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Mini Review

Cardiopulmonary Exercise - ∂

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ABSTRACT

Exercise tolerance reflects a number of prognostically important factors, including cardiac function, oxygen-carrying capacity, and autonomic nervous system balance. Cardiopulmonary Exercise Testing (CPX) is a diagnostic tool used to detect serial changes in exercise capacity and it is of particular benefit for patients with chronic Heart Failure (HF) to assess peak oxygen uptake (peak VO_2) and minute Ventilation/carbon dioxide production (VE/VCO_2) slope since those parameters has functioned as predictors for overall mortality or determinants of risk stratification for such individuals. CPX provides breath-by-breath gas exchange measures of 3 variables: O_2 uptake (VO_2), carbon dioxide output (VCO_2), and ventilation (VE). These 3 measures are used to derive various other gas exchange patterns that reflect organ-specific maladaptive responses to exercise, particularly when CPX is coupled with standard exercise variables (heart rate, blood pressure, and electrocardiogram). In 1991, Mancini et al. demonstrated that peak VO_2 stratifies the risk of cardiovascular death at 1 year in ambulatory patients with advanced HF. So far, we have shown the impact of CPX procedure in patients with various diseases and age for long term. We reviewed the impact of CPX which mainly focused on our research.

Cardiac Reserve by Dobutamine Stress Test and CPX Parameters

The changes in echo cardiographic variables assessed by dobutamine echocardiography are well correlated with peak VO_2 [1-7]. Meanwhile, high VE/VCO_2 slope is a powerful predictor of events in HF patients. However, its direct association with inotropic effect on cardiac hemodynamic has remained unclear. Therefore, in 2013, were ported a potential association between CPX variables and the Left Ventricular (LV) responses during Dobutamine Stress Testing (DST) in ambulatory patients with dilated cardiomyopathy (DCM) [8]. Thirty-eight patients were subjected to CPX as well as cardiac catheterization for measurement of LV pressure. The maximum first derivative of LV pressure (LV dP/dt_{max}) was calculated at baseline and during dobutamine infusion at incremental doses of 5, 10, and 15 μg/kg/min. LV dP/dt_{max} at baseline and the percentage increase in LV dP/dt_{max} (ΔLV dP/dt_{max}) induced by DST served as indices of LV contractility and myocardial contractile reserve, respectively. Peak VO_2, and VE/VCO_2 slope were 18.6 mL/kg/min and 32.3, respectively. Peak VO_2 did not correlate with LV dP/dt_{max} at baseline. However, peak VO_2 significantly correlated with ΔLV dP/dt_{max}, and the correlation became more pronounced as the dose of dobutamine increased. VE/VCO_2 slope did not correlatewith ΔLV dP/dt_{max}. Multivariate linear regression analysis revealed that ΔLV dP/dt_{max} was independently correlated with peak VO_2 ($p = 0.011$). In conclusion, peak VO_2, but not VE/VCO2 slope, may reflect myocardial contractile reserve in ambulatory patients with DCM. This study is a small, and therefore large confirmatory studies are needed.

Prognostic Value of Combination Plasma Brain Natriuretic Peptide (BNP) And Heart Rate Recovery (HRR)

HRR is related to autonomic function and is a prognostic marker in cardiovascular disease. In 2012, were ported to the clinical utility of HRR in addition to BNP levels in ambulatory outpatients with DCM [9]. Seventy-nine NICM outpatients were followed for a mean of 19 months. HRR was defined as the difference in heart rate between peak exercise and 1 min later. On the basis of the lower tertile value, we allocated the patients to two groups: with HRR > 12 bpm ($n = 48$; normal) and with HRR ≤ 12 bpm ($n = 31$, abnormal). The probability of cardiac event–free survival was significantly lower in the abnormal HRR group than in the normal HRR group ($p = 0.002$). Stepwise multivariate analysis revealed that plasma BNP and HRR were independent predictors of cardiac events. Patients with both HRR ≤ 12 bpm and BNP ≥ 200 pg/mL had significantly higher rates of cardiac events than other groups. In conclusion, HRR after exercise testing and plasma BNP levels might be a useful indicator as a predictor for admission due to worsening heart failure and its combination is able to provide additive prognostic information in ambulatory outpatients with DCM.

