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Prognostic Value of Right Ventricular Cardiac Power Output at Rest in Patients with Advanced Heart Failure

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Background: There is supporting evidence that normal right heart function is crucial for the maintenance of normal overall hemodynamics. The heart can be described as a hydraulic pump, and cardiac power reflects the hydraulic function of the heart. The present analysis aimed to evaluate the prognostic value of right ventricular cardiac power output (RV-CPO) at rest in patients with advanced heart failure (HF).
Methods: Between September 2010 and July 2013, 172 patients with advanced HF referred to our hospital were included in this study. Performing right-sided and left-sided heart catheterization simultaneously for each patient at baseline, we evaluated the hemodynamics with longitudinal follow-up of adverse outcomes such as cardiac mortality, ventricular assist device placement, and cardiac transplant (HTx).
Results: The threshold RV-CPO at rest value was 0.15 Watts. Increased RV-CPO (> 0.15 Watts) was correlated with an increase in adverse outcomes. Over 52 months, we observed 50 cardiac deaths, 10 HTx, and 12 ventricular assist device placements. The prognostic value of RV-CPO remained significant after adjustment for age, gender, ejection fraction, cardiac output, mean arterial pressure, valvular heart disease, diabetes, body surface area and mineralocorticoid receptor antagonist medication dummy (hazard ratio 0.052, 95% confidence interval 0.006 to 0.406, p = 0.005).
Conclusions: Higher RV-CPO at rest was an independent predictor of adverse outcomes. Therefore, RV-CPO could be integrated into the clinical evaluation used for individual risk stratification of patients with advanced HF in order to consider earlier HTx listing and/or earlier consideration for mechanical circulatory support device therapy.

Key Words: Heart failure • Mortality • Prognosis • Right ventricular cardiac power output

INTRODUCTION

In the past, a lack of sufficient noninvasive imaging modalities has hindered extensive research of the right ventricle. Therefore, the contribution of the right ventricle to global cardiac pump function has been inadequately represented. In recent years, however, the technological evolution of three-dimensional echocardiography and cardiac magnetic resonance imaging has aroused interest in the role of the right ventricle in the pathophysiology of advanced heart failure (HF). Various studies have demonstrated a strong association between right ventricle pump function and both morbidity and mortality in advanced HF.[1-3] Cardiac power output (CPO) is a hemodynamic measure, which is regarded as the hydraulic pumping ability of the heart on an arterial system for maintaining blood circulation. It has been shown that in patients with advanced HF resting CPO is a strong prognostic factor.[4] However, resting CPO is primarily focused on left ventricular function. Hence, the aim of this study was to evaluate the prognostic value of right ventricular function as represented by cardiac power out-

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put (RV-CPO) at rest in patients with advanced HF.

METHODS

Our study group included 172 patients aged ≥ 18 years old with advanced HF who were referred to the Florence Nightingale Hospital between September 2010 and July 2013 for HF management and/or to be evaluated for heart transplantation (HTx). The Institutional Review Board approved this study, and informed consent was obtained from all patients. The duration of follow-up was defined as the period from the first contact of the patient to either ventricular assist device placement, HTx or all-cause mortality.

To evaluate the hemodynamic measurements used for analysis, we performed simultaneous right and left heart catheterization via femoral access in each patient at baseline. After placing a catheter into the ascending aorta and the pulmonary artery, both an arterial sample and a mixed central venous sample were collected from the tip of the catheter. Using Fick's equation, we calculated cardiac output (CO) and then to obtain the cardiac index (CI) we divided CO by body surface area. For right-sided hemodynamics values a catheter was inserted into the pulmonary artery until the wedge position and subsequently pulmonary capillary wedge pressure (PCWP), pulmonary arterial pressure (PA) and right atrial pressure (RAP) were sequentially measured at steady state at end-expiration. By inserting a cardiac catheter into the ascending aorta, we measured the mean arterial pressure (MAP).

The RV-CPO at rest, in watts (W), was calculated using the equation: RV-CPO = (CO × MPAP) × K (conversion factor 2.22×10^{-3}), where MPAP is mean pulmonary arterial pressure in mm Hg. Following the American Society of Echocardiography guidelines, the left ventricular ejection fraction was calculated using the biplane modified Simpson's method.[5] Collected data included medical history, demographic characteristics, laboratory values, drug and device therapy.

