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Original Article

A new prognostic marker in failing heart: Peak mitral regurgitation velocity to left ventricular outflow tract time velocity integral ratio

Kalp yetersizliğinde yeni bir prognostik belirteç: Pik mitral regurjitasyon velositesinin sol ventrikül çıkış yolu velosite zaman integraline oranı

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Abstract

Aim: Systemic vascular resistance (SVR) is useful for risk estimation and therapy guidance in HF. It has been shown that the ratio of peak mitral regurgitation velocity (MRV) to left ventricular outflow tract velocity-time integral (LVOT VTI) correlated positively with SVR. We aimed to assess the association of MRV/LVOT VTI ratio with established prognostic markers and its prognostic role for predicting one year and long term composite end-points in patients with HF and reduced ejection fraction (HFrEF).

Material and Methods: We prospectively enrolled a total of 72 patients with HFrEF and 10 control subjects. Patients were followed up patients for median 40.5 months. Primary composite endpoint (CEP) was defined as any of these outcomes including requiring mechanical circulatory support, cardiac transplantation, and all-cause mortality.

Results: CEP(+) patients had higher MRV/LVOT VTI ratio than others (0.48±0.15 vs. 0.39±0.18 p=0.012). MRV/LVOT VTI ratio was positively correlated with functional status (β=0.539, p=0<001), serum BNP level (β=0.479, p<0.001),troponin I (β=0.415, p<0.001), and Uric acid level (β=0.235 p=0.018) and negatively correlated with SEATTLE score derived life expectancy (β=-0.248, p=0.032). Adjusted with other parameters, every 0.1 increase in MRV/LVOT VTI ratio increased the one-year CEP risk by 37% and long-term CEP risk by 35%. In Kaplan Meier analysis, patients with MRV/LVOTVTI ratio ≥ 0.39 had more long-term CEP compared to others.

Conclusion: MRV/LVOT VTI ratio seemed to be a useful predictor of poor prognosis associated with other established HF prognostic markers.

Keywords: systemic vascular resistance; heart failure and reduced ejection fraction; peak mitral regurgitation velocity to left ventricular outflow tract velocity-time integral

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Öz

Amaç: Sistemik vaskuler rezistans (SVR), kalp yetersizliğinde risk tahmini ve tedavi klavuzluğunda kullanışlıdır. Pik mitral regurgitasyon velositesinin (MRV) sol ventrikül çıkış yolu velosite zaman integraline (LVOT VTI) oranının SVR ile pozitif yönde korele olduğu gösterilmiştir. Bu çalışmada düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEF-KY) hastalarında MRV/LVOT VTI oranının bilinen prognostik belirteçlerle ilişkisi ve 1 yıllık ve uzun dönem birleşik son noktayi öngördürmedeki prognostik rolünü değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Prospektif olarak 72 DEF-KY hastası ve 10 sağlıklı kontrolü çalışmaya dahil ettik. Hastalar medyan 40.5 ay takip edildi. Birincil birileşik son nokta (BSN) mekanik dolaşım desteği, kalp transplantasyonu ve tüm nedenlere bağlı ölüm olarak tanımlandı.

Bulgular: BSN(+) hastalarında daha yüksek MRV/LVOT VTI oranı saptandı (0.48±0.15 vs. 0.39±0.18 p=0.012). MRV/LVOT VTI oranı fonksiyonel sınıf (β=0.539, p=0<001), troponin I (β=0.415, p<0.001), serum BNP seviyesi (β=0.479, p<0.001), ve ürik asit düzeyi (β=0.235 p=0.018) ile pozitif yönde korele ve SEATTLE skor ile elde edilen yaşam beklentisi (β=-0.248, p=0.032) ile negatif korele izlendi. Diğer parametrelerle birlikte MRV / LVOT VTI oranındaki her 0,1 artış bir yıllık BSN riskini % 27 ve uzun dönem BSN riskini % 24,6 artırdı. Kaplan Meier analizinde MRV / LVOTVTI oranı ≥ 0.39 olan hastalarda diğerlerine göre uzun dönemde daha fazla BSN görüldü.

