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major step toward maximizing the value of HF-related care.

Although we agree that clinical guidance meant to inform and standardize clinical practice should be as accessible and streamlined as possible for busy clinicians, improving the packaging of clinical guidance alone is not sufficient to promote high-value care without first ensuring formalized and transparent mechanisms exist to ensure cost/value is integrated into document development protocols. In addition, although merging documents to provide streamlined global guidance would seem reasonable, dedicated cost/value judgments informed by local health economic analyses are needed for different countries or regions.²

Ultimately, in an era of increasing HF prevalence, therapeutic complexity, and associated patient- and societal-level financial burden,³ we can no longer afford to exclude cost/value assessments and recommendations from practice guidelines meant to inform HF care. Clinical guidance documents must align with central societal goals of achieving the best care with finite resources.² Further, individual patient-level costs are a key component of overall “spending function” in the allocation of HF therapies and are arguably as important as other hemodynamic and laboratory parameters that guide day-to-day clinical decision-making.⁴ As such, attention to individual-level cost and societal value should be commensurate and clearly communicated, ideally alongside efficacy-based recommendations, in clinical practice guidelines that are readily accessible and digestible.

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that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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CPET for Long COVID-19



In a recent issue of *JACC: Heart Failure*, Mancini et al¹ report on cardiopulmonary exercise testing (CPET) in 41 patients with persistent dyspnea more than 3 months after recovery from a severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. The main findings were disordered breathing and decreased peripheral oxygen extraction (EO₂), much like reported in the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Is this enough for a CPET phenotyping of post-acute sequelae of SARS-CoV2 infection, or long coronavirus disease-2019 (COVID-19)?

The results of Mancini et al¹ actually confirm those reported in 581 long COVID-19 patients from 11 studies, which we reviewed in June 2021.² Our meta-analysis uncovered a hazy CPET profile with mild decrease in maximum O₂ uptake (VO₂), decreased anaerobic threshold, normal ventilation to carbon dioxide (V_E/VCO₂) slope on average but somewhat skewed to increased values, preserved ventilatory reserve and decreased EO₂, all suggestive of deconditioning on the recovery of an acute inflammatory process, prolonged bed rest and post-traumatic syndrome (PST).

Mancini et al¹ go into detailed analysis of individual responses. This is prone to false-positive signals as CPET measurements are numerous and exposed to variability, particularly in middle-aged patients with

comorbidities (which were noted in 31 of the reported patients). Comparing with matched controls rather than predicted values would have been preferable. Yet the patients showed erratic increases in respiratory rate, with early CPET tachypnea as typically seen in PTS. There also was a tendency to decreased peripheral EO_2 . This was wrongly calculated as arteriovenous O_2 content differences (DavO2) divided by hemoglobin rather than by arterial O_2 content, but characteristic anyway of deconditioning. Preload failure diagnosed in a subgroup of 7 patients disclosed vagotonic deconditioning as occurs in sedentary overweight subjects. Only 1 patient had upper limit of normal (at 1.97 WU) of pulmonary vascular resistance at exercise, not convincingly diagnostic of exercise-induced pulmonary hypertension.

Long COVID-19 and ME/CFS are patient advocacy-derived entities. Generously funded research to uncover their physiologic or biologic determinants (since 1987 for ME/CFS) has failed until now. Admirable efforts such as those reported by Mancini et al¹ should not distract from adequate attention to their dominant psychological components.

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REPLY: CPET for Long COVID-19



We appreciate the comments from Drs Naeije and Caravita and the citation of their work which was not available at the time our report was written.¹ Drs Naeije and Caravita are correct that we performed a detailed analysis of cardiopulmonary stress tests in 41 patients with long coronavirus disease-2019 (COVID-19).² Careful review of individual tests should not detract from our overall findings which showed ventilatory abnormalities in 88% of this cohort including 41% with elevated VE/VCO_2 , 61% with hypocapnia, and 63% with disordered breathing. Deconditioning is generally not characterized by ventilatory changes. The mechanism underlying these ventilatory abnormalities remain unclear. Anxiety or psychological stress is one potential explanation for the hyperventilation, but altered chemosensitivity, lung thrombotic, or fibrotic changes are also possible. I think we can agree that more research is needed to clarify the significance of our findings and to help find an answer for those patients afflicted with long COVID-19 syndrome.

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