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Prognostic Role of Cardiac Power Index in Ambulatory Patients with Advanced Heart Failure

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Background

Cardiac pump function is often quantified by left ventricular ejection fraction by various imaging modalities. As the heart is commonly conceptualized as a hydraulic pump, cardiac power describes the hydraulic function of the heart. We aim to describe the prognostic value of resting cardiac power index (CPI) in ambulatory patients with advanced heart failure.

Methods and results

We calculated CPI in 495 sequential ambulatory patients with advanced heart failure who underwent invasive haemodynamic assessment with longitudinal follow-up of adverse outcomes (all-cause mortality, cardiac transplantation, or ventricular assist device placement). The median CPI was 0.44 W/m^2 (interquartile range 0.37, 0.52). Over a median of 3.3 years, there were 117 deaths, 104 transplants, and 20 ventricular assist device placements in our cohort. Diminished CPI ($<0.44 \text{ W/m}^2$) was associated with increased adverse outcomes [hazard ratio (HR) 2.4, 95% confidence interval (CI) 1.8–3.1, $P < 0.0001$]. The prognostic value of CPI remained significant after adjustment for age, gender, pulmonary capillary wedge pressure, cardiac index, pulmonary vascular resistance, left ventricular ejection fraction, and creatinine [HR 1.5, 95% CI 1.03–2.3, $P = 0.04$]. Furthermore, CPI can risk stratify independently of peak oxygen consumption (HR 2.2, 95% CI 1.4–3.4, $P = 0.0003$).

Conclusion

Resting cardiac power index provides independent and incremental prediction in adverse outcomes beyond traditional haemodynamic and cardio-renal risk factors.

Introduction

The heart is often conceptualized as a muscular hydraulic pump with the ability to generate both flow ('cardiac output') and pressure. In a purely haemodynamic sense, cardiac output (CO) describes cardiovascular flow through a closed circuit. Cardiac output encompasses not only intrinsic cardiac contractility, but also a complex interplay with vascular compliance and resistance to flow (impedance) in addition to intravascular volume and cardiac filling pressures. The heart and blood vessels are better analogized to a pump creating hydraulic energy and to the pipes that transmit

this energy. In the cardiovascular system, during asystole, blood flow eventually slows to a standstill as a result of dissipative effect of turbulence and flow separation. Therefore, the hydraulic energy of the heart can be characterized by cardiac power output (CPO) or cardiac power index (CPI) as the product of flow (cardiac index, CI) and mean arterial pressure.¹ The product of flow output and systemic arterial pressure is the rate of useful work done, or 'cardiac power output'.²

The heart has a range of power outputs: resting CPO, maximal CPO, and reserve CPO (maximal CPO – resting CPO). As pump dysfunction occurs over time (i.e. incident myocardial

infarction, valvular heart disease, myocarditis, etc.), the maximal CPO decreases with corresponding decrements in reserve CPO, and, if severe, is followed by decrements in resting CPO which may lead to severe heart failure (HF) or even cardiogenic shock.³

In patients with chronic HF, maximal CPO, and reserve CPO, measured non-invasively or invasively during cardiopulmonary stress testing (CPX), are strong predictors of mortality.^{4–9} When measured in the acute setting, resting CPO can help identify different acute HF syndromes including cardiogenic shock,³ and is associated with worsening HF and incident mortality.^{10,11} However, there are few data regarding the prognostic impact of resting CPO in chronic HF.⁹ Because worsening resting CPO may correlate with severity of HF,³ we hypothesize that invasively measured resting CPO indexed to body surface area (commonly known as CPI), is associated with long-term transplant- and ventricular assist device-free survival in an advanced HF cohort.

Methods

Study population

This is a retrospective cohort study comprising ambulatory patients with chronic heart failure seen at the Cleveland Clinic from January 1, 2000, to December 31, 2005. Medical records of all consecutive patients ≥ 18 years old with advanced chronic heart failure (ACHF, >6 months) who had undergone pulmonary artery catheterization (PAC) as part of an outpatient assessment were reviewed. Pulmonary artery catheterization was indicated for assessment of disease severity often secondary to progressive signs or symptoms of heart failure. Patients were excluded if they had complex congenital heart disease, were on long-term inotropic drug infusions, or if they were admitted into the hospital directly after PAC for management of decompensated heart failure. The Cleveland Clinic Institutional Review Board approved the study.

