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ORIGINAL ARTICLE
Heart Failure

Efficacy of Pulmonary Artery Pulsatility Index as a Measure of Right Ventricular Dysfunction in Stable Phase of Dilated Cardiomyopathy

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Background: Right ventricular dysfunction (RVD) in the setting of left ventricular (LV) myocardial damage is a major cause of morbidity and mortality, and the pulmonary artery pulsatility index (PAPi) is a novel hemodynamic index shown to predict RVD in advanced heart failure. However, it is unknown whether PAPi can predict the long-term prognosis of dilated cardiomyopathy (DCM) even in the mild to moderate phase. This study aimed to assess the ability of PAPi to stratify DCM patients without severe symptoms.

Methods and Results: Between April 2000 and March 2018, a total of 162 DCM patients with stable symptoms were evaluated, including PAPi, and followed up for a median of 4.91 years. The mean age was 50.9±12.6 years and the mean LV ejection fraction (EF) was 30.5±8.3%. When divided into 2 groups based on median value of PAPi (low, L-PAPi [<3.06] and high, H-PAPi [≥3.06]), even though there were no differences in B-type natriuretic peptide or pulmonary vascular resistance, the probability of cardiac event survival was significantly higher in the L-PAP than in the H-PAP group by Kaplan-Meier analysis (P=0.018). Furthermore, Cox's proportional hazard regression analysis revealed that PAPi was an independent predictor of cardiac events (hazard ratio: 0.782, P=0.010).

Conclusions: Even in patients identified with DCM in the mild to moderate phase, PAPi may help stratify DCM and predict cardiac events.

Key Words: Dilated cardiomyopathy; Pulmonary artery pulsatility index (PAPi); Prognosis

Dilated cardiomyopathy (DCM) is characterized by a reduction in left and/or right ventricular myocardial contraction, and biventricular cavity dilatation is a major cause of heart failure (HF), with high morbidity and mortality rates. Right ventricular dysfunction (RVD) has recently received attention due to a study showing that 34% of patients with DCM had RVD; it is now being considered as a powerful predictor of impaired prognosis in DCM.[1,2] Multiple mechanisms contribute to RVD, including the following: (1) increased afterload caused by left ventricular (LV) dysfunction, (2) RV systolic and diastolic dysfunction, (3) abnormal preload, (4) altered interdependence, and (5) altered rhythm.[3] In addition, various studies have identified hemodynamic parameters that correlate with RVD, including the RV ejection fraction (RVEF),[4] pulmonary vascular resistance (PVR), RV-fractional area change (RV-FAC), RV stroke work index (RVSWI),[5] pulmonary artery (PA)-proportional pulse pressure (PAPPP),[6] PA capacitance (PAC),[7] and PA elastance (PAE).

The PA pulsatility index (PAPi) is defined as PA pulse pressure (PAPP) divided by right atrial pressure (RAP) and is a novel hemodynamic index shown to predict RV failure in acute inferior myocardial infarction and after LV assist device (LVAD) surgery. These outcomes are predicated on PA systolic pressure as an indicator of RV systolic function against an increased afterload, and elevated RAP as an increased preload. In 2018, Kochav et al reported that PAPi strongly predicted adverse clinical events in patients with advanced HF.[8] PAPP is dependent on both LV/RV stroke volume (SV) and PAC, and the RV SV decreases rapidly as afterload increases, even though LV SV is

