Cardiopulmonary Exercise Testing, Impedance Cardiography, and Reclassification of Risk in Patients Referred for Heart Failure Evaluation

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ABSTRACT

Background: An impaired cardiac output response to exercise is a hallmark of chronic heart failure (HF). We determined the extent to which impedance cardiography (ICG) during exercise in combination with cardiopulmonary exercise test (CPX) responses reclassified risk for adverse events in patients with HF.

Methods and Results: CPX and ICG were performed in 1236 consecutive patients (48±15 years) evaluated for HF. Clinical, ICG and CPX variables were acquired at baseline and subjects were followed for the composite outcome of cardiac-related death, hospitalization for worsening HF, cardiac transplantation, and left ventricular assist device implantation. Cox proportional hazards analyses including clinical, noninvasive hemodynamic, and CPX variables were performed to determine their association with the composite endpoint. Net reclassification improvement (NRI) was calculated to quantify the impact of adding hemodynamic responses to a model including established CPX risk markers on reclassifying risk. There were 422 events. Among CPX variables, peak VO_2 and indices of ventilatory inefficiency (VE/VCO_2 slope, oxygen uptake efficiency slope) were significant predictors of risk for adverse events. Among hemodynamic variables, change in cardiac index, peak cardiac time interval, and peak left cardiac work index were the strongest predictors of risk. Having 5 impaired CPX and ICG responses to exercise yielded a sevenfold higher risk for adverse events compared with having no abnormal responses. Combining ICG responses to CPX resulted in NRIs ranging between 0.34 and 0.89, attributable to better reclassification of events.

Conclusion: Cardiac hemodynamics determined by ICG complement established CPX measures in reclassifying risk among patients with HF. (*J Cardiac Fail 2019;25:961−968*)

Key Words: Heart failure, exercise testing, mortality.

Although cardiovascular disease overall has declined in recent decades, the incidence of chronic heart failure (HF) has continued to increase.[1,2] The growing prevalence of HF reflects a combination of increasing incidence, an aging population, and improvements in the treatment of both acute cardiovascular disease and chronic HF.[1] Older Americans are currently hospitalized for HF more than any other medical condition, and with the aging of the population, the impact of HF is expected to increase dramatically.[3] Thus, efforts are needed to further refine methods to risk stratify patients with HF in order to optimize therapeutic decisions and improve outcomes. HF is characterized by an impairment in the cardiac output (CO) response to exercise, which underlies the hallmark symptom in HF, exercise intolerance.[4−6] The cardiopulmonary exercise test (CPX) has evolved to become an invaluable tool to assess the degree of exertional impairment, help determine the mechanisms underlying symptoms of exercise intolerance, estimate risk, and evaluate therapeutic interventions in patients with HF.[4,7]

The most precise metric for a patient's exercise capacity is maximal oxygen uptake, usually expressed as *peak* VO_2, reflecting the highest volume of oxygen consumed by the body's tissues during maximal effort. Peak VO_2 is considered a surrogate for CO, given the Fick equation (VO_2 = *cardiac output* × *arteriovenous oxygen difference*). The impairment in CO underlies a multitude of other abnormalities derived from CPX, including markers of ventilatory inefficiency (eg, VE/VCO_2 slope, oxygen uptake efficiency

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slope, oscillatory ventilation).[4,6,7] In recent years, these indices have been shown to provide complementary and often superior information to peak VO_2 in terms of estimating risk for adverse events in HF.[4,7] Ideally, CO and other hemodynamic indices would be routinely obtained directly, but obtaining CO directly requires costly and complicated invasive procedures and is particularly difficult to measure during exercise. Our group[8–10] and others[11–18] have recently observed that noninvasive estimates of CO using impedance cardiography (ICG) during exercise are reasonably valid and predict outcomes in patients with HF.

However, the extent to which noninvasively determined exercise hemodynamics complement established CPX responses in classifying patients at risk for adverse outcomes remains unclear. Recently, statistical methods that *reclassify risk* for adverse outcomes have been widely applied in different clinical conditions.[19–21] Net reclassification improvement (NRI) reflects clinically meaningful improvement in risk classification achieved with the addition of a risk marker to an established risk model or risk factor. A second method, termed integrated discrimination index (IDI), expresses whether a risk marker improves discrimination independently of risk categories and helps establish whether a new marker improves discrimination between groups with and without the marker.[19] Such information could be useful to help establish whether a role exists for noninvasive hemodynamic measurements in the clinical assessment of patients with HF. The aim of the current study was to determine whether noninvasive hemodynamic measurements during exercise are effective in reclassifying risk for adverse outcomes beyond established CPX and clinical factors in patients with HF.