Data synthesis and variable definitions

Data abstraction and adjudication has been described previously.¹² If patients had multiple PACs, only data from the first PAC were used. Collected data include demographic characteristics, medical history, drug and device therapy, laboratory values, and underlying heart rhythm. B-type natriuretic peptide (BNP) levels were measured at baseline and at 1- and 6-month follow-up intervals if available. Cardiopulmonary stress test data, including peak-exercise oxygen consumption (peak VO_2) and echocardiographic data, were collected if performed within 1 month of the outpatient clinic visit. Cardiopulmonary stress testing was performed according to the recommendations by the American Heart Association.¹³ The left ventricular ejection fraction (LVEF) was calculated using the biplane modified Simpson's method. Left ventricular end diastolic diameter was measured in the parasternal long axis view. Both tests were read by board-certified cardiologists as part of routine care in accordance with the American Society of Echocardiography guidelines.¹⁴

Assessment of haemodynamics

Pulmonary artery catheterization was performed via cannulation of the internal jugular vein under fluoroscopic guidance with the

patients in the supine position. Filling pressures including right atrial pressure (RAP), pulmonary arterial pressure, and pulmonary capillary wedge pressure (PCWP) were measured at end-expiration at steady state. Mixed central venous blood gas was collected from the tip of the catheter in the pulmonary artery and cardiac output (CO) was estimated using Fick's equation and indexed to body surface area (BSA): $\text{CO}/\text{BSA} = \text{CI}$. Mean arterial pressure was measured non-invasively by an automated blood pressure cuff at the time of PAC. Systemic vascular resistance (SVR) was calculated as the mean arterial pressure – right atrial pressure difference divided by CO. Pulmonary vascular resistance was calculated as: $[\text{mean pulmonary arterial pressure (MPAP)} - \text{PCWP}]/\text{CO}$. The CPO (in W) was calculated by the equation: $\text{CPO} = \text{mean arterial pressure (mmHg)} \times \text{CO [L/min]} \times K$, where $K = 0.0022$ (a conversion factor); and was indexed to body surface area: $\text{CPI (W/m}^2\text{)} = \text{CPO (W)}/\text{body surface area (m}^2\text{)}$.

Endpoints

The time interval from the outpatient visit to either all-cause mortality, heart transplantation, or ventricular assist device placement was defined as the duration of follow-up. All-cause mortality was assessed by analysing data from the electronic health record in addition to querying the Social Security Death Index. All endpoints were censored on December 31, 2007.

Statistical methods

Continuous variables were expressed as either mean \pm standard deviation or median [interquartile range (IQR)] where appropriate. The unpaired Student's *t*-test or Wilcoxon signed-rank test were used to compare parametric and non-parametric continuous variables, respectively. Categorical variables were expressed as percentage (%) with comparisons via Fisher's exact test or the chi-square method. The CPI was divided into two partitions stratified by the median in order to make clinical comparisons of prognostic value. Only non-missing data were analysed. *P*-values of <0.05 were considered significant to reject the null hypothesis that there were no differences in transplant-free survival between subjects stratified by median CPI and, in subgroups with serial BNP levels or with additional stratification by peak VO_2 . Independent variables include CPI levels stratified by median CPI and dependent variables include all-cause mortality, cardiac transplantation, ventricular assist device placement, and serial BNP. Survival analyses were completed via the Kaplan-Meier method and log-rank analysis to compare transplant- and ventricular assist device-free survival curves of CPI stratified by median CPI for the cohort and a subgroup analysis stratified by median peak VO_2 . Cox-proportional hazards models were used to compare time-to-event analyses to determine HRs and 95% CIs for mortality, cardiac transplantation, and ventricular assist device placement for CPI stratified by median CPI. Multivariable models adjusted for age, gender, PCWP, Fick CI, PVR, creatinine, and LVEF. In a subset, BNP levels were added as an additional covariate. Statistical analyses were performed using JMP Pro version 10 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics

Baseline characteristics of our study cohort are described in Table 1, which are representative of a population with advanced

Table 1 Baseline characteristics (n = 495)