Sonuç: MRV / LVOT VTI oranı diğer bilinen DEF-KY prognostik göstergeleri ile ilişkili olarak, kötü prognozun faydalı bir belirteci olarak görünmektedir.

Anahtar kelimeler: sistemik vaskular rezistans; kalp yetersizliği; pik mitral regurgitasyon velositesinin sol ventrikül çıkış yolu velosite zaman integraline oranı

Introduction

In patients with both acute and chronic decompensated heart failure (HF), invasive hemodynamic indices like cardiac index and pulmonary capillary wedge pressure have been widely used [1]. In addition to these indices, systemic vascular resistance (SVR) is useful for risk estimation and therapy guidance in advanced HF [2]. Particularly for the patients with cardiogenic shock, SVR assessment may provide better recognition of ineffective tissue perfusion.

SVR is estimated by the ratio of the transsystemic pressure gradient to the transsystemic flow [3]. However, the only accepted method for SVR estimation is invasive hemodynamic monitoring and using invasive techniques such as routine right heart catheterization for this purpose may lead to potential procedural risks. Fortunately, two-dimensional (2D) echocardiography and Doppler provide the noninvasive assessment of left ventricular function and intracardiac hemodynamics [4–7].Therefore, as a noninvasive technique, Doppler echocardiography may be useful for the estimation of pressure and flow, as well as an indirect estimation of SVR. It has been shown that the ratio of peak mitral regurgitation velocity (MRV) to left ventricular outflow tract velocity-time integral (LVOT VTI) correlated positively with SVR obtained by invasive hemodynamic monitoring [2]. In the literature, there is limited data about the prognostic value of MRV/LVOT VTI ratio in HF.

Herein, we aimed to assess the association of MRV/LVOT VTI ratio with established prognostic markers and its prognostic role for predicting one year and long term composite end-points in patients with HF and reduced ejection fraction (HFrEF)

Material And Methods

Study Participants and Comorbidities

We prospectively enrolled a total of 72 patients with HFrEF and age- and gender-matched 10 apparently-healthy control subjects between November 2013 and April 2014. Patients were followed up for median 40.5 months (min. 0-max 75 months. Patients' comorbidities, medications, physical examination, and laboratory findings were recorded. Patients were categorized according to their New York Heart Association (NYHA) functional classes and cardiomyopathy etiology (ischemic vs nonischemic). Patients with poor echocardiographic windows, primary valvular disease, known malignancy, active inflammatory conditions, cerebrovascular diseases were excluded. We excluded severe mitral regurgitation (grade 4 MR) and also very mild mitral regurgitation which not permit to evaluate MRV. Patients with left Ventricular Ejection Fraction <40 was regarded as HFrEF by

contemporary guidelines. Patients' risk factors were also noted: smoking (smoking history within the last month defined current smoker, otherwise ex-smoker), diabetes mellitus (fasting blood glucose >125 mg/dL, HbA1c >6.5%, and current usage of antidiabetic medication) and hypertension (defined as systolic blood pressure 140 mmHg and/or diastolic blood pressure 90 mmHg or current antihypertensive medication). Patients' medications at admission and discharge as well as during one-year follow-up were also noted.

Admission kidney and liver function tests were measured from routine blood work and cardiac troponin I, Brain Natriuretic Peptide (BNP), and serum uric acid levels were obtained. Patients' baseline vital signs (systolic and diastolic blood pressure, heart rate) were also recorded. SEATTLE derived life expectancy was calculated using The Seattle Heart Failure Model [8] .

Informed consent was obtained from all the patients participating in the study, and all the researchers signed the Declaration of Helsinki. Approval for the study was granted by the local ethics committee.