To the best of our knowledge, there are no available normal RV-CPO values at rest for an average healthy man in the literature. Therefore, we decided to approximate by calculation, as normal MPAP (according to the current guidelines of the European Society of Cardiology/European Respiratory Society normal MPAP = 24 mm Hg)[6] multiplied by normal CO (assuming normal CO = 5 L/min) and divided by K (conversion factor 2.22×10^{-3}), to give an RV-CPO at rest of 0.27 W.

Survival curves of the patients were computed using Kaplan-Meier estimates for both low and high RV-CPO strata, and the log-rank test was used to verify the significance of differences between the strata. To study the effect of covariates on the survival of the patients, we performed stepwise Cox regression.

RESULTS

While compiling the data, 11 of the 172 patients had to be excluded from the study as they did not provide useful lifetime data. The observed lifetime for the remaining 161 patients in the study was defined as the time from the first contact with the patient to an endpoint, which may refer to cardiac death or some form of censoring. Cardiac deaths constituted 50 of these endpoints. The remaining 111 endpoints were censoring instances, of which nine were non-cardiac deaths, 10 were HTx, 12 were left ventricular assist device (LVAD) implantations, and 80 referred to patients who were alive (without HTx or LVAD implantation) at the end of the study.

Panel A in Figure 1 presents potential RV-CPO at rest threshold values and the corresponding chi-squared distance between the survival curves of the patients having RV-CPO at rest values on either side of the threshold. The maximum distance was observed for the threshold value of 0.15. In other words, when the patients were divided into two strata as having RV-CPO at rest below, and above the threshold of 0.15, the log-rank test for survival differences between the two strata returned a chi-squared value of 3.03 ($p = 0.081$), and this was the maximum distance among all possible threshold points. Panel B in Figure 1 illustrates the RV-CPO at rest distribution of all 161 patients, 12 of whom had RV-CPO at rest values less than or equal to the threshold.

The baseline characteristics of the patients in the study, stratified by the resting RV-CPO threshold, are given in Table 1. Categorical variable summaries are reported as percentages, and continuous variable summaries are reported as means (standard deviation). For all

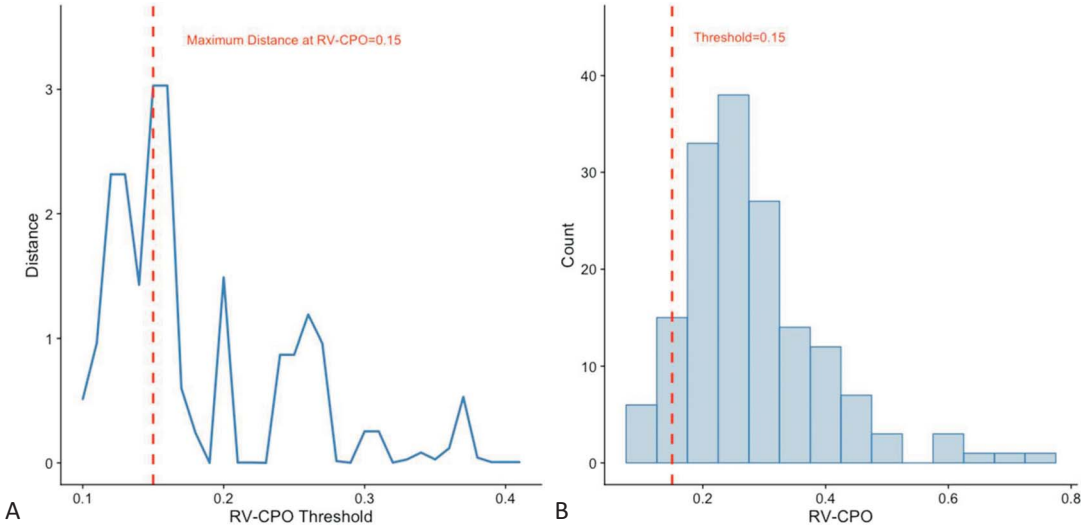

Figure 1. *(A) Search for right ventricular cardiac power output (RV-CPO) threshold. (B) RV-CPO distribution of 161 patients.*