Variable	Overall	CPI <0.44 W/m ² (n = 247)	CPI ≥0.44 W/m ² (n = 248)	P
Age (years)	54 ± 11	55 ± 11	53 ± 12	0.2
Male (%)	75.8	76.1	75.4	0.9
BMI (kg/m ²)	28 ± 6	27 ± 5	29 ± 6	0.002
ICM (%)	48.3	47	49.6	0.6
LVEF (%)	20 (15, 25)	15 (15, 20)	20 (15, 30)	<0.0001
LVEDD (cm)	6.6 ± 1.1	6.8 ± 1.2	6.4 ± 1.0	<0.0001
ICD (%)	38.8	44.1	33.5	0.02
CRT (%)	9.5	10.9	8.1	0.3
NYHA class				
II (%)	3.6	2.8	4.4	0.5
III (%)	90.7	91.9	89.5	
IV (%)	5.5	5.3	5.7	
Medications				
ACEI/ARB (%)	88.3	87.5	87.1	1
Beta-blocker (%)	69.9	69.2	70.6	0.8
MRA (%)	37.9	42.7	33.1	0.03

Abbreviations: CPI, cardiac power index; BMI, body mass index; ICM, ischaemic cardiomyopathy; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Missing values: LVEDD: n = 101 and LVEF n = 106.

*Values in brackets are interquartile range.

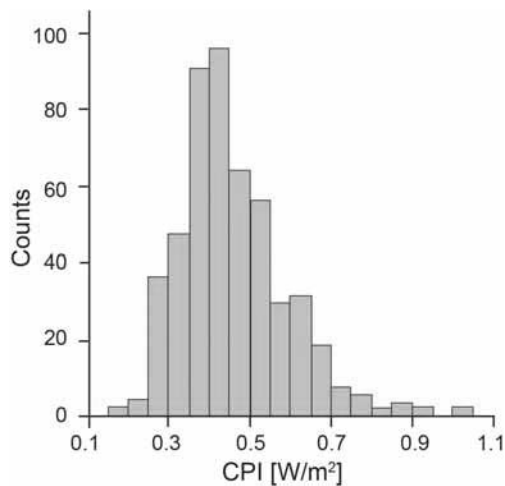


Figure 1 Cardiac power index (CPI) levels in study cohort (n = 495). Mean was 0.46 ± 0.13 W/m² and the median was 0.44 W/m² (IQR 0.37, 0.52).

HF. The CPI levels were distributed with a right skew (Figure 1). The median CPI was 0.44 W/m² (IQR 0.37, 0.52). Lower CPI was associated with features consistent with more advanced disease status, including lower body mass index, higher ICD, and mineralocorticoid receptor antagonist use, with lower LVEF and higher LVEDD.

Baseline CPI, haemodynamics, and laboratory values

Baseline haemodynamics are shown stratified by median CPI (Table 2). Lower CPI was associated with lower mean arterial pressure (MAP) and CI ($P < 0.0001$ for both), but higher RAP, pulmonary arterial pressures, PCWP, SVR, and PVR ($P < 0.001$ for all). Lower CPI was associated with higher baseline creatinine ($P = 0.0008$) and BNP ($P < 0.0001$). In a subset of patients with available BNP data ($n = 135$) at the time of clinical evaluation, baseline BNP and CPI levels were moderately correlated (Spearman's $\rho = -0.43$, $p < 0.0001$). Lower baseline CPI was associated with higher BNP levels at baseline, and subsequently at 1-month and 6-month follow-up visits ($P < 0.001$ for all) (Figure 2).

Cardiac power index and transplant and ventricular assist device-free survival

Of the 495 patients followed for all-cause mortality, cardiac transplantation, or ventricular assist device placement, 234 (47%) patients either died ($n = 117$), underwent cardiac transplantation ($n = 104$), or received a ventricular assist device ($n = 20$) at a median follow-up of 3.3 years after the haemodynamic evaluation. Lower baseline CPI was associated with a significantly lower transplant- and ventricular assist device-free survival (Log-rank, chi-square 43.9, $P < 0.0001$, Figure 3). A CPI below the median predicted a 2.4-fold increase in mortality, cardiac transplantation, or assist device placement (Table 3) when compared with

Table 2 Baseline resting haemodynamic and laboratory values (n = 495)