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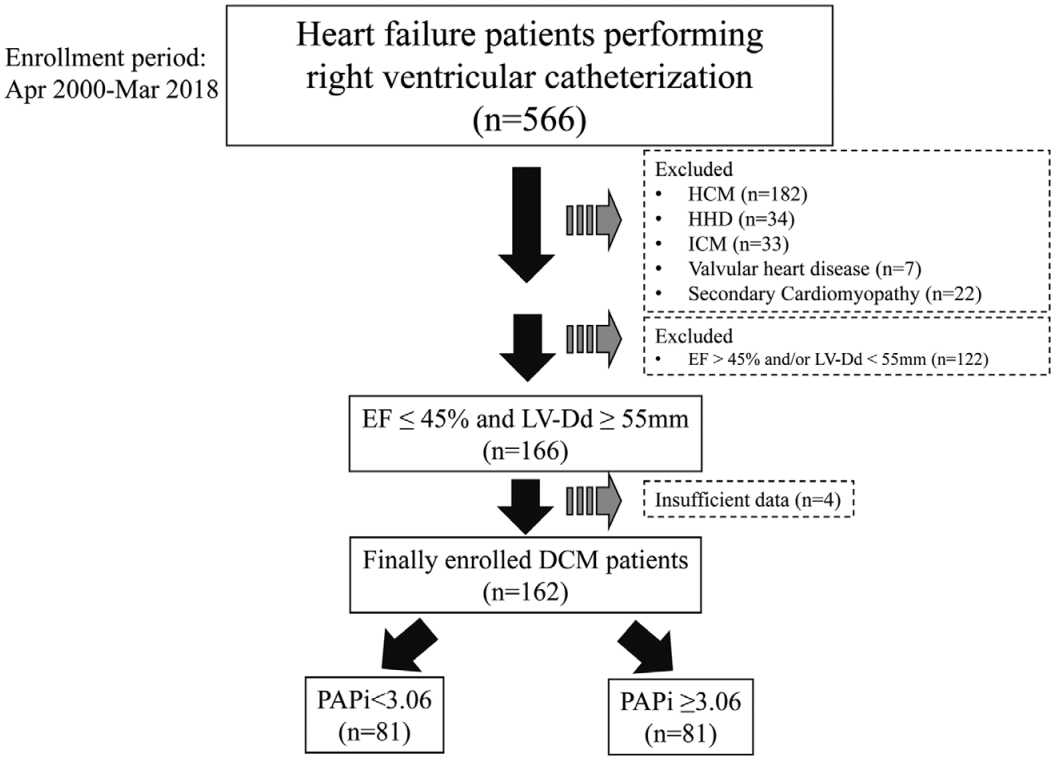

Figure 1. Flowchart of patient enrollment. Consecutive cardiomyopathy patients in whom right ventricular catheterization was performed were enrolled from April 2001 to March 2018.

maintained against an augmented afterload.[3] Because of these sensitive RV reactivities, we hypothesized that PAPi could stratify patients without severe symptoms and predict cardiac events, and aimed to show this in patients with DCM.

Methods

From April 2000 to March 2018, after excluding New York Heart Association (NYHA) Class IV patients, we retrospectively enrolled 566 consecutive asymptomatic patients with cardiomyopathy at rest (NYHA Class ≤III). All patients underwent laboratory measurements, echocardiography, and cardiac catheterization to evaluate their general condition. A diagnosis of dilated cardiomyopathy (DCM) was made based on echocardiographic measurements (LVEF ≤45% and LV end-diastolic dimension [LVDd] ≥55 mm). After excluding secondary cardiomyopathy, ischemic cardiomyopathy, and valvular heart disease, 162 DCM patients were enrolled (**Figure 1**). The study protocol complied with the Declaration of Helsinki and was approved by the appropriate institutional review committee.

Echocardiography

All patients underwent M-mode, 2D echocardiography, Doppler blood flow, and tissue Doppler imaging using a Vivid 7 system (GE Healthcare, WI, USA). LVEF was measured using the modified Simpson's method and the peak flow velocities at the mitral level during rapid filling (E) and atrial contraction (A) and E/A were calculated from pulsed Doppler. We recorded the tissue Doppler imaging wave of the mitral annulus from the septal side of the apical 4-chamber view and analyzed the early diastolic filling velocity (E').

Cardiac Catheterization

All patients underwent biventricular cardiac catheterization analysis. Right heart catheterization was performed at rest using a 7F triple-lumen Swan-Ganz thermodilution PA catheter (Edwards Life Science Co., Irvine, CA, USA). PAPi was calculated as (PA systolic−PA diastolic pressure)/right arterial pressure. RVSWI was calculated as (mean PA pressure−mean RA pressure)×SV index, where the SV index was calculated as cardiac index/heart rate. PAC was calculated as SV/PAPP, where PAPP was calculated as PA systolic pressure−PA diastolic pressure. PAE was calculated as PA systolic pressure/SV. PVR was calculated as transpulmonary gradient/cardiac output, where transpulmonary gradient was calculated as mean PA pressure (PAP)−pulmonary arterial wedge pressure (PAWP). PAPPP was calculated as PAPP/PA systolic pressure.

