EDITORIAL

Taylor & Francis

Check for updates

Cardiopulmonary exercise testing as a vital sign in patients recovering from COVID-19

Ross Arena (D^{a,b} and Mark A. Faghy (D^{a,b,c}

^aDepartment of Physical Therapy, College of Applied Sciences, University of Illinois at Chicago, Chicago, IL, USA; ^bHealthy Living for Pandemic Event Protection (HL – PIVOT) Network, Chicago, II, USA; ^cHuman Sciences Research Centre, University of Derby, Derby, UK

ARTICLE HISTORY Received 20 July 2021; Accepted 22 September 2021

KEYWORDS Aerobic capacity; cardiorespiratory fitness; prognosis; pulmonary hemodynamics; ventilatory efficiency

Countries around the world continue to address the largescale health and wellbeing impacts and the broader societal burden associated with the coronavirus disease 2019 (COVID-2019). From an individual to global level, we continue to increase our understanding of the current and legacy impacts affecting population health. Pathophysiologic seguelae, both acute and chronic, are numerous in the individuals who have been infected [1,2]. Evidence also demonstrates that cardiorespiratory fitness (CRF) can be compromised following COVID-19 infection[2]. The evidence that COVID-19 has upon CRF is not surprising given the potential impact the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has on the cardiac, pulmonary, and skeletal muscular systems, the three systems that have a primary influence on the CRF response [1,3,4]. The impact of COVID-19 on CRF is particularly important given the fact that this clinical measure is now considered a vital sign [5], a designation earned by an evidence base spanning several decades, which clearly demonstrates its robust: 1) prognostic and diagnostic value; 2) ability to gauge therapeutic efficacy; and 3) correlation with functional capacity and quality of life [6]. Of the various approaches to assessing CRF, cardiopulmonary exercise testing (CPX) remains the gold-standard, providing for the most noninvasive, comprehensive, and accurate assessment of CRF. In the context of COVID-19, CPX provides an ideal approach to assess intersection between pathophysiologic and clinical manifestations, allowing for refined account of the impact the viral infection has both cross-sectionally and longitudinally, most importantly during a bout of physical exertion in a controlled environment. Put simply, without CPX, the pathophysiologic impacts of COVID-19 that only manifest during physical exertion, or manifest more profoundly during physical exertion, would be missed entirely, preventing a holistic understanding of the clinical presentation.

Aerobic capacity, quantified by peak oxygen consumption (VO_2) , and ventilatory efficiency, most commonly quantified by the minute ventilation/carbon dioxide production (VE/VCO_2) slope, are two of the most-established measures obtained through CPX and several studies to date report the impact of COVID-19 on both [7]. Pleguezuelos et al. [8] performed CPX on healthy controls, patients diagnosed with ischemic heart disease (IHD), patients diagnosed with chronic obstructive