Variable	Overall	CPI <0.44 W/m ² (n = 247)	CPI ≥0.44 W/m ² (n = 248)	P
Heart rate (bpm)	80 ± 18	79 ± 16	81 ± 19	0.1
MAP (mmHg)	86 ± 13	81 ± 12	91 ± 12	<0.0001
RAP (mmHg)*	7 (4, 10)	8 (5, 12)	6 (3, 9)	<0.0001
PASP (mmHg)*	40 (30, 54)	45 (32, 57)	38 (28, 50)	0.0002
PADP (mmHg)*	20 (12, 25)	22 (16, 27)	18 (12, 22)	<0.0001
MPAP (mmHg)*	27 (19, 35)	30 (21, 37)	24 (17, 32)	<0.0001
PCWP (mmHg)*	18 (23, 10)	20 (13, 25)	14 (10, 21)	<0.0001
Fick CO (L/min)	4.7 ± 1.3	4.1 ± 0.9	5.6 ± 1.2	<0.0001
Fick CI (L/min.m ²)	2.4 ± 0.6	2.0 ± 0.4	2.8 ± 0.5	<0.0001
PVR (WU)	2.4 ± 1.5	2.7 ± 1.7	2.0 ± 1.2	<0.0001
SVR (dyn•s/cm ⁵)	1443 ± 429	1530 ± 461	1357 ± 376	<0.0001
Haemoglobin (g/dL)	13.5 ± 1.7	13.6 ± 1.6	13.4 ± 1.7	0.2
Creatinine (mg/dL)*	1.1 (0.9, 1.4)	1.2 (1.0, 1.5)	1.0 (0.9, 1.3)	0.0008
Sodium (mEq/L)	139 ± 5	139 ± 4	139 ± 6	0.6
BNP (pg/mL)*	348 (137, 782)	605 (230, 1150)	228 (81, 484)	<0.0001

Abbreviations: CPI, cardiac power index; MAP, mean arterial pressure; RAP, right atrial pressure; PASP, pulmonary arterial systolic pressure; PADP, pulmonary arterial diastolic pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; BNP, B-type natriuretic peptide.

Missing values: SVR n = 7; PVR n = 8; haemoglobin n = 47; creatinine n = 39; sodium n = 37; BNP n = 360.

*Values in brackets are interquartile range.

CPI above the median (HR 2.38, 95% CI 1.83–3.11, $P < 0.0001$; c-statistic 0.62, 95% CI 0.59–0.65). After multivariable adjustment for age, gender, PCWP, Fick CI, creatinine, and LVEF lower CPI still remained independently associated with an increased risk of death, cardiac transplantation, or ventricular assist device placement (HR 1.52, 95% CI 1.03–2.28, $P = 0.04$). Furthermore, lower CPI was still independently associated with an increased risk of death, cardiac transplantation, or ventricular assist device placement when BNP was added to the multivariable adjustment mentioned previously (HR 2.8 95% CI 1.2–7.3, $P = 0.02$, $n = 135$). Although SVR index (SVRI) is similar to the inverse of CPI, high SVR was associated with a lower hazard ratio for the composite outcome (HR 1.5, 95% CI 1.1–1.9, $P = 0.0004$). Further, SVRI was modestly correlated with CPI (Spearman rho -0.20 , $P < 0.0001$) and venous adjusted CPI (MAP-RAP, Spearman rho -0.16 , $P = 0.0003$). When analysed as a continuous predictor, CPI was inversely associated with these adverse outcomes in univariable (per 0.05 unit change, HR 0.80, 95% CI 0.76–0.85, $P < 0.0001$; c-statistic 0.66, 95% CI 0.62–0.69) and multivariable analyses (per 0.05 unit change, HR 0.84, 95% CI 0.75–0.94, $P = 0.004$).

Overall, the median CPI levels were not different when stratified by age [<50 years ($n = 140$): 0.45 W/m^2 (0.38, 0.54); 50–65 years ($n = 272$): 0.43 [0.37, 0.52] 0.43 W/m^2 , and >65 years ($n = 83$): 0.42 W/m^2 [0.35, 0.50]; $P = 0.29$). Indeed, the point estimates for hazard ratios were different in subgroups by age. At age <50 years, low CPI was associated with 3.7-fold increased risk of death, cardiac transplantation, or ventricular assist device placement ($n = 56/140$, HR 3.7, 95% CI 2.1–7.1, $P < 0.0001$); at age 50–65 years low CPI was associated with a 2.4-fold increased risk of death, cardiac transplantation, or ventricular assist device placement ($n = 139/272$, HR 2.4, 95% CI 1.7–3.5, $P < 0.0001$); and