Methods

The study sample consisted of 1236 subjects (62.3% male, mean age 48.1±15) referred for evaluation of HF at Stanford University. The sample was consecutive subjects with a broad mixture of etiologies: ~20% had hypertrophic cardiomyopathy; 50% had HF with preserved ejection fraction (ejection fraction >45%); 36% had HF with reduced ejection fraction; and 3.5% had congenital HF. Patients tested between February 2005 and December 2013 were included. All subjects were stable and receiving optimal medical therapy at the time of testing. Written informed consent was obtained using a protocol approved by the Stanford Institutional Review Board.

CPX Procedure and Data Collection

Symptom-limited CPX was performed on all patients using treadmill or cycle ergometer ramping protocols.[22] We previously observed that optimal peak VO_2 and VE/VCO_2 slope threshold values for estimating prognosis were similar irrespective of the mode of exercise in patients with HF.[23] Ventilatory expired gas analysis was performed using CareFusion Oxycon Pro (San Diego, CA) or COSMED Quark (Rome, Italy) metabolic systems. Prior to each test, the equipment was calibrated per the manufacturer's operating guidelines using reference gases. A standard 12-lead electrocardiogram was obtained at rest, each minute during exercise, and for at least 5 minutes during the recovery phase; blood pressure was measured using an automated device (SunTech Tango, Morrisville, NC). Minute ventilation (VE, body temperature and pressure, saturated (BTPS)), oxygen uptake (VO_2, standard temperature and pressure, dry (STPD)), carbon dioxide production (VCO_2, standard temperature and pressure, dry), and other CPX variables were acquired breath-by-breath, averaged over 20 seconds, and expressed in 10-second intervals. VE and VCO_2 responses throughout the entire exercise test were used to calculate the VE/VCO_2 slope via least-squares linear regression ($y=mx+b$, m=slope). Previous work by our group and others has shown this method of calculating the VE/VCO_2 slope to be optimal for estimating prognosis.[24,25] The oxygen uptake efficiency slope (OUES) was calculated using (VO_2[L/min]=m[$\log_{10}$VE] +b, where m=OUES).[24] End-tidal CO_2 pressure ($PetCO_2$, mmHg) was calculated at the ventilatory threshold.[26] Optimal thresholds for each of the CPX variables were as follows: VE/VCO_2 slope (≥34), OUES (≤1.4), $PetCO_2$ (<33 mm Hg), and peak VO_2 (≤14 mL·kg^{-1}·min^{-1}). We previously reported that these were optimal cutpoints when developing and validating a CPX score.[27,28]

Impedance Measurements

An ICG device (PhysioFlow model PF05 Lab1, Manatec Biomedical, Macheren, France) was used to determine stroke volume, CO, and other hemodynamic variables at rest and during exercise. The system differs from other commercially available impedance cardiographs in that it only uses changes in transthoracic impedance (dZ and dZ/dt) in response to an administered electrical current during cardiac ejection to calculate stroke volume, without relying on the impedance baseline (Zo) that has been described as unreliable, particularly during exercise. High-frequency (75 kHz) and low-amperage (3.8 mA peak-to-peak) alternating electrical currents via skin electrodes are emitted.[29] Two pairs of electrodes, one transmitting and the other receiving, were applied above one another so as not to overlap at the supraclavicular fossa at the left base of the neck and at the midpoint of the thoracic region of the spine. An additional pair of electrodes was used to monitor a single lateral ECG lead (V_1/V_6 positions). Hemodynamic variables were determined continuously at rest and during exercise and averaged over 20 seconds. Validation studies using the PhysioFlow device have been performed during exercise by several laboratories[29–32]; the association between peak CO derived from the device and direct Fick has been shown to be high at rest (r = 0.89, P < .001),[29] submaximal exercise (r = 0.85, P < .001),[29] and maximal exercise (r = 0.94, P < .01).[31] The PhysioFlow technology also features a proprietary advanced motion cancellation filter.