pulmonary disease (COPD) and patients hospitalized for COVID-19; CPX was performed two months post-hospital discharge in the COVID-19 group. Compared to healthy controls [32.31(28.32–36.31) mlO₂·kg⁻¹·min⁻¹], peak VO₂ was significantly reduced (p < 0.001) in all groups [COVID-19 group: 17.30 (14.82–19.78) $mIO_2 \cdot kg^{-1} \cdot min^{-1}$, COPD group: 14.35 (12.97–15.73) $mIO_2 \cdot kg^{-1} \cdot min^{-1}$, and IHD group: 18.82 (15.64– 22) mlO₂·kg⁻¹·min⁻¹]. Skjorten et al. [9] found 31% of the cohort has a percent-predicted peak VO₂ less than 80% in patients that were hospitalized with COVID-19 and undertook a CPX three months post-discharge. Compared to subjects reporting no dyspnea during activities of daily living (n = 67, n)62%), those reporting dyspnea (n = 59, 38%) had a significantly lower peak VO₂ (31.9 ± 9.3 vs. 23.6 ± 7.9 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$, p < 0.001) and significantly higher VE/VCO₂ slope (26.6 ± 4.4 vs. 28.9 ± 4.5, p < 0.01). Raman et al. [2] compared 58 patients hospitalized for COVID-19 to a healthy control group. Two to three months following hospital discharge due to COVID-19, 64% of the patients continued to report dyspnea and 55% continued to report fatigue. Compared to healthy controls, percent-predicted peak VO₂ was significantly lower (80.5 ± 23.1% vs. 112.7 ± 27.0%, p < 0.0001), and the VE/VCO₂ slope was significantly higher [33.4 (29.2-40.3) vs. 28.2 (26.7-30.0), p < 0.0001] in those hospitalized with COVID-19. Aparisi et al. [10] reported similar findings in a cohort previously hospitalized for COVID-19 and undergoing CPX at three-month follow-up; peak VO₂ was significantly lower [17.8 (15.8-21.2) vs. 22.8 (18.8-27.7) $mlO_2 \cdot kg^{-1} \cdot min^{-1}$, p < 0.001], and the VE/VCO₂ slope was significantly higher [32.0 (28.1–37.4) vs. 29.4 (26.9–31.4), p < 0.05] in the 41 subjects (58.6%) who reported persistent dyspnea following discharge compared to the 29 subjects (41.4%) who were asymptomatic. These findings indicate that CPs can be safely performed in these patients represent an emerging phenotype in a significant percentage of patients hospitalized due to COVID-19 several months following discharge resulting in diminished aerobic capacity and ventilatory inefficiency with the primary subjective symptom indicative of these responses being persistent exertional dyspnea.

As previously noted, CRF is now considered a vital sign, a designation particularly due to its robust prognostic significance [5]. Peak VO_2 is a proven and established prognostic

CONTACT Ross Arena arena@uic.edu HI-pivot, Department of Physical Therapy, College of Applied Health Sciences, University of Illinois Chicago, 1919 W. Taylor Street (MC 898), Chicago, IL 60612, USA