Echocardiographic Examination and MRV/ LVOT VTI Ratio

Patients' echocardiographic examinations were done by using a 3.5-MHz transducer (Vivid 7, GE-Vingmed Ultrasound AS, Horten, Norway).Echocardiographic examinations were done to ambulatory patients without HF exacerbations who maintained at least 30 minutes supine position. All echocardiographic examinations performed according to the recommendations of the American Society of Echocardiography [9]. Left ventricular ejection fraction (LVEF) was assessed by modified Simpson Method. Left ventricular dimensions were evaluated by M mode recordings. Mitral and tricuspid regurgitation was graded by color flow area assessment. MRV was measured in apical four-chamber view by continuous Doppler. LVOT VTI was measured in apical three-chamber view, 3-5 mm length sample volume was positioned in left ventricular side just proximal before flow acceleration.

Assessment of Clinical Outcomes

Primary composite endpoint (CEP) was defined as patients confronting any of these outcomes including requiring mechanical circulatory support, cardiac transplantation and suffering all-cause mortality.

Follow-up data of all the patients were obtained from the hospital database and records of the Ministry of Health. Patients, whose follow- data could not be received through these systems, were reached by telephone interview with patients or their relatives

Statistical Analysis

The continuous variables were reported as the mean±standard deviation (SD) and the categorical variables were expressed as the number of patients and percentages. Kolmogorov-Smirnov tests were used to assess the normality of the data distribution. The correlation analysis was made with Pearson and Spearman's correlation coefficient. We analyzed the effects of different variables on the occurrence of CEP in univariate Cox regression analysis and determined the variables with an unadjusted p-value <0.1 as potential risk markers. In addition to MRV/LVOT VTI parameter, we included the contributors of this formula to the univariate analysis and evaluated the individual predictive value of each parameter. Multicollinearity analysis was performed before multivariate analysis. We composed the final model by using backward elimination at multivariate Cox regression analysis. Receiver operating curve (ROC) analysis was performed to investigate the efficacy of MRV/LVOT VTI ratio in predicting one-year and long-term mortality and the cut-off values were determined. Based on the cut-off values, patients were divided into two groups for MRV/LVOT VTI ratio parameter. Kaplan–Meier curve analysis was used for survival analysis in between these groups. Statistical significance was defined as $P < 0.05$. Data were analyzed by using SPSS 20.0 software.

Reproducibility Analysis

To evaluate the intraobserver variability of MRV/LVOT VTI ratio measurements, 20 patients were randomly selected and second set of echocardiographic examinations of these patients were performed on consecutive days. To evaluate interobserver variability, two echocardiographers (MSC and EHOC) examined the same patients on the same day separately. The intraobserver agreement on MRV/LVOT VTI ratio measurement was very good: the intraclass coefficient of correlation was 0.96. The interobserver agreement was also very good: the intraclass coefficient correlation was 0.94.

Results

MRV/LVOT VTI ratio was almost two times higher in HF group (0.47±0.16 vs. 0.26±0.04, p<0.001 respectively). While comparing patients with CEP (-), CEP(+) patients had higher MRV/LVOT VTI ratio than others (0.48±0.15 vs. 0.39±0.18 p=0.012). The comparison of baseline characteristics, laboratory and echocardiographic parameters between CEP (+) and CEP (-) groups were summarized in Table 1 and Table 2. There was an incremental trend for MRV/LVOT VTI ratio through advanced HF classes, and it reached the highest in NYHA class 3-4 group (p<0.001).