Initially, stroke volume index was determined (SVi, mL/m^2) during an autocalibration procedure based on 30 consecutive heartbeats recorded in a resting, seated position (SVical). The autocalibration stores the largest impedance

variation during systole (Zpeak − Zmin) and the largest rate of variation of the impedance signal known as the contractility index (dZ/dt_{peak}). SVi calculation is dependent on the thoracic flow inversion time (TFIT; m/s) measured on the first mathematical derivative of the impedance signal. The TFIT is the time interval between the first peak (dZ/dt_{max}) following the beginning of the cardiac cycle (start of the QRS complex on the ECG) and the first zero after the nadir of the ejection velocity (dZ/dt_{min}) During data acquisition, the variation in parameters was analyzed and compared with those values obtained during calibration. SVi calibration was calculated according to the following formula: $SVical = k \ x \ ([dZ/dt_{max}]/[Z_{max} - Z_{min}]) \times W(TFIT_{cal})$, where k is an empirically adjusted constant and W is a proprietary correction algorithm. Each displayed SV represented the mean over a 20-second artifact-free period.[29,31] Estimation of CO was based on the formula (CO=HR·SVi·BSA), where CO is expressed in liters per minute, HR is based on the R−R interval measurement determined on the ECG first derivative over time (dECG/dt), SVi is determined as above, and BSA is the body surface area calculated according to the formula of Haycock ($BSA = 0.024265 \cdot BM^{0.5378} \cdot H^{0.3964}$), where BM is body mass in kilograms and H is height in centimeters. Other hemodynamic variables derived from ICG included rest and peak ejection fraction (EF), left cardiac work index (LCWi), cardiac time interval (CTI), end-diastolic filling ratio (EDFR), and change in confidence interval (CI) and CO from rest to peak exercise (delta CI and delta CO).

Endpoints

A composite endpoint was used as the primary outcome, which included cardiac-related death, hospitalization for worsening HF, cardiac transplantation, and left ventricular assist device (LVAD) implantation. Outcomes were determined using computerized medical records. Clinicians conducting the CPX were not involved in decisions regarding cause of death or heart transplant/LVAD implantation.

Statistical Analysis

Analyses were performed using SPSS software v22.0 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY). Follow-up time is presented as median (IQR), as well as mean±SD, determined from the date of the exercise test to the date of the composite event. Continuous variables are presented as mean±SD and categorical variables as relative frequencies (%). Unpaired t tests were used for comparisons of continuous variables at baseline, and comparisons between categorical variables were assessed using χ^2 tests. Using receiver operating characteristic (ROC) curve analyses from our previous data,[27,28] optimal threshold values were defined for each CPX and hemodynamic response. Z tests were used to compare the areas under the ROC curves for CPX and noninvasive hemodynamic responses. Survival analyses were performed unadjusted and adjusted for age and gender. Cox proportional hazards analyses were used to determine which clinical, hemodynamic, and CPX variables were independently associated with the composite outcome. The proportional hazard assumption was tested and met for each of the models using the scaled Schoenfeld residuals test. The analyses were performed incrementally, with key CPX and hemodynamic variables initially assessed independently, followed by multivariate analyses using the most powerful independent predictors. To assess relative risks for adverse outcomes, we considered subjects with no CPX or hemodynamic abnormalities as the reference (normal) group, and determined hazards for the incremental addition of each of five abnormalities, with and without adjustment for age and gender.

Reclassification characteristics of hemodynamic responses relative to standard CPX variables were assessed using the continuous category-free NRI and the IDI. The baseline model for these analyses was derived from our previous observations using peak VO_2, the VE/VCO_2 slope, OUES, and $PetCO_2$ at the ventilatory threshold.[27,28] These analyses were modified for right censored survival data according to the methods proposed by Pencina et al.[19] The NRI results were corrected for over-optimism using 1000 bootstrap replicates and reported as the median results and bootstrap estimated standard errors. For the bootstrapped data, the median, 25% quartile, and 95% quartile of the Kaplan−Meier survival estimates were calculated for all subjects as a whole and the cohort of subjects reclassified upward versus downward with the addition of the variable in question. NRI and IDI analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria; SurvIDINRI and PrectABLE 2014 package).