Table 1. Baseline characteristics

Variable	Overall (n = 161)	RV-CPO ≤ 0.15 (n = 12)	RV-CPO > 0.15 (n = 149)	p value
Age* (years)	58.7 (11.2)	57.6 (15.3)	58.8 (10.9)	0.71
Gender* (male)	73.9%	74.6%	66.7%	0.51
Ejection fraction*	27.4 (4.7)	25.5 (4.8)	27.6 (4.7)	0.14
Mean arterial pressure	85.1 (13.6)	81.5 (15.6)	85.3 (13.4)	0.42
Pulmonary capillary wedge pressure*	21.7 (8.9)	11.6 (4.8)	22.5 (8.7)	< 0.0001
Right arterial pressure*	9.7 (5.4)	5.7 (3.98)	10.03 (5.4)	0.005
Cardiac output*	3.95 (1.1)	3.3 (0.57)	4.0 (1.1)	0.02
Body surface area	1.878 (0.194)	1.767 (0.184)	1.887 (0.193)	0.048
Estimated glomerular filtration rate dummy (1 if ≤ 60; 0 if > 60)*	17%	8.3%	17.6%	0.7
Cardiac resynchronization therapy-defibrillator	45.3%	41.6%	45.6%	1
Chronic obstructive pulmonary disease*	13.0%	8.3%	13.4%	1
Hypertension	57.76	58.33	57.71	1
Diabetes*	34.78	16.67	36.24	0.22
Valvural heart disease*	10.56	8.33	10.74	1
Chronic renal failure*	21.12	25	20.8	0.718
Atrial fibrillation*	8.69	16.67	8.05	0.279
Medication				
Mineralocorticoid receptor antagonist*	65%	66.7%	64.8%	0.66
Diuretic*	68.3%	58.3%	69.1%	0.53
Angiotensin converting enzym inhibitors/angiotensin II receptor blockers*	73.91	91.67	72.48	0.187
Beta blocker*	83.23	91.67	82.55	0.692

* Nonparametric test. RV-CPO, right ventricular cardiac power output.

categorical variables, either a chi-squared test or nonparametric Fisher's exact test (when the number of observations in cells was low) was used for testing differences between proportions in RV-CPO strata. For all continuous variables, either a Student's t test or nonparametric Wilcoxon test (when normal distribution assumption was rejected by Shapiro-Wilk's test) was used for testing the differences between means of RV-CPO strata. We observed one death and 11 censoring instances in the low RV-CPO strata, and 49 deaths and 100 censoring

instances in the high RV-CPO strata.

The estimated Kaplan-Meier survival curves for both strata are given in Figure 2. The figure also reports the number at risk with respect to time in both strata, which refers to the number of patients in the study after removing the deaths and censored observations. The patients with RV-CPO at rest less than or equal to 0.15 had significantly higher survival probabilities and therefore were considered to be lower-risk patients. Figure 3 presents a scatterplot of MPAP values of patients against their RV-CPO at rest levels. The correlation between the two variables was 0.65 ($p < 0.0001$), indicating a significant association.

The cross-classification of all patients with respect to chronic obstructive pulmonary disease (COPD, present/absent) and RV-CPO at rest (low: ≤ 0.15, high: > 0.15) resulted in a 2×2 contingency table with one patient in the present/low category, 20 patients in the present/high category, 11 patients in the absent/low category, and 129 patients in the absent/high category. Fisher's exact test returned a p-value very close to 1 indicating no association between COPD and RV-CPO at rest.

Figure 4 presents the box plots of specific variables above and below the RV-CPO at rest threshold. The two-sample Kolmogorov-Smirnov test was also used to test the differences between the estimated distributions, and the result was statistically significant.

Several univariate and multivariate Cox regression models were considered to investigate the effects of all variables on the survival of the patients. The effect of RV-CPO at rest was studied with a dummy variable, which was 1 for RV-CPO ≤ 0.15 and 0 otherwise. In addition to age and gender, the 13 significant variables given by the

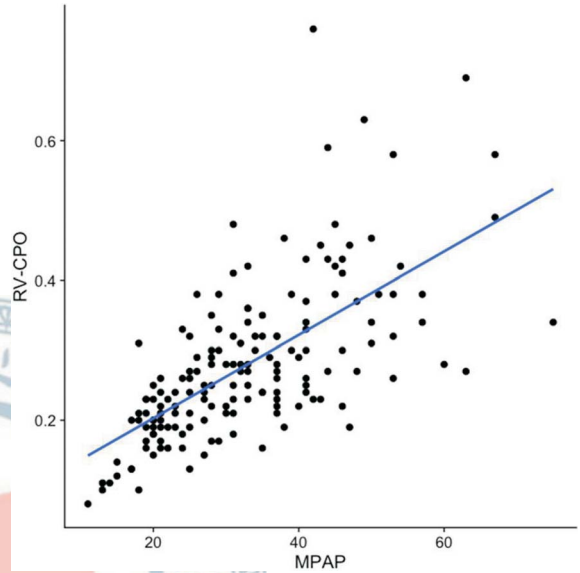

Figure 3. *Association between MPAP and RV-CPO. MPAP, mean pulmonary arterial pressure; RV-CPO, right ventricular cardiac power output.*