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Table 1. Baseline characteristics and physical examination findings of study cohort

Variable	CEP (+) (n=51)	CEP (-) (n=31)	P
Age, years	57.2±14.2	55.4±13.8	0.564
Sex, male, n (%)	39 (76.5)	26 (83.9)	0.423
BMI	27.8±5.3	27.7±4.8	0.877
Ischemic CMP, n (%)	36 (70.6)	11 (35.5)	0.002
Hypertension, n (%)	22 (43.1)	17 (54.8)	0.304
Hyperlipidemia, n (%)	18(35.3)	8(25.8)	0.371
DM, n (%)	28 (54.9)	10 (32.3)	0.046
NYHA III-IV, n (%)	38 (74.5)	8 (25.8)	<0.001
Systolic Blood Pressure, mmHg	103.7(15.9)	118.1±22.3	0.001
Diastolic Blood Pressure, mmHg	65.3(12.5)	71.7(13.7)	0.040
Raller, n (%)	32 (62.7)	9 (29.0)	0.003
PND,n (%)	43(84.3)	10(32.3)	<0.001
Pretibial edema, n (%)	30(58.8)	5(16.1)	<0.001
Diuretic, n (%)	46 (90.2)	15 (48.4)	<0.001
ACEinh/ARB, n (%)	46(92.0)	25(86.2)	0.411
Beta blocker, n (%)	46(92.0)	24(82.8)	0.213
MRA, n (%)	34(68.0)	17(58.6)	0.401
Atrial fibrillation, n (%)	10 (19.6)	3 (9.7)	0.233
MCS, n (%)	6 (11.8)	0 (0)	0.060
All-cause Mortality, n (%)	47 (92.2)	0 (0)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CEP, composite endpoint; CMP, cardiomyopathy; DM, Diabetes mellitus; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnea.

Table 2. Laboratory and echocardiographic parameters of study cohort

Variable	CEP (+) (n=51)	CEP (-) (n=31)	P
Hemoglobin, g/dL	12.5±1.9	13.7±1.8	0.008
HCT(%)	39.8±5.1	41.6±5.2	0.115
WBC	7.7±2.5	7.1±1.8	0.246
hsCRP, mg/L	31.8±25.6	9.8±8.5	0.165
Glucose, mg/dL	144.6±70.4	130.2±62.6	0.352
Creatinine, mg/dL	1.4±0.6	1.0±0.5	0.003
AST,	53.4±118.4	24.7±1.9	0.191
Uric acid, mg/dL	9.5±2.3	6.7±1.9	<0.001
Albumin, mg/dL	3.7±0.5	4.3±0.4	<0.001
BNP,pg/mL	1766.5±1377	1088.7±1027	0.023
Sodium, mmol/L	133.9±5.3	137.2±4.5	0.005
Potassium, mmol/L	4.4±0.7	4.3±0.5	0.532
LVEF, %	24.1±10.2	37.2±17.9	<0.001
LVEDD, mm	64.6±9.5	55.0±9.6	<0.001
LVESD, mm	55.1±10.3	41.8±12.8	<0.001
LAD,mm	49.0±7.5	41.8±7.6	<0.001
TAPSE,mm	14.9±4.7	20.1±5.1	<0.001
MR grade 2 and 3	25 (49.0)	9 (29.0)	0.075
MRV	4.3±0.5	5.0±0.7	<0.001
LVOT VTI	10.3±4.0	14.7±5.8	<0.001
MRV/LVOT VTI	0.48±0.15	0.39±0.18	0.012

Abbreviations: CEP, composite endpoint; HCT, hematocrit; hsCRP, high sensitive C-reactive protein; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVOT VTI; left ventricular outflow tract velocity time integral; MRV, mitral regurgitation velocity; TAPSE, Tricuspid Annular Plane Systolic Excursion;

MRV/LVOT VTI ratio was positively correlated with functional status (β=0.539, p=0<001), serum BNP level (β=0.479, p<0.001), troponin I (β=0.415, p<0.001), and Uric acid level (β=0.235 p=0.018) and negatively correlated with SEATTLE score derived life expectancy (β=-0.248, p=0.032) (Figure 1)