Results

Clinical, demographic, and exercise test variables in the entire sample and those with and without an adverse event are shown in Table 1. The sample was 62% male with a BMI of 27.9±7.3 kg/m^2. There were 422 composite events over a mean follow-up of 3.1±3.6 years (median 3.0; IQR 1.6−4.0 years). Notable differences between subjects who did and did not experience an adverse event include a lower peak VO_2, a lower peak heart rate, a lower peak CO, a lower delta CI, and a higher VE/VCO_2 slope among those who experienced an event.

During the follow-up there were 92 deaths, 72 transplantations, 33 LVAD implantations, and 279 hospitalizations for worsening heart failure. Independent Cox proportional hazards analysis results using hemodynamic and CPX variables are presented in Table 2. Each of the key CPX and hemodynamic variables were significant predictors of the composite outcome, with the exception of peak EDFR. After an exploratory analysis of different multivariate models using resting and exercise hemodynamic responses, the strongest predictors of the composite outcome were peak CTI, delta CI, peak LCWi, and peak CI. Using these hemodynamic variables, we then determined the hazards associated with the combination of the best performing CPX responses (peak VO_2 and VE/VCO_2 slope) with these

Table 1. Clinical, Demographic, and Exercise Test Variables in the Entire Sample and Those With and Without an Adverse Event

	All Subjects	Non-Event Population	Event Population	*P* Value
N	1236	814	422	
Age	48.1 ± 15.0	47.4 ± 15.4	49.6 ± 14.1	.01
Male	62.3% (771/1236)	61.2% (501/814)	63.9% (270/422)	.80
Height (in.)	67.8 ± 5.4	67.6 ± 4.9	68.1 ± 6.3	.14
Weight (lb)	183.8 ± 45.3	181.7 ± 44.7	187.9 ± 46.2	.02
BMI (kg/m^2)		27.7 ± 7.8	28.4 ± 6.2	.09
Ejection Fraction (%)	56.7 ± 14.1	56.4 ± 13.6	57.3 ± 15.3	.38
Medications				
Glycosides	10.7% (132/1236)	9.1% (74/814)	13.7% (58/422)	.01
Anticoagulants	30.8% (381/1236)	28.3% (230/814)	35.8% (151/422)	.67
Beta blockers	42.0% (519/1236)	41.7% (341/814)	41.9% (178/422)	.99
Diuretics	23.8% (294/1236)	19.7% (160/814)	31.8% (134/422)	<.001
ACE inhibitor	25.8% (319/1236)	24.7% (200/814)	28.2% (119/422)	.80
Calcium channel Blockers	9.5% (118/1236)	9.8% (80/814)	9.2% (38/422)	.18
Statins	23.9% (296/1236)	22.5% (183/814)	27.0% (113/422)	.63
Aldosterone antagonists	15.9% (197/1236)	15.9% (130/814)	16.1% (67/422)	.22
Vasodilators	5.1% (63/1236)	4.7% (38/814)	5.9% (25/422)	.66
Antiarrhythmic	7.4% (91/1236)	4.8% (39/814)	12.3% (52/422)	.81
Bronchodilators	3.6% (45/1236)	3.8% (31/814)	3.3% (14/422)	.40
Cardiopulmonary exercise test variables				
Resting HR (bpm)	74.3 ± 17.4	75.0 ± 18.5	72.9 ± 14.6	.005
Peak HR (bpm)	139.3 ± 29.8	141.4 ± 29.9	134.6 ± 29.1	<.001
Peak VO_2 (mL/kg·min)	22.9 ± 10.9	24.7 ± 11.4	19.5 ± 9.2	<.001
OUES	2.064 ± 0.903	2.178 ± 0.922	1.841 ± 0.823	<.001
VE/VCO_2 slope	31.1 ± 7.1	30.2 ± 6.0	32.9 ± 8.5	<0.001
Hemodynamic variables				
Resting CO (L/min)	5.0 ± 1.8	5.1 ± 1.9	4.7 ± 1.8	.01
Resting CI (L/min/m^2)	2.5 ± 0.8	2.6 ± 0.9	2.4 ± 0.9	.001
Peak CO (L/min)	16.8 ± 7.4	17.2 ± 7.4	15.7 ± 7.4	.005
Peak CI (L/min/m^2)	8.7 ± 3.8	9.0 ± 3.9	7.8 ± 3.5	<.001
Delta CI (L/min/m^2)	6.0 ± 3.9	6.3 ± 4.0	5.4 ± 3.6	.008
Peak CTI	456.5 ± 440.1	451.0 ± 422.7	468.7 ± 476.6	.56
Peak LCWi	10.4 ± 5.4	10.8 ± 5.5	9.5 ± 5.3	.001