Prognostic Value of Combination Late Gadolinium Enhancement (LGE) on Cardiovascular Magnetic Resonance (CMR) and Peak VO_2

Peak VO_2 and LGE on CMR are prognostic in HF. In 2014, we investigated whether combined LGE-CMR and peak VO_2 had additive impact in patients with DCM [10]. Fifty-seven DCM patients were performed CMR and CPX. Cardiac events were cardiac death, hospitalization for decompensated HF, or lethal arrhythmia. Twenty-five (44%) were LGE positive. The median peak VO_2 was 18.5 mL/kg/min. On multivariate analysis, positive LGE ($p = 0.048$) and peak VO_2 ($P = 0.003$) were independent cardiac event predictors. Cardiac event risk was significantly higher with a positive LGE and peak $VO_2 < 18.5$ mL/kg/min than with a negative LGE and peak $VO_2 \geq 18.5$ mL/kg/min (hazard ratio 12.5; 95% CI 1.57–100; $p = 0.017$). In three patient groups (group A: no LGE, peak $VO_2 \geq 18.5$ mL/kg/min, $n = 18$; group B: positive LGE or peak $VO_2 < 18.5$ mL/kg/min, n = 24; group C: positive LGE and peak $VO_2 < 18.5$ mL/kg/min, $n = 15$) during follow-up (71 ± 32 months), group C had higher cardiac event rates than the others. In conclusion, combined assessment of LGE-CMR and peak VO_2 provides additive prognostic information in ambulatory DCM.

Pulmonary Hypertension (PH) Detected by percentage of Predicted Peak VO_2 (%Peak VO_2) in DCM

Recently, it has become increasingly recognized that PH is a particularly threatening result of left-sided heart disease. However, there have been few investigations of the impact of CPX variables on PH in DCM. Therefore, in 2016, we evaluated the usefulness of crucial CPX variables for detecting elevated Pulmonary Arterial Pressure (PAP) in patients with DCM [11]. Ninety subjects with DCM underwent cardiac catheterization and CPX at our hospital. Receiver Operator Characteristic (ROC) analysis was performed to assess the ability of CPX variables to distinguish between the presence and absence of PH. Overall mean values were: mean PAP (mPAP), 18.0 ± 9.6 mmHg; plasma brain natriuretic peptide, 233 ± 295 pg/mL; and left ventricular ejection fraction, 30.2% ± 11.0%. Patients were allocated to one of two groups on the basis of their mPAP, namely DCM without PH (mPAP < 25 mmHg; $n = 75$) and DCM with PH (mPAP ≥ 25 mmHg; $n = 15$). A cut-off achieved %Peak VO_2 of 52.5% was the best predictor of an mPAP ≥ 25 mmHg in the ROC analysis (area under curve: 0.911). In the multivariate analysis, %Peak VO_2 was the only significant independent predictor of PH (Wald 6.52, odds ratio 0.892, 95% CI 0.818 to 0.974; $p = 0.011$).In conclusion, %Peak VO_2 was strongly associated with the presence of PH in patients with

DCM. Taken together, these findings indicate that CPX variables could be important for diagnosing PH in patients with DCM.

Circulatory Power (CP) or Ventilator Power (VP) and Health-Related Quality of Life (HRQOL) Change in Pulmonary Arterial Hypertension

Many therapeutic options are available for patients with Pulmonary Arterial Hypertension (PAH). However, little is known about the effects of sequential combination therapy on exercise capacity. Here we reported exercise capacity [12] and HRQOL [13] in 2017 andin 2019, respectively. We observed the benefit of using a peak VO_2 cut-off of 15 mL/kg/min to guide combination therapy. Thirty patients newly diagnosed with PAH were treated with goal-oriented sequential combination therapy. Endothelin receptor antagonists (ERA) were the first-line treatment, with phosphodiesterase type 5 inhibitors (PDE-5i) as the preferred combination partner. The patients underwent cardiac catheterization at baseline and after 12 months and therapeutic CPX and HRQOL effects at baseline and after 3, 6, and 12 months. Circulatory Power (CP) was defined as the product of peak VO_2 uptake and peak Systolic Blood Pressure (SBP) and Ventilator Power (VP) was defined as peak SBP divided by the minute ventilation–CO_2 production slope. After 12 months, ERA had been administered to 100% of the study patients and PDE-5i to 82%. Mean CP at baseline and after 3, 6, and 12 months was 1807, 2063, 2248, and 2245 mm Hg•mL/min/kg, respectively, and mean VP was 2.93, 3.53, 4.16, and 3.68 mm Hg, respectively. CP was greater after 6 months than at baseline (p = 0.047); VP was greater after 3 months than at baseline (p = 0.019) with further improvement at 6 months compared with the 3 months (p = 0.040). The mean Physical Component Summary (PCS) score was 33.5 at baseline, 41.2 at 3 months, 40.8 at 6 months, and 42.0 at 12 months, and the mean Mental Component Summary (MCS) scores were 45.6, 47.0, 50.0, and 50.1, respectively. PCS score was significantly greater at 3 months than at baseline (p = 0.035). MCS score was comparable at 3 months and at baseline, but was significantly greater at 6 and 12 months than at baseline (p = 0.033, p = 0.028, respectively). Thus, PCS score improved soon after initiation of therapy, and MCS score improved later.