After collecting the baseline hemodynamic data, an endomyocardial biopsy was performed to exclude secondary cardiomyopathies such as storage disorders and specific heart muscle diseases. Several biopsy specimens were obtained from the right side of the interventricular septum using a 6F cardiac bioptome catheter (Myocardial Biopsy Forceps, Technowood®, Tokyo, Japan).

Table 1. Baseline Characteristics of the Study Patients (n=162)

	Total (n=162)	L-PAPi <3.06 (n=81)	H-PAPi ≥3.06 (n=81)	P value
Age, years	50.9±12.6	48.0±11.9	53.8±12.7	0.003
Female, n (%)	40 (24.7)	16 (19.8)	24 (29.6)	0.144
BMI, kg/m^2	24.4±4.9	25.1±4.7	23.7±5.0	0.071
NYHA functional class I,II/III, n	150/12	74/7	76/5	0.567
DM, n (%)	32 (19.8)	14 (17.3)	18 (22.2)	0.429
AF, n (%)	25 (15.4)	17 (21.0)	8 (9.9)	0.080
CRT, n (%)	6 (3.7)	5 (6.2)	1 (1.2)	0.105
Laboratory measurements				
Serum creatinine, mg/dL	0.911±0.391	0.939±0.491	0.885±0.257	0.383
eGFR, mL/min/1.73 m^2	71.4±21.3	72.9±21.7	69.9±21.0	0.369
Serum hemoglobin, g/dL	14.3±1.8	14.4±1.6	14.1±1.9	0.357
Plasma BNP, pg/mL	128.7 (57–310)	108.4 (55.6–333.7)	135.9 (57.2–287.4)	0.880
Echocardiography				
LVDd, mm	65.9±7.7	66.6±8.1	65.2±7.3	0.240
LVDs, mm	56.2±8.4	56.7±8.9	55.6±8.0	0.422
LVEF, %	30.5±8.3	30.5±8.9	30.6±7.7	0.904
E/A ratio	1.24±0.89	1.32±0.94	1.17±0.84	0.375
E/e' ratio	16.6±9.1	15.1±7.2	17.8±10.4	0.131
Dct, ms	182.4±66.1	182.0±65.8	182.7±66.8	0.952
TRG, mmHg	25.0±11.1	24.0±9.9	25.9±12.3	0.477
Cardiac catheterization				
HR, beats/min	77.8±14.0	79.0±14.2	76.7±13.9	0.295
RAP, mmHg	5.9±3.1	8.0±2.6	3.8±1.8	<0.001
Mean PAP, mmHg	18.2±7.3	20.0±7.5	16.6±6.7	0.004
PAWP, mmHg	13.5±6.8	15.2±7.2	11.8±6.0	0.001
CI, L/min/m^2	2.74±0.66	2.79±0.71	2.70±0.60	0.434
PVR, Wood	1.1±1.0	1.0±0.8	1.1±1.2	0.561
RAP/PAWP	0.49±0.23	0.59±0.21	0.38±0.22	<0.001
PAC, mL/mmHg	4.6±2.6	5.3±2.9	3.9±1.9	<0.001
PAE, mmHg/mL	0.48±0.24	0.49±0.26	0.48±0.23	0.991
RVSWI, g·m/m^2/beat	5.9±3.2	5.7±3.0	6.2±3.4	0.409
PAPPP	0.58±0.13	0.51±0.11	0.65±0.11	<0.001
PAPi	4.16±4.01	1.98±0.57	6.33±4.74	<0.001
Medications at pre-examination				
RASI, n (%)	112 (69.1)	56 (69.1)	56 (69.1)	>0.99
β-blocker, n (%)	85 (52.5)	45 (55.6)	40 (49.4)	0.265
Carvedilol equivalent, mg/day	5 (2.5–10)	5 (2.5–10)	5 (2.5–10)	>0.99
Aldosterone antagonist, n (%)	76 (46.9)	37 (45.7)	39 (48.1)	0.438
Diuretic, n (%)	102 (63.0)	43 (53.1)	59 (72.8)	0.007
Amiodarone, n (%)	14 (8.6)	12 (14.8)	2 (2.5)	0.005
Medication at follow-up period				
RASI, n (%)	137 (84.6)	65 (80.2)	72 (88.9)	0.096
β-blocker, n (%)	146 (90.1)	73 (90.1)	73 (90.1)	>0.99
Carvedilol equivalent, mg/day	10 (5–15)	10 (5–15)	10 (5–15)	>0.99
Aldosterone antagonist, n (%)	85 (52.5)	42 (51.9)	43 (53.1)	0.500
Diuretic, n (%)	87 (53.7)	47 (58.0)	40 (49.4)	0.172
Amiodarone, n (%)	24 (14.8)	13 (16.0)	11 (13.6)	0.413