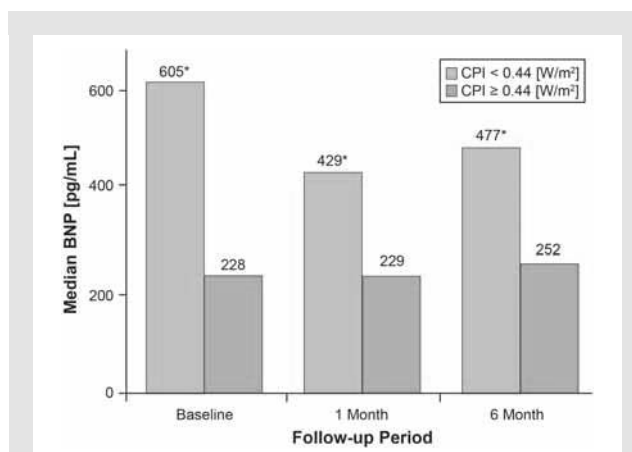


Figure 2 Follow-up B-type natriuretic peptide (BNP) levels stratified by cardiac power index (CPI) level. * $P < 0.001$. Subset with serial BNP: $n = 121$. Values are expressed as median and P -values calculated via Wilcoxon Signed Rank Test.

at age >65 years there was a non-significant trend towards increased risk of death, cardiac transplantation, or ventricular assist device placement with low CPI ($n = 46/83$, HR 1.6, 0.9–2.8, $P = 0.14$). Patients taking all evidence-based therapies (beta-blocker, renin-angiotensin system blocker, and mineralocorticoid antagonist, $n = 124$ (25.1%)), below median CPI still remained associated with adverse outcomes (HR 1.99, 95% CI 1.18–3.49, $P = 0.01$). In a sensitivity analysis for outcomes censored at 1 year of follow-up (death, $n = 29$; cardiac transplantation, $n = 65$; and ventricular assist device placement, $n = 10$), below median CPI

Table 3 Cox proportional hazards models according to resting cardiac power index (CPI) for death, mortality, and ventricular assist device placement

Variable	Hazard ratio*	95% Confidence Interval	P
Unadjusted			
Age (years)	1.02	1.004–1.03	0.006
Male	1.31	0.97–1.81	0.08
PCWP (mm Hg)	1.05	1.03–1.06	<0.0001
Fick CI (L/min/m ²)	0.38	0.29–0.49	<0.0001
PVR (WU)	1.22	1.14–1.29	<0.0001
Creatinine (mg/dL)	1.64	1.32–2.01	<0.0001
LVEF (%)	0.97	0.95–0.98	<0.0001
CPI†	2.38	1.83–3.11	<0.0001
Adjusted			
Age (years)	1.81	0.99–1.02	0.20
Male	1.32	0.91–1.97	0.14
PCWP (mm Hg)	1.01	0.99–1.03	0.16
Fick CI (L/min/m ²)	0.69	0.45–1.04	0.08
PVR (WU)	1.12	1.03–1.21	0.007
Creatinine (md/dL)	1.51	1.12–1.98	0.007
LVEF (%)	0.98	0.96–1.00	0.06
CPI†	1.52	1.03–2.28	0.04
CPI†‡	2.84	1.17–7.30	0.02

Abbreviations: CPI, cardiac power index; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide.

*Per unit change if continuous.

†CPI ≥ 0.44 vs. CPI < 0.44 W/m², 241 events.

‡Multivariable adjustment for the previous variables with the addition of BNP in a subset ($n = 135$) with available BNP values.

remained associated with an increased risk after multivariable adjustment (HR 2.24, 95% CI 1.12–4.47, $P = 0.02$).