hemodynamic variables (Table 3). An abnormal peak VO_2 combined with an abnormal VE/VCO_2 slope doubled the risk of an adverse outcome (adjusted HR=2.1, 95% CI: 1.7−2.6, $P<$ .001). Adding the hemodynamic variables to CPX responses incrementally raised the hazard ratio and increased the specificity, but lowered the sensitivity.

Relative risks associated with having incrementally greater numbers of CPX and hemodynamic responses versus normal responders are shown in Table 4. Each additional risk marker from 1 to 4 abnormal responses raised the adjusted relative risk by a unit of ∼1; having 5 abnormal responses resulted in a hazard ratio of ∼7 (95% CI: 4.8−10.5, $P <$ .001). NRI and IDI results evaluating the utility of adding noninvasive hemodynamic markers to CPX responses are shown in Table 5. Significant reclassification of risk was observed for each of the key hemodynamic variables, with delta CI adding the greatest net reclassification (89%, $P=$ .009), followed by peak ejection fraction (76%, $P<$ .001) and peak CTI (74%, $P<$ .001).

Table 2. Independent Cox Hazard Analysis Using CPX and Hemodynamic Variables

Variable	Cutpoint	Cox Hazard	Confidence Interval	*P* Value
Cardiopulmonary exercise variables				
Peak VO_2 mL·kg·min^{-1}	<14 mL·kg·min^{-1}	1.54	1.25−1.89	<.0001
VE/VCO_2 Slope	≥34	1.66	1.36−2.04	<.0001
OUES	<1.4	1.37	1.11−1.71	.004
$PetCO_2$ at VT	>36.1 mmHg	1.68	1.31−2.15	<.0001
Hemodynamic variables				
Peak cardiac index	<10.1 L/min/m^2	1.59	1.20−2.11	.001
Peak ejection fraction	<69%	1.99	1.57−2.54	<.0001
Peak stroke volume	<115 mL/min	1.67	1.32−2.12	<.0001
Peak cardiac time interval	<320 ms	2.11	1.66−2.68	<.0001
Resting ejection fraction	<53%	1.74	1.37−2.20	<.0001
Peak left cardiac work index	<11.3	2.01	1.54−2.62	<.0001
Peak end diastolic filling ratio	<94.5	1.17	0.92−1.48	.205
Delta cardiac index	<6.3 (L/min/m^2)	1.98	1.49−2.62	<.0001

Table 3. Hazards Associated With Having Risk Factors From the Proposed Model

Abnormal Risk Factor	Unadjusted Cox Hazard		Age- & Gender-Adjusted Cox Hazard		Sensitivity	Specificity
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value		
Peak VO_2	1.54 (1.25−1.89)	<.0001	1.58 (1.27−1.96)	<.0001	0.61	0.58
Peak VO_2 & VE/VCO_2 slope	2.05 (1.69−2.50)	<.0001	2.09 (1.70−2.55)	<.0001	0.41	0.74
All risk factors[†]	2.83 (2.08−3.85)	<.0001	2.75 (2.01−3.75)	<.0001	0.12	0.93

[†]Peak VO_2 (mL/kg·min) + VE/VCO_2 + Delta CI + Peak CTI + Peak LCWi.

Table 4. Hazards Associated With Having Incrementally Greater Number of Risk Factors From the Proposed Model

	Unadjusted Cox Hazard		Age- & Gender-Adjusted Cox Hazard	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Normal risk factors	1.00	<.0001	1.00	<.0001
1 Abnormal risk factor	1.84 (1.32−2.57)	<.01	1.83 (1.31−2.55)	<.01
2 Abnormal risk factors	2.93 (2.16−3.96)	<.0001	3.04 (2.24−4.13)	<.0001
3 Abnormal risk factors	3.90 (2.66−5.71)	<.0001	4.12 (2.80−6.06)	<.0001
4 Abnormal risk factors	5.11 (3.59−7.29)	<.0001	5.34 (3.73−7.65)	<.0001
5 Abnormal risk factors*	6.97 (4.73−10.28)	<.0001	7.11 (4.80−10.53)	<.0001

Standardized so that 0 risk factors has a risk of 1.0.
*Five risk markers: peak VO_2 (mL/kg·min); VE/VCO_2; Delta CI; Peak CTI; Peak LCWi.