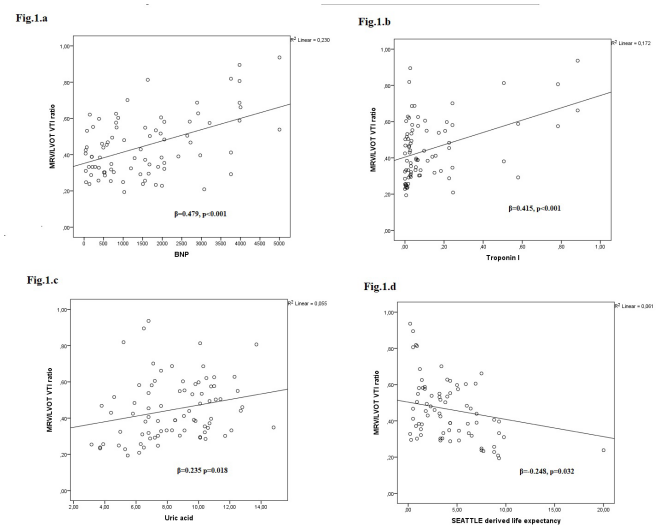

Figure 1. Correlations between MRV/LVOT VTI with Brain Natriuretic Peptid (Fig 1.a), troponin I (Fig 1.b), uric acid (Fig 1.c), SEATTLE score derived life expectancy (Fig 1.d). Each dot represents one patient; the straight line represents the best fit line obtained by linear regression analysis.

Abbreviations: MRV/LVOT VTI: peak mitral regurgitation velocity to left ventricular outflow tract velocity-time integral

In multivariate Cox regression analysis, adjusted with diastolic blood pressure, hemoglobin, every 0.1 increase in MRV/LVOT VTI ratio increased the one-year CEP risk by 37% (HR=1.371, 95% CI: 1.113-1.690 p=0.003) (Table 3). Additionally, adjusted with diastolic blood pressure, hemoglobin,creatinine level, every 0.1 increase in MRV/LVOT VTI ratio increased the long-term CEP risk by 35 % (HR=1.350, 95% CI: 1.139-1.601 p=0.001) (Table 4).

In ROC analysis, a cut of value 0.45 for MRV/LVOT VTI ratio 65.2% sensitivity and 65.5% specificity for prediction of one- year mortality (AUC=0.645 95%CI:0.515-0.776, p=0.042). In Kaplan Meier analysis, patients with MRV/LVOT VTI ratio ≥0.45 .had more one-year CEP compared to others (Chi-square:6.391, p=0.011) (Figure 2a and Figure 2b). Additionally, patients in ≥0.45 MRV/LVOT VTI ratio group had 3.3 times higher risk of CEP during one-year follow-up (HR: 3.268, CI 95%: 1.382-7.727, p=0.007)

For the prediction of long term mortality, a cut of value 0.39 for MRV/LVOT VTI ratio demonstrated 68% sensitivity and 67.7% specificity (AUC=0.706 95% CI:0.580-0.833, p=0.002). In Kaplan Meier analysis, patients with MRV/LVOT VTI ratio ≥0.39 had more long-term CEP compared to other patients (Chi-square:9.048, p=0.003) (Figure 2c and Figure 2d). Besides, adjusted with other parameters, being in the high MRV/LVOT VTI group increased the long-term CEP risk approximately 3 times (HR:2.750, 95%CI: 1.464-5.166, p=0.002).