	Primary CP	X Variables		
Percent-Predicted VO _{2peak} ^a		VE/VCO ₂ slope		
≥100% predicted		Ventilatory Class I		
75-99% predicted		V	<30.0 entilatory Class II	
15-9976 predicted		30.0-35.9		
50-74% predicted		Ventilatory Class III		
<500/ mg ti ta 1		36.0-44.9		
<50% predicted		Ventilatory Class IV >45.0		
	Standard ET Variables			
Hemodynamics	1	ECG	HRR	
Rise in systolic BP during ET: 10mmHg/3.5		arrhythmias, ectopic	>12 beats at one min recovery	
mLO ₂ •kg ⁻¹ •min ⁻¹ increase in VO ₂ and no change/slight decrease in Diastolic BP	foci, and/or ST segment changes during ET and/or in recovery			
Hypertensive Response: Excessive rise in	Altered rhythm, ectopic foci, and or		≤12 beats at one min recovery	
systolic BP during exercise: ≥20 mmHg/3.5	ST segment changes during ET		,	
mLO ₂ •kg ⁻¹ •min ⁻¹ increase in VO ₂	and/or in recovery: did not lead to			
and/or increase in Diastolic BP: did not lead to test termination	test termination			
lead to test termination				
Hypertensive Response: Excessive rise in		, ectopic foci, and or		
systolic BP during exercise: ≥20 mmHg/3.5	ST segment changes during ET			
mLO ₂ •kg ⁻¹ •min ⁻¹ increase in VO ₂ and/or increase in diastolic BP: led to test	and/or in recovery: led to test termination			
termination		innation		
Hypotensive Response: Flat response or				
decrease in Systolic BP during exercise: led				
to test termination				
Pa	tient Reason for	Test Termination		
Lower extremity muscle fatigue			Angina or	
	Internet		Dyspnea	
	Interpr	etation		
 All variables in Green: Normal exercise 	se response and e	xcellent prognosis with	viral infection	
 All variables in Green: Normal exercises Normal VO_{2peak} suggestive of 				
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica 	good immune hea tive of normal ga	Ith and low systemic in s exchange at the cardio	flammation ppulmonary interface	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I 	good immune hea ative of normal ga HRR and test tern	Ith and low systemic in s exchange at the cardio nination response indica	flammation ppulmonary interface	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially 	good immune hea ative of normal gat HRR and test tern y low systemic in	Ith and low systemic in s exchange at the cardio nination response indica flammation	flammation pulmonary interface tive of overall good health and	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potential! Greater number of CPX and standard 	good immune hea ative of normal ga HRR and test tern y low systemic in ET variables in re	Ith and low systemic in s exchange at the cardio nination response indica flammation ed/yellow/orange indica	flammation pulmonary interface tive of overall good health and tive of abnormal exercise response	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potential! Greater number of CPX and standard 	good immune hea tive of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm	Ith and low systemic in s exchange at the cardio nination response indica flammation ed/yellow/orange indica	flammation pulmonary interface tive of overall good health and	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indica Abnormally low VO_{2peak} 	good immune hea attive of normal gath HRR and test term y low systemic in ET variables in re- ative of poor imm ith viral infection	Ith and low systemic in s exchange at the cardii nination response indica flammation d/yellow/orange indica nune health, increased sy	flammation pulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indic risk of poor acute outcomes wi Abnormally high VE/VCO₂ slo increased risk of poor acute ou 	good immune hea titve of normal ga HRR and test term y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of tcomes with viral	Ith and low systemic in s exchange at the cardin ination response indica flammation d/yellow/orange indica une health, increased sy poor gas exchange at th infection	flammation pulmonary interface tive of overall good health and tive of abnormal exercise response (stemic inflammation and increased e cardiopulmonary interface and	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indica risk of poor acute outcomes wi Abnormally high VE/VCO₂ slo increased risk of poor acute ou An exagerrated systolic BP res 	good immune hea tive of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of itcomes with viral sponse to exercise	Ith and low systemic in s exchange at the cardin ination response indica flammation d/yellow/orange indica une health, increased sy poor gas exchange at th infection	flammation pulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indicarisk of poor acute outcomes with Abnormally high VE/VCO₂ slinicreased risk of poor a cute out An exagerrated systolic BP resincreased systemic inflammatic 	good immune hea tive of normal ga HRR and test teny low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of tcomes with viral sponse to exercise on	Ith and low systemic in s exchange at the cardin ination response indica flammation d/yellow/orange indica uue health, increased sy poor gas exchange at th infection , arrythmias during exe	flammation pulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indica risk of poor acute outcomes wi Abnormally high VE/VCO₂ slo increased risk of poor acute ou An exagerrated systolic BP res 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of tcomes with viral