9% in NYHA I-II, 17.9% in NYHA III) and a higher LVEF (32, range 25.8-37.3) compared to Legris (mean LVEF 26.60 ± 7.74). Lower LVEF and higher NYHA classification may intensify lung congestion, affecting PASP. Univariate analysis of FAC/RVSP and S'/RVSP revealed no correlation with 6-MWD, and multivariate analysis did not find significant correlations (p-values: 0.448, 0.192, 0.106, respectively). Despite our efforts, these results suggest that other unexplored factors may influence exercise capacity. The intricate nature of relationships within our study cohort, coupled with sample size limitations and patient population characteristics, should be considered when interpreting these findings.

Right ventricular pulmonary artery coupling and left sided parameters

Our multivariate analysis revealed a significant correlation between FAC/RVSP and LAVi (r = -0.522, p = 0.028). This correlation remained significant in univariate analysis (r = -0.522, p = 0.001), yielding the regression equation y = 57.4 – 11.97x. Similarly, S'/RVSP correlated with LAVi in univariate analysis (β=-48.31, R2=0.237, p=0.002). This suggests that FAC/RVSP and S'/RVSP could potentially predict changes in LAVi and, consequently, left ventricular dysfunction. This insight offers a new perspective on selecting RV-PA coupling parameters, proposing FAC/RVSP or S'/RVSP as more insightful indicators for predicting diastolic function or LAVi compared to alternatives like TAPSE/PASP.

V. CONCLUSION

Right ventricular – Pulmonary artery coupling cannot be used to predict exercise. Among RVPAc ratios, FAC/RVSP and S'/RVSP are correlated with LAVi.

REFERENCES

1. **GBD 2017** Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7
2. **Ikeda I, Yamada T, Morita T, et al.** P3983ADMIRE-HF risk score improves the

prognostic power of 6-minute walk test in patients with chronic heart failure: a long-term follow-up comparative study. *European Heart Journal*. 2017;38(suppl_1):ehx504.P3983. doi:10.1093/eurheartj/ehx504.P3983

3. **Voelkel NF, Quaife RA, Leinwand LA, et al.** Right Ventricular Function and Failure. *Circulation*. 2006;114(17):1883-1891. doi:10.1161/CIRCULATIONAHA.106.632208
4. **Legris V, Thibault B, Dupuis J, et al.** Right ventricular function and its coupling to pulmonary circulation predicts exercise tolerance in systolic heart failure. *ESC Heart Fail*. 2022;9(1):450-464. doi:10.1002/ehf2.13726
5. **He Q, Lin Y, Zhu Y, et al.** Clinical Usefulness of Right Ventricle–Pulmonary Artery Coupling in Cardiovascular Disease. *J Clin Med*. 2023;12(7):2526. doi:10.3390/jcm12072526
6. **Benjamin EJ, Virani SS, Callaway CW, et al.** Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation*. 2018;137(12):e67-e492. doi:10.1161/CIR.0000000000000558
7. **Guazzi M, Bandera F, Pelissero G, et al.** Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. *Am J Physiol Heart Circ Physiol*. 2013;305(9):H1373-1381. doi:10.1152/ajpheart.00157.2013
8. **Guazzi M, Naeije R, Arena R, et al.** Echocardiography of Right Ventriculoarterial Coupling Combined With Cardiopulmonary Exercise Testing to Predict Outcome in Heart Failure. *Chest*. 2015;148(1):226-234. doi:10.1378/chest.14-2065
9. **Ghio S, Guazzi M, Scardovi AB, et al.** Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur J Heart Fail*. 2017;19(7):873-879. doi:10.1002/ejhf.664
10. **Bosch L, Lam CSP, Gong L, et al.** Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. *Eur J Heart Fail*. 2017;19(12):1664-1671. doi:10.1002/ejhf.873