Data are mean±SD or median (interquartile range). AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CI, cardiac index; CRT, cardiac resynchronization therapy; Dct, deceleration time; DM, diabetes mellitus; E/A ratio, ratio of early transmitral flow velocity to atrial flow velocity; E/e' ratio, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; HR, heart rate; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAC, pulmonary artery capacitance; PAE, pulmonary artery elastance; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PAPPP, pulmonary arterial proportional pulse pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RASI, renin-angiotensin system inhibitor; RVSWI, right ventricular stroke work index; TRG, tricuspid valve regurgitation pressure gradient.

Measurement of Collagen Volume Fraction

Myocardial fibrosis in biopsy specimens was assessed using Sirius red staining, and the positive region was quantified as the collagen volume fraction (CVF). The CVFs were digitized and quantified using BZ-H3C and BZ-X 710 microscopes (Keyence, Osaka, Japan).

Clinical Follow-up

The follow-up duration was calculated from the date of catheterization to the date of the last clinical visit. Composite cardiac events were defined as sudden cardiac death or admission for worsening HF, the latter defined as hospitalization for medication with signs and symptoms of HF diagnosed by a cardiologist.

Statistical Analysis

All statistical analyses were performed with JMP pro version 14.0 (SAS Institute, Cary, NC, USA). Normally distributed data are presented as mean±SD and non-normally distributed variables as median with interquartile ranges. Intergroup differences were compared using Student's t-test for parametric variables and Mann-Whitney U-test for non-parametric variables. Categorical variables were compared using the Pearson chi-squared test or Fisher's exact test as appropriate. Cox proportional hazard regression analysis was performed to identify the independent predictors of cardiac events. A stepwise forward selection procedure was applied. Cumulative cardiac event estimates were calculated by the Kaplan-Meier method, with differences between the survival curves assessed by the log-rank test. Receiver-operating characteristic (ROC) analysis was performed to assess the clinical utility of PAPi for discriminating the cardiac events. A value of $P<0.05$ was considered to indicate statistical significance.

Results

The median follow-up time was 4.91 years. Baseline clinical characteristics are shown in **Table 1**. The median PAPi of all study patients was 3.06 and we divided the study patients into 2 subgroups based on this: high (H)-PAPi group (PAPi ≥3.06; n=81) and low (L)-PAPi group (PAPi <3.06; n=81) (**Figure 1**). PA catheterization hemodynamics are also shown in **Table 1**. The mean age of the study patients was 50.9 years and the majority (75.3%) of patients were male. There were no significant differences between the H-PAPi and L-PAPi groups for creatinine, B-type natriuretic peptide (BNP), LVEF, or cardiac index, but the rate of diuretic use at pre-therapy was significantly higher in the H-PAPi group than in the L-PAPi group, and PAWP, PAC, and the prescription rate of amiodarone at pre-therapy were significantly lower in the H-PAPi group than in the L-PAPi group. Echocardiographic parameters are also shown in **Table 1**, with no significant differences between groups.

Table 2. Composite Cardiac Events

	All patients	
	PAPi <3.06 (n=81)	PAPi ≥3.06 (n=81)
SCD, n (%)	4 (4.9)	2 (2.5)
HF, n (%)	19 (23.5)	10 (12.3)

HF, admission for worsening HF; PAPi, pulmonary artery pulsatility index; SCD, sudden cardiac death.