Table 5. NRI and IDI Values Evaluating the Utility of Adding Noninvasive Hemodynamic Markers to Cardiopulmonary Exercise Markers

	Peak VO_2 (mL/kg·min) + VE/VCO_2 + OUES + $PetCO_2$ (AT)				
	NRI ± SE	Event NRI ± SE	Non-Event NRI ± SE	*P* Value	IDI
Peak cardiac index	0.54 ± 0.09	0.63 ± 0.08	−0.09 ± 0.04	<.0001	0
Peak ejection fraction	0.76 ± 0.09	0.66 ± 0.08	0.10 ± 0.04	<.0001	0.029
Peak stroke volume	0.64 ± 0.09	0.59 ± 0.08	0.05 ± 0.04	<.0001	0.007
Peak cardiac time interval	0.74 ± 0.09	0.67 ± 0.08	0.07 ± 0.04	<.0001	0.017
Resting ejection fraction	0.55 ± 0.10	0.56 ± 0.09	−0.002 ± 0.04	<.0001	0.016
Peak left cardiac work index	0.56 ± 0.09	0.66 ± 0.07	−0.10 ± 0.04	<.0001	0.003
Peak end diastolic filling ratio	0.34 ± 0.10	0.34 ± 0.09	−0.003 ± 0.04	.001	0.008
Delta cardiac index	0.89 ± 0.08	0.86 ± 0.07	0.03 ± 0.05	<.0001	0.009

Discussion

In the current study, we examined the relative prognostic utility of ICG-determined hemodynamic variables and CPX responses to incremental exercise in patients evaluated for HF. The recent American Heart Association (AHA) Scientific Statement on CPX in Adults[24] provided support for the application of noninvasive CO for stratifying risk in patients with HF. This is based on the concept that the prognostic value of CPX in some studies is enhanced by the noninvasive determination of CO.[8,9,12–16] However, the AHA statement also suggested that additional studies are needed to further explore the utility of noninvasive hemodynamic measurements during exercise. The use of NRI and IDI in the current study was unique in this context in that these indices are designed to provide information on risk reclassification achieved by adding a new marker to an established risk model.[19–21] An additional Scientific Statement from the AHA on criteria for evaluation of cardiovascular risk[33] recommended these approaches to provide a more thorough assessment of the incremental value of a risk marker beyond standard risk assessment.

Although there are a number of relatively small studies in this area, the current findings extend previous studies by quantifying the extent to which adding noninvasive hemodynamic responses to exercise *reclassified risk* for adverse outcomes beyond standard CPX data. Our results confirm the prognostic utility of CPX responses in this population, including indices of ventilatory inefficiency and peak VO_2 (Tables 2 and 3). In addition, we observed that several noninvasive estimates of cardiovascular hemodynamics provided significant reclassification of risk beyond conventional CPX responses. To our knowledge, this is the largest study to evaluate noninvasive hemodynamic measurements along with CPX responses in the context of risk stratification in HF. The contribution of noninvasively-derived hemodynamic responses to established CPX risk markers was evidenced by the incremental increases in risk observed by adding hemodynamic responses to CPX data (Tables 3 and 4), and by the ≈30 to 90% net reclassification improvement achieved by

combining hemodynamic data with an established CPX risk model (Table 5). The NRI is an expression of the net change in risk among subjects after the addition of a marker to a baseline model (in the current case, established CPX responses). Thus, in practical terms, this suggests that adding peak CI for example, to established CPX variables improves risk reclassification for adverse events by 54% of the subjects. Notably, the change in NRI that occurred by adding hemodynamic data was attributable almost entirely to correctly reclassifying cardiac events and had minimal impact on correctly reclassifying non-events (Table 5). Given the fact that obtaining these hemodynamic measurements is relatively simple, requiring only the use of several additional surface electrodes, it suggests that impedance measurements could routinely be applied to enhance risk stratification when conducting CPX in patients with HF.