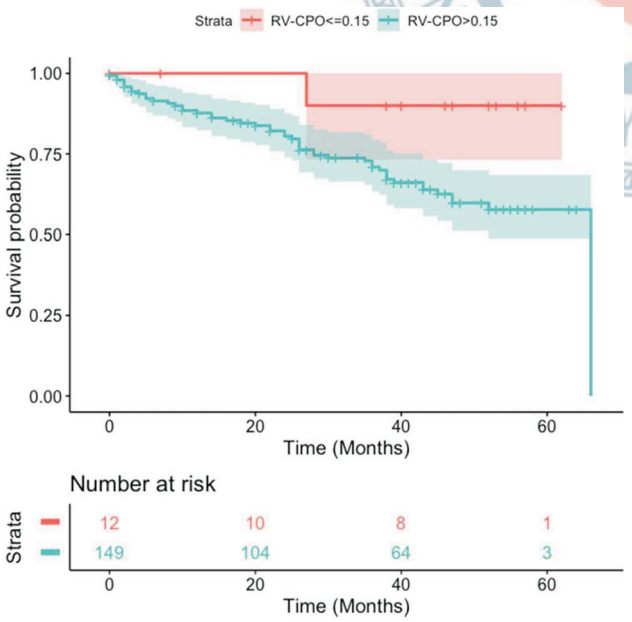

Figure 2. *Kaplan-Meier estimates of survival functions. RV-CPO, right ventricular cardiac power output.*

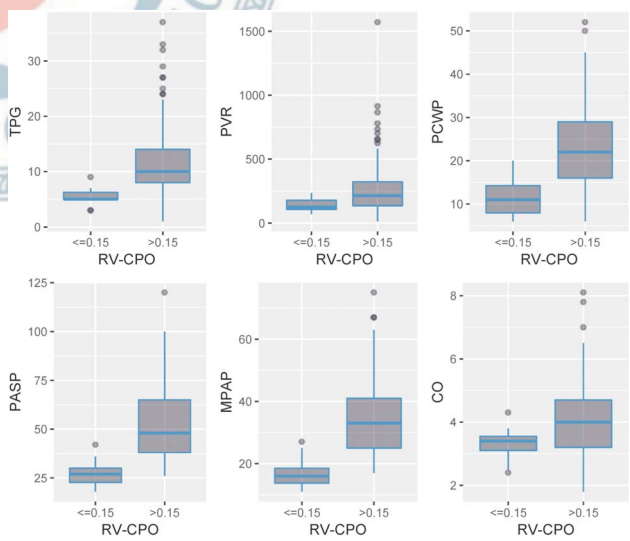

Figure 4. *Box plots of several variables based on RV-CPO strata. CO, cardiac output; MPAP, mean pulmonary arterial pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV-CPO, right ventricular cardiac power output; TPG, transpulmonary pressure gradient.*

univariate regression models were RV-CPO at rest dummy, MAP, RAP, CO, CI, pulmonary vascular resistance (PVR), ejection fraction (EF), mineralocirtiocoid receptor antagonist (MRA), COPD, PCWP, diabetes dummy (DIAB), valvular heart disease dummy (VHD), and body surface area (BSA). After this preliminary screening, we focused on these 15 variables and carried out a stepwise procedure to build a multiple Cox regression model to study the adjusted effects of all these variables. Table 2 gives the details of this procedure, and shows that the additional variables entered into the model (in order of entry) were EF, CO, RV-CPO, MAP, VHD, DIAB, BSA, and MRA. Including the remaining variables increased the Akaike Information Criterion (AIC); therefore, they were not accepted in the model. The final model had 10 predictors and an AIC value of 391.5.