Table 2 summarizes the incidence of cardiac events: 35 patients (21.6%) experienced cardiac events, including 6 (3.7%) with sudden cardiac death and 29 (17.9%) hospitalized for worsening HF. The cumulative probability event-free survival curves are shown in **Figure 2**. These Kaplan-Meier survival curves demonstrated a significantly higher probability of cardiac events in the L-PAPi group than in the H-PAPi group (P=0.018). There was no relationship between PAPi and PAWP (**Figure 3**). In the pathological analysis, there was no difference in CVF between H-PAPi (7.50 (5.05–12.30)) and L-PAPi (7.40 (4.65–11.55)) (**Figure 4**).

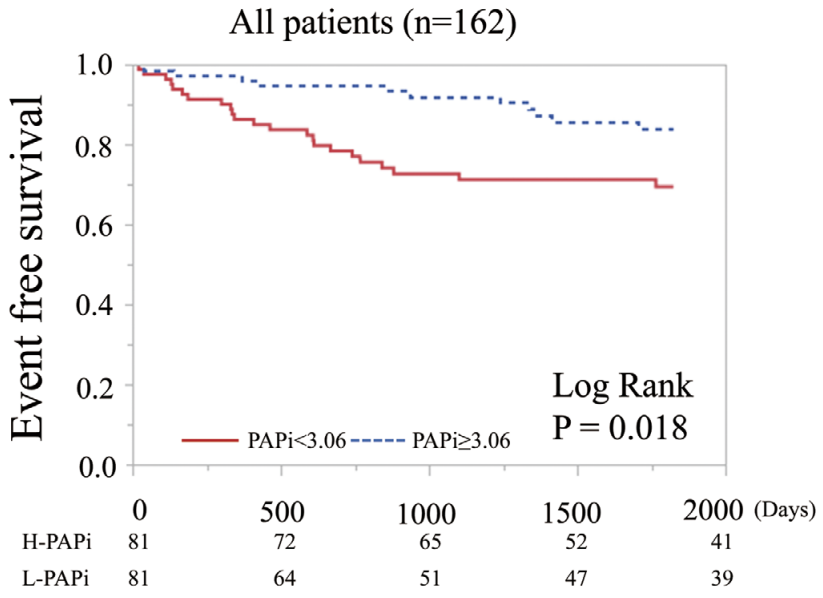

Figure 2. Kaplan-Meier analysis of probability of cardiac events for inpatients with DCM divided into 2 groups according to median PAPi (high (H); low (L)). The L-PAPi group (red) showed a significantly higher probability of a cardiac event than the H-PAPi group (blue) (P=0.018; log-rank test). DCM, dilated cardiomyopathy; PAPi, pulmonary artery pulsatility index.

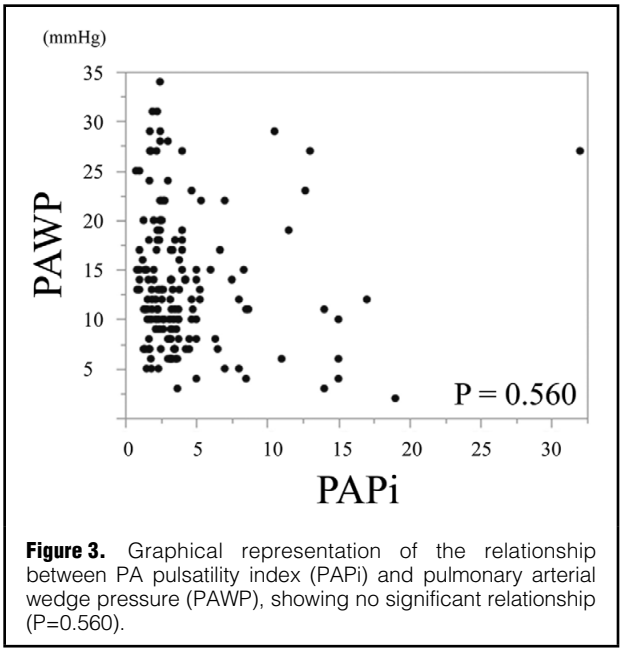

Figure 3. Graphical representation of the relationship between PA pulsatility index (PAPi) and pulmonary arterial wedge pressure (PAWP), showing no significant relationship (P=0.560).