Table 3: Univarite and multivariate Cox regression analysis demonstrating the predictors of one-year composite end point

Parameter	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	0.980 (0.952-1.009)	0.980		
Male, yes	1.300 (0.516-3.275)	0.578		
Ischemic CMP	0.487 (0.262-0.905)	0.023		
NYHA	2.752 (1.663-4.554)	<0.001		
Systolic Blood Pressure	0.946 (0.918-0.975)	<0.001		
Diastolic Blood Pressure	0.931 (0.890-0.973)	0.002	0.928 (0.883-0.975)	0.003
Rales	2.701 (1.119-6.522)	0.027		
ACEi/ARB	0.787 (0.344-1.799)	0.570		
Beta blocker	2.115 (0.631-7.092)	0.323		
MRA	1.081 (0.587-1.993)	0.225		
Hemoglobin	0.691 (0.543-0.879)	0.003	0.777 (0.606-0.996)	0.047
WBC	0.925 (0.765-1.117)	0.417		
Platelets	1.001 (0.997-1.006)	0.589		
Creatinine	2.299 (1.250-4.228)	0.007		
Na	0.887 (0.819-0.961)	0.003		
K	0.842 (0.430-1.649)	0.616		
CRP	1,003 (0.999-1.008)	0.163		
LVEF	0,909 (0,849-0.972)	0.005		
sPAB	1.023 (0.996-1.051)	0.090		
MR Grade 2 and 3	1.211 (0.542-2.704)	0.640		
MRV	0.117 (0.047-0.291)	<0.001		
LVOT VTI	0.821 (0.723-0.933)	0.003		
MRV/LVOT VTI (per 0.1)	1.240 (1.002-1.536)	0.018	1.371 (1.113-1.690)	0.003

* Because of the multicollinearity issues between NYHA and LVEF parameters were excluded from multivariate Cox regression analysis.

Table 4: Univarite and multivariate Cox regression analysis demonstrating the predictors of long term composite end point

Parameter	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.002 (0.981-1.023)	0.882		
Male, yes	1.390 (0.726-2.658)	0.320		
Ischemic CMP	0.626 (0.443-0.886)	0.008		
NYHA III-IV	4.424(2.339-8.369)	<0.001		
Systolic Blood Pressure	0.968 (0.952-0.985)	<0.001		
Diastolic Blood Pressure	0.959(0.934-0.985)	0.002	0.942 (0.913-0.973)	<0.001
Rales	2.468(1.391-4.377)	0.002		
ACEi/ARB	1.445(0.519-4.021)	0.481		
Beta blocker	1.676(0.601-4.671)	0.323		
MRA	1.081(0.587-1.993)	0.802		
Hemoglobin	0.777(0.666-0.906)	0.002	0.848 (0.729-986)	0.032
WBC	1.045(0.924-1.183)	0.184		
Platelets	1.000(0.997-1.004)	0.876		
Creatinine	2.173(1.390-3.399)	0.001	2.274(1.382-3.742)	0.001
Na	0.906(0.857-0.958)	0.001		
K	1.124(0.715-1.766)	0.613		
CRP	1,004 (1.000-1.008)	0.034		
LVEF	0,924 (0,889-0.961)	<0.001		
sPAB	1.032 (1.014-1.050)	<0.001		
MR Grade 2 and 3	1.613(0.929-2.800)	0.089		
MRV	0.193(0.106-0.350)	<0.001		
LVOT VTI	0.865(0.808-0.927)	<0.001		
MRV LVOT VTI (per 0.1)	1.193(1.034-1.378)	0.016	1.350 (1.139-1.601)	0.001

* Because of the multicollinearity issues, LVEF and NYHA parameters were excluded from multivariate cox regression model.

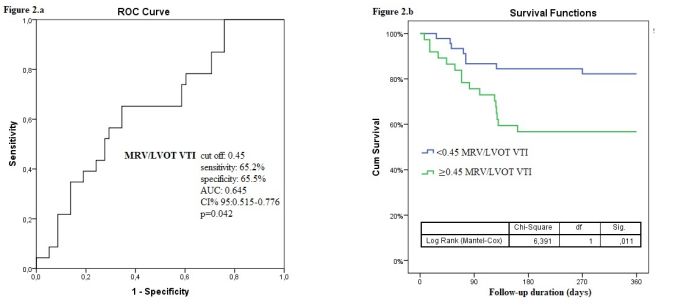

Figure 2.ROC curve analysis showing the predictive value of MRV/LVOT VTI to predict one-year composite endpoint (Fig 2.a), Kaplan-Meier survival curve demonstrating one-year composite endpoint among groups specified based on MRV/LVOT VTI ratio cut-off value 0.45 (Fig 2.b).ROC curve analysis showing the predictive value of MRV/LVOT VTI to predict long term composite end point (Fig 2.c), Kaplan-Meier survival curve demonstrating long-term composite endpoint among groups specified based on MRV/LVOT VTI ratio cut-off value 0.39 (Fig 2.d).