In conclusion, repeated CPX assessments, including measurement of CP and VP, can provide useful information regarding the efficacy of goal-oriented treatment for PAH. In addition, goal-oriented sequential combination therapy based on exercise capacity improves HRQOL in patients with PAH.

Therapeutic Strategy by using Peak VO_2 In PAH

Recently, many therapeutic options are available for patients with PAH. However, specific recommendations for long-term treatment of these patients are unavailable. In 2019, we compared prognosis in PAH patients receiving goal-oriented, sequential combination therapy evaluated by using CPX parameters or conventional empiric therapy [14]. The Goal-oriented Therapy Evaluated by Cardiopulmonary Exercise Testing for Pulmonary Arterial Hypertension (GOOD EYE) study was a multicenter, retrospective/prospective study. A total of 129 patients with newly diagnosed PAH were enrolled (goal-oriented therapy, 42 patients; conventional empiric therapy, 87 patients). Patients in the goal-oriented therapy group received sequential combination therapy, the efficacy of which was regularly evaluated by using a peak VO_2 cut-off of 15 mL/kg/min to guide combination therapy. Another group received conventional empiric therapy. The primary endpoint was cardiovascular death. In the goal-oriented therapy group, plasma BNP, mPAP, pulmonary vascular resistance, and six-minute walking test were significantly improved at 12 months compared to baseline. Survival in the goal-oriented therapy group at 1, 2, and 3 years (97.6%, 95.2%, and 86.0%, respectively) tended to be higher than that in the conventional empiric therapy group (p = 0.082). In conclusion, goal-oriented sequential combination therapy by using a peak VO_2 may provide a better prognosis compared with conventional empiric therapy in patients with newly diagnosed PAH.

Frailty Status and Peak Work Rate (WR) In Elderly Patients with Heart Failure

Frailty is a syndrome associated with aging that produces subclinical dysfunction across multiple organ systems, leading to increased risk of mortality [15]. The Kihon Check List (KCL) was developed by the Japanese Ministry of Health, Labor and Welfare to identify older persons with frailty in need of care. It is a reliable tool for predicting general frailty in the elderly [16]. Given the emerging importance of detecting frailty in an increasing elderly HF population [17,18], and the already established role of CPX in the HF setting, determining the suitability of using CPX to identify patients with frailty is an important research endeavor. However, there are no studies in the literature examining the associations between CPX parameters and frailty in HF patients. In 2019, we reported using CPX parameters to detect frailty in elderly patients with stable HF [19]. Ninety-two elderly patients with stable HF were evaluated using CPX and the KCL. A KCL score was classified 0–3 as robust, 4-7 as pre-frail, and ≥ 8 as frail. Mean age, peak VO_2, and KCL score were 81.7 years, 13.2 mL/kg/min, and 10.7, respectively. KCL score significantly correlated with peak VO_2 (r = −0.527, P< 0.001) and peak WR (r = −0.632, p < 0.001). The peak WR was significantly lower than it in patients without frailty (n = 29; 39.9 versus 69.5 W, respectively; p < 0.001).On multivariate analysis, peak WR and peak SBP were independent predictors of frailty (β = −0.108 and −0.045, respectively). A cutoff value for peak WR of 51.9 W was the best predictor of frailty. Frailty status was significantly associated with peak WR and peak SBP in elderly patients with stable HF. Therefore, CPX may be useful for assessing frailty status in this patient population.

So far, we have shown the clinical significance of CPX in patients with DCM, PH, and elderly HF. HF is a major and growing public health problem, for especially elderly patients. In addition, CPX is an established assessment tool in HF populations [20]. A major advantage of CPX is that it provides an accurate measurement of exercise capacity. The degree to which ventilation is abnormally heightened during exercise is related directly to HF severity and a strong marker of prognosis. In addition, CPX can be performed with adjunctive imaging modalities for diagnostic assessment, and it has already proven useful for diagnosing HF. Recently, in several design papers, peak VO_2 will use as one of the secondary end points to investigate the efficacy of new drugs even in obstructive hypertrophic cardiomyopathy [21] or non-diabetic HF [22] patients. CPX will spread to assess cardiac function, therapeutic effect, and prognosis in various diseases. We hope that many physicians could use it approximately to evaluate accurate pathophysiology, and lead to appropriate medical strategies in the clinical and research settings.

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