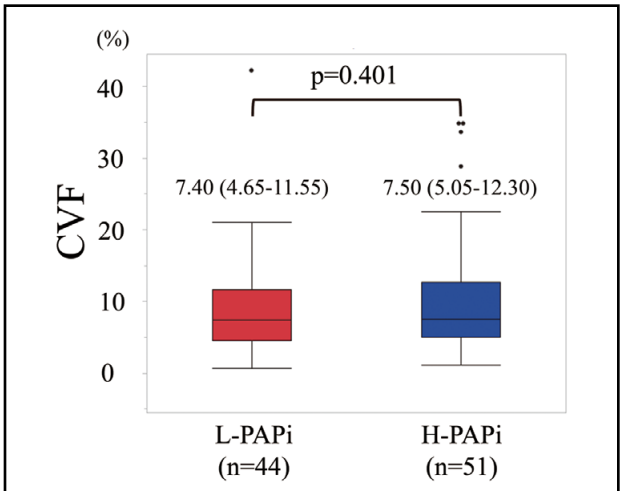

Figure 4. Box plot of collagen volume fraction (CVP), showing no significant difference in the distribution of CVF between the L-PAPi (7.40 (4.65–11.55), n=44) and H-PAPi (7.50 (5.05–12.30), n=51) groups (P=0.401). PAPi, pulmonary artery pulsatility index (high (H); low (L)).

Table 3. Cox Proportional Hazard Regression Analysis for Cardiac Events

Factor	HR (95% CI)	X^2 value	P value
Univariate analysis			
Age, years	0.973 (0.948–0.999)	4.0	0.045
Serum creatinine, mg/dL	1.337 (0.647–2.051)	0.8	0.360
Serum hemoglobin, g/dL	0.832 (0.690–1.009)	3.5	0.061
BNP, pg/mL*	1.012 (1.003–1.019)	6.7	0.009
LVEF, %	0.935 (0.895–0.975)	10.2	0.001
E/e' ratio	1.034 (0.994–1.070)	2.8	0.093
PAWP, mmHg	1.072 (1.024–1.121)	8.5	0.004
PVR, Wood	1.035 (0.745–1.421)	0.0	0.838
RAP/PAWP	0.982 (0.222–4.037)	0.0	0.980
PAC, mL/mmHg	1.046 (0.900–1.182)	0.4	0.531
PAE, mmHg/mL	1.605 (0.323–6.525)	0.4	0.544
RVSWI, g·m/m²/beat	1.049 (0.951–1.135)	1.0	0.311
PAPi	0.854 (0.701–0.985)	4.9	0.027
Multivariate analysis			
Age, years	0.996 (0.964–1.028)	0.0	0.794
BNP, pg/mL*	1.005 (0.995–1.014)	0.8	0.364
LVEF, %	0.950 (0.906–0.996)	4.5	0.035
PAWP, mmHg	1.046 (0.990–1.106)	2.4	0.120
PAPi	0.782 (0.616–0.994)	6.6	0.010

The final model included all univariate predictors. *Per 10-pg/mL increments. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

The univariate and multivariate Cox regression analyses of factors possibly associated with cardiac events are shown in **Table 3**. In the univariate analysis, age, BNP, LVEF, PAWP, and PAPi were significantly associated with cardiac events. In the multivariate analysis, PAPi and LVEF were independent predictors of cardiac events (hazard ratio: 0.782, P=0.010 and hazard ratio: 0.950, P=0.035, respectively). With regard to the indices of RV function, RAP/PAWP and RVSWI were not associated with cardiac events, but PAPi and LVEF were significantly associated with cardiac events. The cumulative probability event-free survival curves in patients grouped according to the coupling between median PAPi and median LVEF are shown in **Figure 5**. When a ROC analysis was calculated using PAPi, the ROC curve identified a PAPi cutoff value for cardiac events of 4.0 (area under the curve: 0.633, sensitivity: 94.1%, specificity: 32.8%) (**Supplementary Figure 1**). Furthermore, Kaplan-Meier survival curves divided by the cutoff value (PAPi=4.0) are shown in **Supplementary Figure 2** and show the significantly higher probability of