Cardiac power index and transplant and ventricular assist device-free survival in a subset with cardiopulmonary stress testing

A total of 174 of the original 495 patients had cardiopulmonary stress testing (Figure 4) and were followed cardiac transplantation, ventricular assist device placement, or all-cause mortality. There was no linear association with baseline CPI and peak VO₂ levels ($R^2 = 0.001$). In total, 85 (49%) patients either died ($n = 38$), underwent cardiac transplantation ($n = 39$), or received a ventricular assist device ($n = 8$) at a median follow-up of 3.1 years after the initial clinical visit. The median peak VO₂ was 14.6 mL/kg.min and below-median peak VO₂ was associated with a trend towards increased mortality (HR 1.47, 95% CI 0.98–2.23, $P = 0.06$). Regardless of median stratified peak VO₂, lower CPI remained a strong predictor of cardiac transplantation, ventricular assist device placement, or all-cause mortality (Log-Rank, chi-square 21.6, $P < 0.0001$ at 3 years; Figure 5).

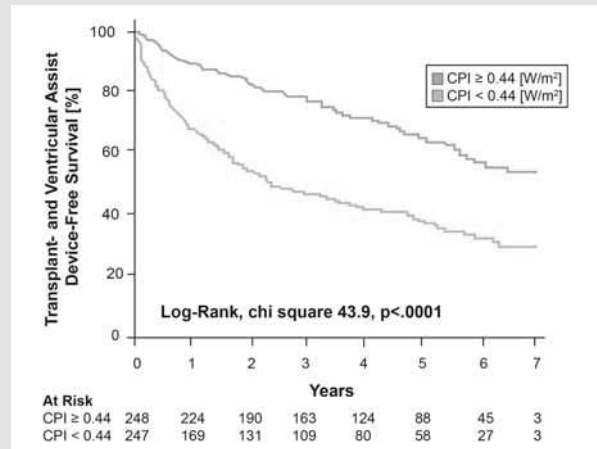


Figure 3 Kaplan–Meier estimates of transplant and ventricular assist device-free survival according to cardiac power index (CPI) level. Log-rank, χ^2 43.9, $P < 0.0001$. A total of 117 deaths, 104 orthotopic heart transplants, and 20 ventricular assist device placements occurred during a median follow-up of 3.34 years (IQR 1.35, 5.32).

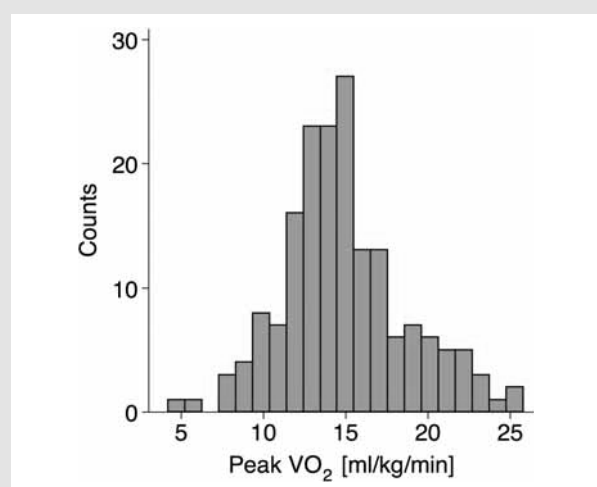


Figure 4 Peak-stress oxygen consumption (Peak VO₂) in the subset with cardiopulmonary stress testing ($n = 174$). Mean was 14.9 ± 3.8 mL/kg.min and median was 14.6 (IQR 12.6, 16.9) mL/kg.min.

Discussion

Our cohort has several key findings that add to our understanding of the clinical consequences of cardiac hydraulic function in ambulatory patients with advanced HF. First, resting CPI was associated with other common markers of severity of HF at baseline and over time. Second, in a large cohort of ambulatory patients with advanced HF, we observed a strong association between CPI and transplant- and ventricular assist device-free survival. Being the largest series of patients on this topic with long-term follow-up,