sponse to exercise on igh VE/VCO2 slo	Ith and low systemic in s exchange at the cardit ination response indica flammation d/yellow/orange indica uune health, increased sy poor gas exchange at th infection , arrythmias during exc ope following viral infect	flammation pulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indica risk of poor acute outcomes wi Abnormally high VE/VCO₂ slo increased risk of poor acute ou An exagerrated systolic BP res increased systemic inflammati Abnormally low VO_{2peak} and h pathophysiologic response and Test termination secondary to 	good immune hea tive of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of itcomes with viral sponse to exercise on igh VE/VCO2 sld I limitations in fuu dyspnea followin	Ith and low systemic in s exchange at the cardit ination response indica flammation d/yellow/orange indica une health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec totional capacity	flammation pulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, 1 prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indic risk of poor acute outcomes wi Abnormally high VE/VCO₂ sl increased risk of poor acute ou An exagerrated systolic BP res increased systemic inflammati Abnormally low VO_{2peak} and h pathophysiologic response and Test termination secondary to response and limitations in furu 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in rr ative of poor imm ith viral infection ope indicative of ttcomes with viral ponse to exercise on tigh VE/VCO2 slc l limitations in fuu dyspnea followin ctcional capacity	Ith and low systemic in s exchange at the cardit ination response indica flammation d/yellow/orange indica uune health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec totional capacity g viral infection indicat	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indic risk of poor acute outcomes with Abnormally high VE/VCO₂ slope increased risk of poor acute outoones with a commaling the VE/VCO₂ slope increased systemic inflammatiantiantiantiantiantian and the pathophysiologic response and Test termination secondary to response and limitations in fundocuments. 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of ttcomes with viral ponse to exercise on igh VE/VCO2 slo I limitations in fun dyspnea followin otional capacity ion if low VO2peal	Ith and low systemic in s exchange at the cardit ination response indica flammation d/yellow/orange indica uune health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec totional capacity g viral infection indicat	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indicarisk of poor acute outcomes with Abnormally high VE/VCO2 slope increased risk of poor acute out An exagerrated systolic BP resincreased systemic inflammatiant Abnormally low VO_{2peak} and h pathophysiologic response and Test termination secondary to response and limitations in fun Consider referral to rehabilitat are detected following viral limitations 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of itcomes with viral sponse to exercise on igh VE/VCO2 slot Il minitations in fur dyspnea followin ictional capacity ion if low VO2peal fection	Ith and low systemic in s exchange at the cardin ination response indica flammation d/yellow/orange indica une health, increased sy poor gas exchange at th infection a, arrythmias during exe ope following viral infec- totional capacity g viral infection indicate , high VE/VCO ₂ slope	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response ystemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal VE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indic risk of poor acute outcomes wi Abnormally high VE/VCO₂ slope increased risk of poor acute out An exagerrated systolic BP res increased systemic inflammati Abnormally low VO_{2peak} and h pathophysiologic response and Test termination secondary to response and limitations in fun Consider referral to rehabilitat are detected following viral init Abnormal hemodynamic, ECC dysfunction and increased risk 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of tcomes with viral ponse to exercise on ligh VE/VCO2 slo limitations in fu dyspnea followin tctional capacity ion if low VO2peal fection 5, HRR or test ter for cardiovascula	Ith and low systemic in s exchange at the cardit initation response indica flammation d/yellow/orange indica uune health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec- ted capacity g viral infection indicat , high VE/VCO2 slope mination secondary to a r events	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response stemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic or exercise-limiting exertional dyspnea ngina are indicative of cardiovascular	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indicarisk of poor acute outcomes with Abnormally high VE/VCO₂ slop increased risk of poor acute out An exagerrated systolic BP restincreased systemic inflammati Abnormally low VO_{2peak} and h pathophysiologic response and Test termination secondary to response and limitations in fun Consider referral to rehabilitat are detected following viral init 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of tcomes with viral ponse to exercise on ligh VE/VCO2 slo limitations in fu dyspnea followin tctional capacity ion if low VO2peal fection 5, HRR or test ter for cardiovascula	Ith and low systemic