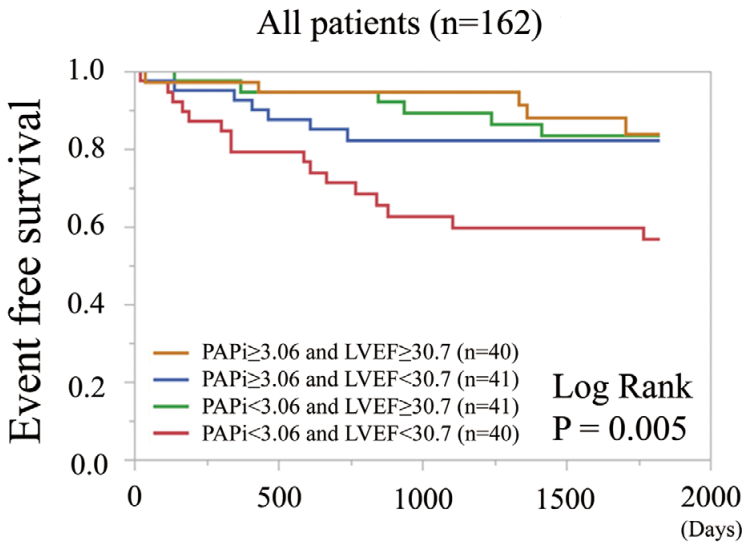

Figure 5. Kaplan-Meier analysis of the probability of cardiac events for 162 DCM patients divided into 4 groups according to median PAPi and median LVEF revealed a significant difference (P=0.005). LVEF, left ventricular ejection fraction; PAPi, pulmonary artery pulsatility index.

cardiac events in the PAPi <4.0 group than in the PAPi ≥4.00 group (P=0.035).

Discussion

In this study, we found that PAPi strongly predicted composited cardiac events even after adjustment for age, BNP, LVEF, and PAWP in DCM patients without severe symptoms. Furthermore, PAPi was able to stratify DCM patients with PVR and RVSWI in the normal ranges. Because of the simplicity of the PAPi calculation, this result is widely useful for stratification of high-risk patients in the mild to moderate phase.

Over the past few decades, various studies have reported that DCM is associated with poor prognosis and increased afterload, and that impaired RV function may be an important prognostic marker. Since Gulati et al reported that RVD was detected in 34% of DCM patients and found this dysfunction to be a powerful and independent predictor of mortality,[1] there has been increasing appreciation of the potential effect of RVD on cardiac events. RVD may develop in association with LV dysfunction via multiple mechanisms; increased RV afterload due to rising LV end-diastolic pressure and LV volume have been determined as important factors.[9] When performing an estimation of both right and left cardiac function, right heart catheterization is considered the gold standard and is used to guide therapy in multiple scenarios.[10,11] On the other hand, echocardiography and magnetic resonance imaging are also useful for evaluating RVD noninvasively, and in some specific studies, tricuspid annular plane systolic excursion (TAPSE),[12] RV longitudinal strain, tissue Doppler,[13,14] echo-PAC,[15] RV-FAC or RV-fractional long-axis change measurements[16] by 2D echocardiography have been adopted. Although echocardiography is rapid and noninvasive and provides point-of-care information, it is contingent on the presence of adequate views, and it is difficult to evaluate agreement between institutions and variability within and between observers.[17] On the other hand, cardiovascular magnetic resonance (CMR) is the gold standard for both LV and RV function;[1] in a previous study, RVD defined by RVEF ≤45% remained an independent predictor of the primary endpoint (hazard ratio 3.9, P<0.001) and impaired RV long-axis strain (RV-LAS) was also associated with poor cardiac outcomes.[9,18,19] CMR is certainly an attractive modality, but is not itself able to estimate PAP directly and requires administration of a gadolinium contrast agent. Ghio et al reported that increased PAP coupled with reduced systolic function of the RV had poor clinical prognosis, although in this report reduced RV function in echocardiography alone did not exhibit an additional risk.[4] This report showed the importance of direct estimation of intracardiac pressure.