The details of the final adjusted multiple regression model, along with the unadjusted univariate regression details for each variable in the final model are given in Table 3. The reported hazard ratios corresponded to the exponentials of regression coefficients, and they represented the relative risk introduced by the variables. The hazard ratio of RV-CPO dummy variable seemed to have a significant effect on hazard (p-value = 0.005), and the

Table 2. Forward stepwise Cox regression with akaike ınformation criterion (AIC)

	Variable to enter	AIC
Base model	Age and gender	458.5
Step 1	Ejection fraction (recorded as %)	441.5
Step 2	Cardiac output (L/min)	428.8
Step 3	Right ventricular cardiac power output dummy (1 if ≤ 0.15; 0 if > 0.15)	421.1
Step 4	Mean arterial pressure (mmHg)	405.7
Step 5	Valvular heart disease dummy (1 if present; 0 if not)	394.6
Step 6	Diabetes dummy (1 if present; 0 if not)	392.8
Step 7	Body surface area (m^2)	392.0
Step 8	Mineralocirtiocoid receptor antagonist medication dummy (1 if used; 0 if not used)	391.5

Table 3. Cox regression models

Variable	Hazard ratio	95% confidence ınterval	p value
Unadjusted			
Age (years)	1.01	0.982-1.04	0.48
Gender (1 = male, 0 = female)	0.931	0.494-1.756	0.82
Ejection fraction (recorded as %)	0.918	0.862-0.979	0.009
Cardiac output	0.539	0.398-0.730	< 0.0001
Right ventricular cardiac power output (1 if ≤ 0.15; 0 if > 0.15)	0.205	0.028-1.483	0.116
Mean arterial pressure (mmHg)	0.973	0.951-0.995	0.017
Valvular heart disease dummy	2.602	1.214-5.576	0.0139
Diabetes dummy	1.643	0.937-2.88	0.0828
Body surface area (m^2)	0.079	0.015-0.421	0.0029
Mineralocirtiocoid receptor antagonist medication dummy	2.227	1.111-4.466	0.024
Adjusted			
Age (years)	1.004	0.972-1.038	0.78
Gender (1 = male, 0 = female)	1.198	0.541-2.654	0.65
Ejection fraction (recorded as %)	0.898	0.834-0.967	0.004
Cardiac output	0.431	0.290-0.638	< 0.0001
Right ventricular cardiac power output (1 if ≤ 0.15; 0 if > 0.15)	0.052	0.006-0.406	0.005
Mean arterial pressure (mmHg)	0.947	0.921-0.973	0.0001
Valvular heart disease dummy	6.532	2.735-15.6	< 0.0001
Diabetes dummy	2.069	1.098-3.9	0.024
Body surface area (m^2)	0.166	0.02-1.395	0.098
Mineralocortiocoid receptor antagonist medication dummy	1.678	0.822-3.423	0.154

corresponding hazard ratio was 0.052 with a 95% confidence interval of 0.006 to 0.406. Therefore, patients with RV-CPO values less than or equal to 0.15 could be considered to have a significantly lower hazard ratio (< 1) and could be considered to be lower-risk patients. However, this finding should be interpreted with caution as there was only one observed death (and 11 censoring instances) in the low RV-CPO strata, resulting in a considerably large confidence interval. The coefficient of determination for the multiple Cox regression model, which reports the proportion of the variation in survival times that can be explained by the variation in predictor variables, was 0.295, with a maximum possible value of 0.941.

DISCUSSION

The results of the present study, based on the only investigation of RV-CPO at rest in patients with advanced HF to date with long-term follow-up, confirm previous reports describing the effect of pulmonary hypertension (PH) on right ventricular failure. In addition, an RV-CPO > 0.15 W was shown to have an independent impact on mortality.

It is essential to understand the physiopathological relationship between elevation of left-sided heart filling pressures and pulmonary artery pressure in patients with advanced HF. Left ventricular dysfunction and remodeling lead to functional mitral regurgitation and thus to elevation of left-sided heart filling pressures with loss of compliance.[7] The increase of left-sided heart filling pressures will be transmitted to pulmonary artery pressure in a nearly 1:1 proportion,[7] leading to the development of PH due to left-sided HF. This means increased afterload for the right ventricle, which is usually coupled with high compliance and low resistance of the pulmonary vasculature. It is well-known that the right ventricle is more sensitive to increases in afterload than preload. Therefore, an increase in right ventricular afterload by developing PH secondary to left-sided HF has been considered to be the primary mechanism of right ventricular dysfunction.[8,9] In this regard, we expected that the cut-off value for the impact on mortality in patients with advanced HF would be above the upper normal value of 0.27 W, but interestingly, we found a cut-off value of 0.15 W, which is lower than expected.