in s exchange at the cardit initation response indica flammation d/yellow/orange indica uune health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec- ted capacity g viral infection indicat , high VE/VCO2 slope mination secondary to a r events	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response stemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic or exercise-limiting exertional dyspnea ngina are indicative of cardiovascular	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indicarisk of poor acute outcomes with Abnormally high VE/VCO₂ slope inflammation An exagerrated systolic BP restince as dystemic inflammatii Abnormally low VO_{2peak} and h pathophysiologic response and Test termination secondary to response and limitations in fun Consider referral to rehabilitat are detected following viral init Abnormal hemodynamic, ECC dysfunction and increased rise drive 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of tcomes with viral ponse to exercise on ligh VE/VCO2 slo limitations in fu dyspnea followin tctional capacity ion if low VO2peal fection 5, HRR or test ter for cardiovascula	Ith and low systemic in s exchange at the cardit initation response indica flammation d/yellow/orange indica uune health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec- ted capacity g viral infection indicat , high VE/VCO2 slope mination secondary to a r events	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response stemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic or exercise-limiting exertional dyspnea ngina are indicative of cardiovascular	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potential! Greater number of CPX and standard Abnormally low VO_{2peak} indicarisk of poor acute outcomes with the standard of the standard of	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of tcomes with viral ponse to exercise on igh VE/VCO2 slo l limitations in fu dyspnea followin tctional capacity ion if low VO2peal fection 5, HRR or test ter for cardiovascula for all abnormal r	Ith and low systemic in s exchange at the cardit initation response indica flammation d/yellow/orange indica uune health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec- ted cardity g viral infection indicat , high VE/VCO2 slope mination secondary to a r events esponses and implement	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response stemic inflammation and increased e cardiopulmonary interface and rcise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic or exercise-limiting exertional dyspnea ngina are indicative of cardiovascular t corrective interventions	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indicarisk of poor acute outcomes with the standard of the standard o	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of ttcomes with viral sponse to exercise on igh VE/VCO2 sld limitations in fun dyspnea followin ctional capacity ion if low VO2peal fection 3, HRR or test ter for cardiovascula for all abnormal r	Ith and low systemic in s exchange at the cardinination response indica flammation d/yellow/orange indica une health, increased sy- poor gas exchange at the infection s, arrythmias during exe- ope following viral infec- ted and capacity g viral infection indicate shigh VE/VCO2 slope of mination secondary to a re events esponses and implement assessment of Short-	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response stemic inflammation and increased e cardiopulmonary interface and reise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic or exercise-limiting exertional dyspnea ngina are indicative of cardiovascular t corrective interventions to Long-term Effects During Viral	
 Normal VO_{2peak} suggestive of Normal VE/VCO₂ slope indica Normal NE/VCO₂ slope indica Normal hemodynamic, ECG, I prognosis as well as potentially Greater number of CPX and standard Abnormally low VO_{2peak} indicarisk of poor acute outcomes with Abnormally high VE/VCO₂ slope inflammation Abnormally high VE/VCO₂ slope inflammatiin Abnormally low VO_{2peak} and h pathophysiologic response and Test termination secondary to response and limitations in fun Consider referral to rehabilitat are detected following viral int Abnormal hemodynamic, ECC dysfunction and increased risk Explore possible mechanisms 	good immune hea titve of normal ga HRR and test tern y low systemic in ET variables in re ative of poor imm ith viral infection ope indicative of fitcomes with viral sponse to exercise on igh VE/VCO2 skt limitations in fur dyspnea followin tectional capacity fection i, HRR or test ter for all abnormal r Infection and Ac	Ith and low systemic in s exchange at the cardin ination response indica flammation ad/yellow/orange indica une health, increased sy poor gas exchange at th infection , arrythmias during exe ope following viral infec- totional capacity g viral infection indicate , high VE/VCO ₂ slope of mination secondary to a ar events esponses and implement seessment of Short-	flammation ppulmonary interface tive of overall good health and tive of abnormal exercise response stemic inflammation and increased e cardiopulmonary interface and reise or a low HRR may indicate etion indicate a persistent es a persistent pathophysiologic or exercise-limiting exertional dyspnea ngina are indicative of cardiovascular t corrective interventions to Long-term Effects During Viral	