Abbreviations: AUC: area under the curve; MRV/LVOT VTI: peak mitral regurgitation velocity to left ventricular outflow tract velocity-time integral; ROC: receiver operating curve.

Discussion

The present study demonstrated that MRV/LVOTVTI ratio independently and significantly predicted the one year and long term CEP in HFrEF patients. Additionally, MRV/LVOT VTI ratio showed positive correlations with functional capacity, troponin I and serum BNP, uric acid and negative correlation with SEATTLE score derived life expectancy. Therefore, MRV/LVOT VTI ratio seemed to be useful predictor of poor prognosis associated with other established HF prognostic markers.

Patients with symptomatic heart failure have lower long-term survival rates of approximately less than five years [10]. Although prognostic evaluation is challenging, it is essential in the management of HF patients for deciding more advanced and individualized therapies. HF affects multiple organs and systems, and neurohormonal activation takes a mainstay role in the HF progression [11,12]. Previously, the activation of the sympathetic nervous and renin-angiotensin system was reported in HF [13,14]. Therefore, an increase in SVR may be expected due to the increased levels of vasoconstrictive neurohumoral factors in the course of the disease and also may suggest progression of the HF. In advanced HF and cardiogenic shock, alterations in vascular tone determine the SVR and cardiac output [1] In this context, assessment of SVR may be helpful in therapy guidance by adjusting the vascular volume, inotropes, and vasodilators. However, the determination method of SVR limits its use due to the potential complications related to the invasive monitoring process. In the prompting study about the non-invasive determination of SVR, Abbas et al. showed that SVR positively correlated with an echocardiographic index that was simply calculated by dividing the MRV to the LVOT VTI, and this formula allowed indirect and noninvasive assessment of SVR [2].

In the setting of HF hospitalizations, SVR is valuable in the diagnosis of pulmonary edema [1]. While SVR was found elevated in exacerbated systolic HF, it was found extremely high in the patient group with pulmonary edema [1]. Accordingly, indirect measurement of SVR may be useful in HF diagnosis, because, HF generates a gradual decline in cardiac contractility and to overcome this, neurohormonal vascular tone increases causing an elevated SVR. In our study, we found that MRV/LVOT VTI ratio significantly elevated in patients with HF compared with the healthy subjects that may point to the underlying pathophysiology of HF. In the patient group, we observed that MRV/LVOT VTI ratio positively correlated with NYHA functional classes. Moreover, it showed positive correlations with troponin and BNP which are already described as prognostic markers in HF [15,16]. Interestingly, this echocardiographic index negatively correlated with SEATTLE score derived life expectancy, which was previously developed by reviewing the clinical trials and published data to predict HF prognosis[8]. Especially in the advanced HF population, this scoring system revealed better discrimination of high-risk patients [17]. In the present study, Cox regression analysis showed that MRV/LVOT VTI ratio was an independent predictor of CEP for one-year and long term follow-up. The significant relation between SEATTLE score derived life expectancy and MRV/LVOT VTI ratio may indicate that non-invasive assessment of cardiac hemodynamics with Doppler echocardiography may provide a further determination of patients with poor prognosis.