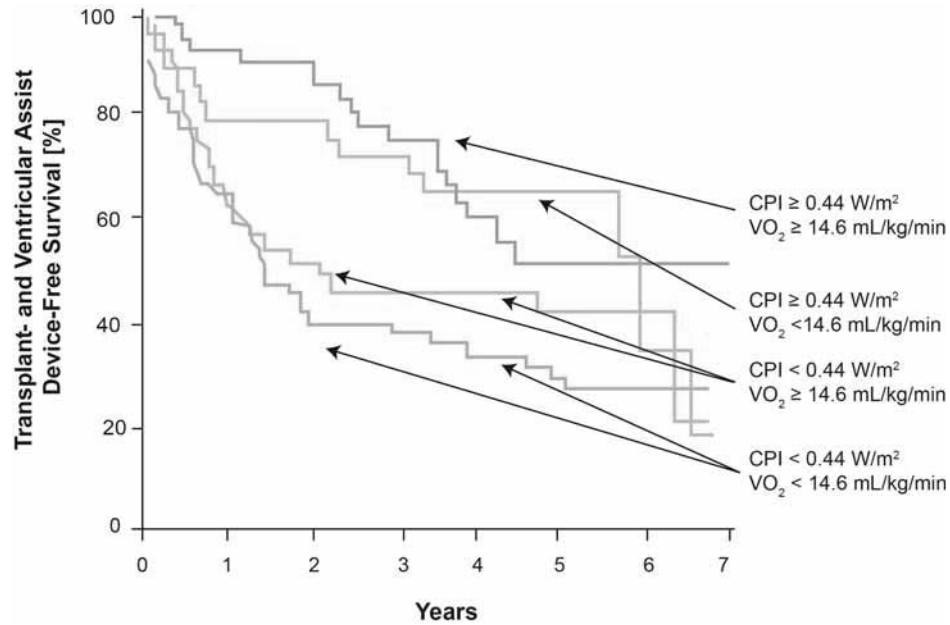


Figure 5 Kaplan–Meier estimates of transplant and ventricular assist device-free survival according to cardiac power index (CPI) and peak VO₂. Subset with peak-stress oxygen consumption (Peak VO₂) measured, $n = 174$. A total of 38 deaths, 39 orthotopic heart transplants, and eight ventricular assist device placements occurred during a median follow-up of 3.12 years [IQR 0.97, 4.83]. Log-Rank, χ^2 21.6, $P < 0.0001$ for outcomes at 3 years. Units are W/m² for CPI.

we had the opportunity to conduct a more rigorous evaluation to understand the determinants of resting CPI. We observed that the prognostic value of CPI remained robust after multivariable adjustment for demographic, laboratory, and adverse haemodynamic risk factors including renal function and BNP. Third, although peak VO₂ is a well known prognostic factor in advanced HF,¹⁵ there was no correlation with CPI and peak VO₂ during CPX. Yet, CPI was independently associated with mortality, incident cardiac transplantation, and incident ventricular assist device placement despite stratification by peak VO₂. These findings highlight the potential for resting CPI to be a useful metric in stratifying risk in patients with advanced HF.

Cardiac output and systemic arterial pressure are both measures of cardiac function, but one does not necessarily predict the other. For example, cardiogenic shock is characterized by both low CO and MAP, whereas distributive shock is characterized by a high CO in the setting of low MAP. However, CPI is an integration of both measures and is a more accurate representation of cardiac pump efficiency.

In this study, resting CPI was associated with common markers of worsening cardiac dysfunction. Because invasive haemodynamic measurements, including elevated right- and left-sided filling pressures, PVR, and CI, are commonly associated with adverse events including renal dysfunction and death in HF,^{16–18} it is not surprising that these factors are associated with and may be secondary to cardiac pump function. Plasma natriuretic peptide levels are markers of myocardial stress and are strongly correlated with adverse outcomes in chronic HF.^{19,20} Renal function, a marker of end-organ

perfusion, is also strongly associated with both mortality and progression of HF in patients with left ventricular dysfunction.²¹ Our observation regarding the inverse relationship between baseline resting CPI and baseline BNP or creatinine and higher BNP on follow-up assessment suggested that factors related to cardio-renal disease progression may represent the consequences of cardiac inefficiency and suggest that the incremental prognostic value of CPI is a combined metric of the severity of HF.

The concept of cardiac power has been previously put forward in single-centre clinical studies with small sample sizes and event rates. In a series of 50 HF patients with New York Heart Association (NYHA) Class II and III symptoms,⁹ patients who had adverse cardiac events (admission owing to HF, pulmonary oedema, or ventricular arrhythmia) or died during follow-up (21.2 ± 1.2 months, total 19 events) had a non-significant trend towards lower resting CPO. In another series with 219 patients with HF, resting CPO was associated with survival in univariable analyses (total 12 events), but not after multivariable adjustment for other exercise-derived parameters. The present study provided adequate event rates to demonstrate a robust association with resting cardiac pump function and transplant- and ventricular assist device-free survival. This association was independent of haemodynamic and cardio-renal risk factors, and thus supports the hypothesis that resting CPI provides clinically meaningful prognostic information that may be used when stratifying ACHF patients for left ventricular assist device or heart transplantation.