Vo_{2peak}, valid if peak RER is ≥ 1.00 or test terminated ^a(Vo_{2peak} from CPX/predicted Vo_{2peak}) × 100

Use mode-specific prediction equation proposed by Fitness Registry and the Importance of Exercise: An International Data Base (FRIEND)¹¹: Vo_{2pask}(mLO₂-kg⁻¹-min⁻¹) = 45.2–0.35 × age (yr) – 10.9 × sex (male = 1; female = 2) – 0.15 × weight (b) + 0.68 × height (in) – 0.46 × exercise mode (treadmill = 1; bike = 2)

Figure 1. Cardiopulmonary exercise testing algorithm for viral infection.

Info Infe Abbre excha

Permission needed: Cardiopulmonary Exercise Testing Algorithm for Viral Infection

ASSESSING HEALTH RISK AND SHORT- TO LONG-TERM EFFECTS. Arena, Ross PhD, PT, FAACVPR; Myers, Jonathan PhD, FAACVPR; Kaminsky, Leonard A. PhD, FAACVPR. Journal of Cardiopulmonary Rehabilitation and Prevention: July 2021 – Volume 41 – Issue 4 – p E7-E8

doi: 10.1097/HCR.000000000000614

marker in apparently healthy individuals, those with risk factors for chronic disease and patients with a confirmed diagnosis of one or more chronic disease. The peak VO₂ response is primarily driven by left sided cardiac output, but skeletal muscle function also plays an important role, as indicated by the Fick equation [11]. Given both the cardiac and skeletal muscle systems can be negatively impacted by COVID-19, it is not surprising to see a diminished peak VO₂ response in a significant percentage of individuals infected, particularly those who have been hospitalized due to increased pathophysiologic severity due to the virus. The VE/VCO₂ slope has emerged as an extremely important prognostic marker, particularly in patients with heart failure (HF) and pulmonary arterial hypertension (PAH). Studies in patients with HF and PAH have demonstrated the VE/VCO₂ slope is significantly correlated with pulmonary pressures and right-sided cardiac function and is a strong prognostic marker [7,12]. There is growing concern that PAH can be a sequela of COVID-19 [3,4,13] and as such, an elevated VE/VCO₂ slope should prompt further assessment of pulmonary

hemodynamics, particularly when values exceed 36 [7,12]. Given the trends, we are seeing in patients hospitalized for COVID-19 infection, a strong case can be made to incorporate CPX as a core clinical assessment during follow-up post discharge. It should be noted that, while peak VO₂ and the VE/VCO₂ slope have been highlighted as primary CPX measures in this editorial, subjective symptoms, hemodynamics, electrocardiography, and the heart rate response during exercise and recovery should also be assessed. Our group has recently proposed a CPX algorithm (Figure 1) highlighting these CPX measures and thresholds for favorable vs. unfavorable responses[14]. As more research is conducted in this patient population, additional variables obtainable during CPET (e.g. pulmonary function testing, flow volume loops during exercise, etc.) may prove to provide important clinical insight.

Given the total number of COVID-19 infections globally, it is not feasible or warranted to refer all individuals for CPX testing. For individuals who recover from COVID-19 and return to pre-infection functional activities without new subjective symptomatology, in particular exertional dyspnea, referral for CPX is likely not indicated. However, persistent exertional dyspnea following acute recovery from infection should be a primary indication for CPX referral, to assess current CRF status and inform rehabilitative strategies. In fact, exertional dyspnea is a well-established indication for CPX in other patient populations, including HF and PAH. Moreover, there is now a clear recognition of long COVID syndrome and the need to develop bespoke rehabilitation strategies to alleviate prolonged symptom profile and restore functional capacity [1]. CPX should therefore be considered a core assessment, both at baseline to guide the initial exercise prescription and post intervention to assess efficacy.

There is of course a need for more research related to the value of CPX in the COVID-19 population moving forward. At this point, findings indicate a significant percentage of patients hospitalized with COVID-19 have diminished CRF as measured by CPX. Future research should extend the time from viral infection to CPX as well as include individuals confirmed to have COVID-19 but had milder symptoms that did not require hospitalization. Moreover, studies assessing the relationship between lasting pathophysiology associated with COVID-19 and variations in CRF are needed to determine the ability of CPX to determine system dysfunction (e.g. PAH, skeletal muscle myopathy, cardiac dysfunction, etc.). Identifying CPX phenotypes associated with specific COVID-19-induced pathophysiology will enhance clinical application and interpretation of this exercise assessment. The prognostic value of CPX in the COVID-19 population should also be explored. To achieve this with an appropriately powered sample size, an international registry that includes high-guality CPX laboratories conducting tests in patients with COVID-19 and tracking outcomes would be ideal. The Fitness Registry and the Importance of Exercise National Database (FRIEND) serves as an excellent model for this approach [15]. Lastly, as pharmacologic and rehabilitation interventions are developed to treat patients suffering from chronic system dysfunction and symptoms due to COVID-19 are developed, CPX should

be employed to determine their ability to gauge therapeutic efficacy. Conducting research in these areas will further solidify the utility of CPX in the COVID-19 population.