Besides, we had additional points that deserve to be mentioned. The components of MRV/LVOT VTI may have certain individual affects on outcomes. In univariate analysis, decrease in individual contributors (MRV and LVOT VTI) were found to be associated with poor prognosis. However, we evaluated MRV/LVOT VTI along with its individual contributors and found that this compound parameter was an independent predictor of worse clinical outcomes better than its contributors. Intuitively, higher MRV/LVOT VTI may result from low LVOT VTI values in the setting of a combination of decreased systolic blood pressure

and elevated left atrial pressure, which are already proven mortality markers of HfrEF. MRV/LVOT VTI seems to predict outcomes more accurately than its contributors.

Our study is preliminary investigating the prognostic value of MRV/LVOT VTI in HFrEF. We determined the cut-off values of MRV/LVOT VTI in predicting the occurrence of CEP and organized study population based on these cut-offs. We found that being in higher MRV/LVOT VTI group was associated with increased CEP risk by nearly three times. These findings should be assessed in large scale studies.

Study Limitations

Although the present study provided valuable information about the non-invasive and indirect measurement of SVR in patients with HF, the number of recruited patients was relatively small. Also, invasive analysis of SVR was not applied because it is an invasive method and the implementation is effortful, and for our study patients as they were not admitted with acute decompensated HF, the indication of this assessment is debatable.

Conclusion

In patients with HFrEF, MRV/LVOT VTI ratio as an indirect measure of SVR emerged as an independent prognosticator of one-year and long term CEP, associated with established HF prognostic markers. This simple, easily measurable non-invasive parameter may be feasible in determining the high-risk subjects and tailoring more individualized therapies.

Declaration of conflict of interest

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References

1. Cotter G, Moshkovitz Y, Kaluski E et al. The role of cardiac power and systemic vascular resistance in the pathophysiology and diagnosis of patients with acute congestive heart failure. Eur J Heart Fail 2003; 5: 443–51.
2. Abbas AE, David Fortuin F, Patel B, Moreno CA, Schiller NB, Lester SJ. Noninvasive measurement of systemic vascular resistance using Doppler echocardiography. Journal of the American Society of Echocardiography 2004; 17: 834–8.
3. Kumar A, Parrillo JE. Shock: Classification, Pathophysiology, and Approach to Management. Critical Care Medicine 2008: 379–422.
4. Hatle L, Angelsen BA, Tromsdal A. Non-invasive estimation of pulmonary artery systolic pressure with Doppler ultrasound. Br Heart J 1981; 45: 157–65.
5. Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. Am J Cardiol 1990; 66: 493–6.
6. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984; 70: 657–62.
7. Ommen SR, Nishimura RA, Appleton CP et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788–94.
8. Levy WC, Mozaffarian D, Linker DT et al. The Seattle Heart Failure Model. Circulation 2006; 113: 1424–33.
9. Gardin JM, Adams DB, Douglas PS, Feigenbaum H, Forst DH, Fraser AG, et al. Recommendations for a standardized report for adult transthoracic echocardiography: A report from the American Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. Journal of the American Society of Echocardiography 2002; 15: 275–90.
10. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More "malignant" than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001; 3: 315–22.
11. Hastillo A, Willis H, Hess M. The heart as a target organ of immune injury. Current Problems in Cardiology 1991; 16: 381–442.
12. James TN. Myocarditis and cardiomyopathy. N Engl J Med 1983; 308: 39–41.
13. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. Circulation 1988; 77: 721–30.
14. Mancia G. Neurohumoral activation in congestive heart failure. Am Heart J 1990; 120: 1532–7.
15. Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation 2013;128.
16. Lund LH, Aaronson KD, Mancini DM. Validation of peak exercise oxygen consumption and the Heart Failure Survival Score for serial risk stratification in advanced heart failure. The American Journal of Cardiology 2005; 95: 734–41.
17. Kalogeropoulos AP, Georgiopoulou VV, Giamouzis G et al. Utility of the Seattle Heart Failure Model in Patients With Advanced Heart Failure. Journal of the American College of Cardiology 2009; 53: 334–42.