Whereas most studies have focused on resting and peak CO, it is noteworthy that peak CTI and peak LCWi were also observed to be strong predictors of risk in the current study. The latter indices are estimates of contractility; LCWi is an estimate of the energy requirements of the left ventricle when ejecting blood against aortic pressure, and CTI is analogous to LV ejection time (LVET), or the period that blood flows across the aortic valve. CTI and LVET determined by pulse wave Doppler echocardiography at rest have been demonstrated to be significant predictors of cardiovascular outcomes including ischemic heart disease, hypertension, and HF,[34–36] and to predict HF incidence in a community-based cohort,[37] but few data are available regarding *peak exercise* CTI and outcomes in patients with HF. Further studies are needed to assess the extent to which indices of cardiac contractility and other hemodynamic responses during exercise estimated by ICG predict risk in patients with HF.

Although peak VO_2 is considered the gold standard noninvasive marker of cardiopulmonary function largely because it is considered an indirect reflection of CO,[38] it is also known that peak VO_2 can be confounded by numerous factors (including age, gender, obesity, motivation, deconditioning, peripheral neuropathy, and other localized muscle conditions). Thus, peak VO_2 does not accurately reflect the CO response to exercise in many patients, and this has given rise to the concept that noninvasive hemodynamic measures may provide important prognostic information.[8,9,12–18] Studies are mixed in terms of whether noninvasive estimates of CO during exercise outperform peak VO_2 in stratifying risk in patients with HF.[13] Although the prognostic power of CPX markers of ventilatory efficiency are well-established,[4,7,24] the current observations suggest that metrics derived from ICG during exercise are complementary to CPX responses in terms of stratifying risk. Therefore, the best models may well include the combination of peak VO_2, ventilatory efficiency, and noninvasive hemodynamic indices, as suggested in Table 3. This approach more accurately captures the broad range of HF abnormalities elicited by exercise and provides superior estimates of risk than any of these indices independently. Further exploration of this concept is needed using larger datasets and different etiologies of HF.

A small but growing number of studies have examined the association between ICG and other noninvasive methods to assess hemodynamic responses to exercise and outcomes in patients with HF. Rosenblum et al[16] followed 127 patients with HF for a mean of 404 days. Peak cardiac power, defined as the product of peak mean arterial pressure and CO (determined noninvasively using a bioreactance technique) divided by 451, had a similar association with adverse outcomes as peak VO_2, but added prognostic power to peak VO_2 among patients with advanced HF (those achieving <14 mL/kg/min). Williams et al[39] estimated CO during exercise using a CO_2 rebreathing technique among 219 patients with HF and followed them for a median of 8.6 years. They observed that delta CO was the most powerful multivariate predictor of mortality; subjects in the lowest tertile of delta CO ($\leq$5.8 L/min) had a survival rate of 36.1%, whereas subjects in the highest tertile ($>$8.1 L/min) had a survival rate of 89%. Our group previously assessed the combination of CPX responses and cardiac hemodynamics determined by ICG in 639 patients with HF.[8] We observed that among hemodynamic variables, peak CI was the strongest predictor of risk for composite adverse outcomes (cardiac-related death, hospitalization for worsening HF, cardiac transplantation, and LVAD implantation). In a multivariate analysis including CPX and noninvasively determined hemodynamic variables, the most powerful predictive model included the combination of peak VO_2, peak CI, and the VE/VCO_2 slope, with each contributing significantly and independently to predicting risk; an abnormal response for all three yielded a fivefold higher risk for adverse events.

Limitations

Our sample was comprised of consecutive patients evaluated for HF, and the sample varied considerably in terms of disease etiology and severity. The group was comparatively young and stable, and the results may differ in patients with more severe disease. Although our sample was larger than most other studies assessing the clinical utility of noninvasive hemodynamic responses to exercise, larger samples would nonetheless permit the assessment of patients with differing types or degrees of HF (eg, reduced or preserved EF), and to assess different outcomes separately. The limited sample size also did not permit an evaluation with a validation cohort, nor did it allow us to compare results between men and women. Finally, we did not have direct measures of CO with which to compare our results, although the ICG system we used has been extensively validated using direct Fick methods by others.[29–32]

Summary

ICG, a noninvasive method of estimating CO and other hemodynamic responses to exercise, provides significant risk reclassification beyond established CPX data for estimating risk in patients with HF.

Disclosures

None.

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