In conclusion, we are working toward a transition from addressing the pandemic through vaccination to managing patients infected with COVID-19 who continue to experience lasting effects. Some of the pathophysiologic effects of COVID-19, as well as the related symptomatology, manifest more profoundly or only during a bout of physical exertion. As such, performing clinical assessments during a controlled bout of exercise is imperative to more fully understanding the effects of COVID-19 and developing optimally effective treatment strategies. Cardiopulmonary exercise testing is the gold-standard approach to clinical exercise testing whose use should be expanded and considered a core assessment in the COVID-19 population.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

ORCID

Ross Arena (b) http://orcid.org/0000-0002-6675-1996 Mark A. Faghy (b) http://orcid.org/0000-0002-8163-7032

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

- Silva RN, Goulart CDL, and Oliveira MR, et al. Cardiorespiratory and skeletal muscle damage due to COVID-19: making the urgent case for rehabilitation. Expert Rev Respir Med. 2021;15(9):1107–1120.
- Important: Comprehensive review of COVID-19 effects and makes strong case for rehabilitation.
- Raman B, Cassar MP, Tunnicliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine. 2021;31:100683.
- Khan AW, Ullah I, Khan KS, et al. Pulmonary arterial hypertension post COVID-19: a sequala of SARS-CoV-2 infection? Respir Med Case Rep. 2021;33:101429.
- Suzuki YJ, Nikolaienko SI, Shults NV, et al. COVID-19 patients may become predisposed to pulmonary arterial hypertension. Med Hypotheses. 2021;147:110483.
- 5. Ross R, Blair SN, Arena R, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: a Case for Fitness as a Clinical Vital Sign: a Scientific Statement From the American Heart Association. Circulation. 2016;134:e653–e699.
- •• Highly important: Makes strong case for CRF to be used as a vital sign.
- Faghy MA, Sylvester KP, Cooper BG, et al. Cardiopulmonary exercise testing in the COVID-19 endemic phase. Br J Anaesth. 2020;125:447–449.
- Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise

testing data assessment in specific patient populations. Circulation. 2012;126:2261–2274.

- Pleguezuelos E, Del Carmen A, Llorensi G, et al. Severe loss of mechanical efficiency in COVID-19 patients. J Cachexia Sarcopenia Muscle. 2021;12:1056–1063.
- 9. Skjørten I, Ankerstjerne OAW, Trebinjac D, et al. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. Eur Resp J. 2021;58:2100996.
- Aparisi Á, Ybarra-Falcón C, García-Gómez M, et al. Exercise ventilatory inefficiency in Post-COVID-19 syndrome: insights from a prospective evaluation. J Clin Med. 2021;10:2591.
- 11. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128:873–934.

- Guazzi M, Cahalin LP, Arena R. Cardiopulmonary exercise testing as a diagnostic tool for the detection of left-sided pulmonary hypertension in heart failure. J Card Fail. 2013;19:461–467.
- Tudoran C, Tudoran M, Lazureanu VE, et al. Evidence of Pulmonary Hypertension after SARS-CoV-2 infection in subjects without previous significant cardiovascular pathology. J Clin Med. 2021;10:199.
 - Important: Highlights the potential for pulmonary arterial hypertension in COVID-19 patients.
- 14. Arena R, Myers J, Kaminsky LA. Cardiopulmonary Exercise Testing Algorithm for Viral Infection: assessing health rish and shore- to long-term effects. J Cardiopulm Rehabil Prev. 2021;41:E7–e8.
- 15. Kaminsky LA, Arena R, Beckie TM, et al. The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association. Circulation. 2013;127:652–662.