In 2012, Korabathina et al first reported that PAPi helped to identify high-risk patients after inferior myocardial infarction with severe RVD. PAPi is calculated as PAPP/RAP, and as PAPP reflects both RV contractility and left atrial filling pressure, this index is considered as the RV adaptive response to afterload. The denominator of the PAPi is defined by RA pressure, which serves as a marker of RV preload. Thus, PAPi incorporates both preload and afterload of the RV.[20] Morine et al showed that preoperative PAPi may identify patients at high risk of developing RV failure after LVAD surgery,[21] and recently Mazimba et al reported an association between PAPi and survival in PA hypertension patients.[22] These studies all support the fact that PAPi has important prognostic implications in patients with RVD. Though previous studies showed evidence of the utility of PAPi in patients with advanced HF, such as NYHA Class IV or post LVAD, our study showed the efficacy of PAPi for DCM patients in NYHA Class III or less.

PVR is also used as a marker of remodeling of the PA. Drakos et al reported that after LVAD implantation, high PVR had a higher risk of RVF than low PVR,[23] but in our study of mild to moderate stage DCM patients with low PVR (mean PVR 1.1 Wood units), PVR could not predict cardiac events because there was little dispersion of PVR (**Table 3**). This might be explained by PAC's hyperbolic relationship with PVR. PAC is defined as the ratio of SV

over PAPP and represents the distensibility of the PA. Because this score was within normal range in this study (PAC: 4.6±2.6 mL/mmHg), differences in PAC resulted in only minimal changes in PVR,[24] and led to the prognostic ineffectiveness of PVR in this study.

RVSWI is another hemodynamic index for the RV, which is affected by SV and has a normal range of 5–10 g·m/m²/beat. Even though RVSWI is significantly associated with cardiac events in patients with PA hypertension,[5] this might not apply for DCM without severe PA hypertension (mean PAP 18.2 mmHg) and in our study, RVSWI was not associated with composite cardiac events.

Although PAWP was significantly elevated in the L-PAPi group, which is consistent with other studies,[20–22] there was not a significant relationship between PAWP and PAPi (**Figure 3**). PAPi would increase as a result of increasing PAWP,[25] but compensating mechanisms contribute to the blunting of PAPi elevation even with high PAWP in NYHA Class III or less. And with further progression of HF stage, this compensating mechanism might not work properly. Taken together, these results mean that independent of LV function, PAPi may reflect PA stiffness, capacitance, elastance, and RV diastolic function, and an influence on prognosis other than stroke work even inNYHA Class III or less.

In this study, 149 patients had endomyocardial biopsies performed in order to exclude secondary cardiomyopathies and 95 patients were assessed using Sirius red staining. Even though an increase in RV fibrosis in patients with PA hypertension has been reported,[26] surprisingly, our study showed no difference in RV fibrosis between patients with L-PAPi and H-PAPi. This result might be due to the phase of patients in our study, and might suggest that PAPi has a potent prognostic value for patients without severe myocardial fibrosis.

Study Limitations

Firstly, this was a single-center study with a small number of patients and a small number of cardiac events. Secondly, calculation of PAPi requires catheterization, which is relatively invasive, and leads to difficulty in repeated calculations. Thirdly, PAPi is affected by RAP, which might lead to underestimation of the PAPi score when the calculation is performed in the over-volume status. In order to avoid this error, we enrolled patients with characteristics such as stable volume status and few symptoms. When using PAPi as a prognostic indicator, it is very important that the patient targets are a homogeneous group, because PAPi is changed by PAC degree and volume status.

In conclusion, RVD estimated by PAPi was a strong independent predictor of the occurrence of cardiac events in this study and may be useful for risk stratification of DCM patients without severe symptoms.

Declarations of Interest

T.O. received lecture fees from Ono Yakuhin, Medtronics, and Otsuka, and received research grants from Ono Yakuhin, Bayer, Daiichi-Sankyo, and Amgen Astellas (not in connection with the submitted work). T.M. received lecture fees and unrestricted research grants from Bayer, Daiichi-Sankyo, Dainippon Sumitomo, Kowa, MSD, Mitsubishi Tanabe, Boehringer Ingelheim, Novartis, Pfizer, Sanofi-Aventis, Takeda, Astellas, Otsuka, and Teijin.

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None.

Data Availability

The deidentified participant data will not be shared.

Disclosures

T.M. is a member of *Circulation Journal*' Editorial Team.

IRB Information

Clinical Research Review Committee of Nagoya University, No. 2006-0359.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-20-0279