To understand this result, it is important to realize the physiopathological relationship between increased pulmonary artery pressure due to left-sided HF and right ventricular function in patients with advanced HF. The elevated pulmonary artery pressure due to left-sided HF results in endothelial dysfunction at the pulmonary capillary level which is characterized by the overproduction of endothelin-1, decreased production of nitric oxide and activation of the renin-angiotensin-aldosterone system as well as neurogenic activation.[7,8] This then leads to both pulmonary artery vasoconstriction and pulmonary vascular resistance increase. Next, increased pulmonary artery pressure results in vascular damage with pathological remodeling of the pulmonary arterioles, such as thickening of the alveolar-capillary membrane, medial hypertrophy, and neointimal proliferation,[10] and thus leading to PH due to left-sided HF. Finally, the right ventricular function is highly afterload-dependent. Therefore, the elevation of afterload progressively leads to decreased right ventricular stroke volume. Over time, the right ventricle adjusts itself to the elevated afterload due to left-sided HF. Initially, normalizing right ventricular wall stress (Laplace law) and thus right ventricular myocardial oxygen demand leads to remodeling of the right ventricle which is characterized by right ventricular hypertrophy.[7] This right ventricular adaptation procedure is followed by dilatation, leading to increased right ventricular wall tension and oxygen consumption, thereby resulting in changes at the cellular level, leading to myofibrosis and increased right ventricular stiffness, and thus right ventricular HF. As the disease progresses, both MPAP and CO may decrease in the late stage of HF due to severe right and left ventricular dysfunction, leading to an adverse short-term prognosis.[11] Taken together, these findings and considering the components of the formula used to calculate RV-CPO at rest can explain the lower cut-off value of 0.15 W in our study population compared to healthy people.

The concept of resting right ventricular cardiac power was previously demonstrated in a single-center clinical study with small sample size. Using right ventricular cardiac power index at rest as a hemodynamic parameter of right ventricular performance, Russ et al. demonstrated that levosimendan infusion for cardiogenic shock following acute myocardial infarction improved right

ventricular performance.[12] However, the present analysis is the only study to date with a sufficient sample size and long-term follow-up to demonstrate an association between RV-CPO at rest and mortality in patients with advanced HF.

Of note, some people will develop both severe PH secondary to left-sided HF and right ventricular dysfunction, but others will not. The underlying cause of this predisposition is unknown. However, the cause and effect link between environmental and, genetic factors and the duration of left ventricular dysfunction are potential influencing variables. To better understand the causal relationships, further research is required.

Study limitations

Due to the study design, several limitations shoul be considered when interpreting our results. First, the presence of selection bias for consecutive patients with advanced HF who were referred to a tertiary care center for HF management and/or to be evaluated for HTx cannot be excluded. However, owing to the severity of the disease, patients with advanced HF are likely to have adverse outcomes. Second, based on analyzing RV-CPO at rest at only one time point, it is unclear whether intermediary transient hemodynamic changes were consistent with clinical outcomes. Based on the severity of the disease, however, an improvement in health status cannot be expected during follow-up. Thus, we believe that one value of RV-CPO at rest is prognostic informative. Third, we cannot exclude that endpoints such as LVAD implantation and HTx might be biased by selection criteria for mechanical circulatory support and donor heart availability. Another limitation of our study was that the data were acquired in an era with non-contemporary risk stratification, meaning without cardiopulmonary stress testing. However, a prior study illustrated that over 50% of HTx candidates with reduced peak VO_2 level had only mild or moderate hemodynamic dysfunction,[13] and another previous study demonstrated that resting cardiac pump function was not associated with peak VO_2 but with HTx- and ventricular assist device-free survival independent of peak VO_2.[14] In addition, an earlier study showed that right ventricular ejection fraction was a better predictive factor of survival in patients with advanced HF than peak oxygen consumption.[15] Furthermore, the concentration of B-type natriuretic peptide (BNP) level was not measured. However, in a previous study, there was no significant imbalance between the control group and BNP-guided HF treatment.[16]

CONCLUSIONS

We illustrated that in patients with advanced HF, RV-CPO at rest was associated with increased mortality. Hence, we suggest that RV-CPO at rest might be an important prognostic marker for individual risk stratification of patients with advanced HF who would benefit from a timely listing for HTx and/or consideration for mechanical circulatory support device therapy.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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