In patients with HF, the combination of reduced cardiac pumping capacity of the heart in conjunction with dysregulated vascular

tone can lead to impaired circulatory delivery of oxygen to the peripheral muscles.²² It is therefore not surprising that peak VO_2 on CPX is associated with peak cardiac pumping performance²³ and as maximal pump function declines mortality risk increases. Indeed, both lower peak exercise CPO and reserve CPO, invasively or non-invasively measured during CPX, are correlated with mortality in patients with varying severities of chronic HF.^{4–9} To fully understand how the heart fulfils its performance as a pump, the relationship between the resting pump function (resting CPO, or CPI) to the peak exercise CPO (and thus reserve CPO) may also clarify the progression of cardiac dysfunction in HF.¹ As cardiac dysfunction progresses, peak exercise and reserve CPO likely lower to a point when cardiac pump function at rest begins to decline (resting CPO).²⁴

Results from cardiopulmonary stress testing can be used to risk-stratify patients with advanced HF.²⁵ Peak exercise VO_2 during CPX is a strong prognostic measure with the ability to stratify patients with ACHF during evaluation for HT.¹⁵ Indeed, peak VO_2 and peak cardiac pump function are correlated when measured during CPX.²³ However, as our results suggest, resting cardiac pump function may not be related to peak VO_2 and was associated with transplant and ventricular assist device-free survival independent of peak VO_2 . This is congruent with earlier findings that abnormalities in central haemodynamic function are poorly correlated with peak exercise capacity.²⁶ Furthermore, peak VO_2 may be affected by multiple factors, including age, gender, and body mass.^{27,28} Whereas, CPI may provide more specific information of cardiac pump function. Therefore, peak cardiac pump function and resting cardiac pump function may provide independent information from each other and these results support the use of CPI when stratifying risk in patients with ACHF. They do not, however, suggest CPX results are any less valuable. Because cardiac pump function can be assessed non-invasively^{4,7,8} during CPX with good reproducibility,²⁹ these results support an expanded role for CPX. There are many risk prediction models of patients with heart failure, but few if any have invasive haemodynamic measurements and none incorporate CPI.³⁰ Based on these results, CPI is a robust prognostic factor in patients with advanced heart failure and provides incremental information to other factors. Its prognostic role needs to be validated in other cohorts.

Our results must be interpreted in the context of several limitations in our study design. We cannot exclude the presence of selection bias for patients undergoing evaluation and treatment for ACHF at a tertiary care centre. However, because of the high severity of illness, this cohort is uniquely powered to compare adverse heart failure outcomes, while still maintaining external validity as a majority of patients were taking evidence-based chronic HF therapies during evaluation. Because resting CPI was only analysed at one time-point, it is unknown whether intermediary transient haemodynamic changes correlate with outcomes. However, because BNP levels remain persistently elevated during follow-up, one value of resting CPI is prognostically and phenotypically informative. We cannot exclude that cardiac transplantation and ventricular assist device placement as endpoints may be biased by donor availability and selection criteria for mechanical circulatory support. Moreover, these data were obtained in an era with non-contemporary

device therapies. Although, a majority were on renin–angiotensin system blockers, beta-blockers, and a portion on mineralocorticoid antagonists. The QRS duration was not available in all subjects, some were paced so this was not included in the multivariable analysis. The subjects' estimated metabolic rate was used in lieu of measured oxygen consumption (at the time of haemodynamic assessment) in order to compute cardiac output by the Fick principle. We also cannot exclude error introduced by calculating the MAP via non-invasive blood pressure measurements, although this bias would be non-differential.

Conclusion

Lower resting CPI is associated with higher left- and right-sided filling pressures and abnormal cardio-renal biomarkers at baseline and follow-up. Resting CPI provides independent and incremental prediction in transplant- and ventricular assist device free-survival beyond haemodynamic, demographic, and cardio-renal risk factors or cardiopulmonary stress testing. These findings suggest that CPI is a robust phenotypic and prognostic measure and support its use for risk stratification in patients with advanced heart failure.

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