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Invited Review Article

Expanding the concept of pharma-cise: A graphical primer for clinicians, researchers and industry

Ross Arena, PhD [a,b,c,*], Jonathan Myers, PhD [c,d,e], Nicolaas P. Pronk, PhD [b,c,f]

[a] Department of Physical Therapy, College of Applied Science, University of Illinois, Chicago, IL, USA
[b] Healthy Living for Pandemic Event Protection (HL – PIVOT) Network, Chicago, IL, USA
[c] HealthPartners Institute, Minneapolis, MN, USA
[d] Division of Cardiovascular Medicine, VA Palo Alto Health Care System, CA, USA
[e] Department of Medicine, Stanford University, Stanford, CA, USA
[f] Department of Health Policy and Management, University of Minnesota, Minneapolis, MN, USA

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ABSTRACT

A human's ability to transfer oxygen from the environment to skeletal muscle and conversely remove carbon dioxide from skeletal muscle back to the environment during physical exertion is a critical representation of healthy longevity and functional capacity. Cardiorespiratory fitness (CRF) is the accepted construct for the assessment of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) – CRF is most accurately quantified through cardiopulmonary exercise testing (CPET) in the clinical setting. All pharmacological interventions, from experimental to approved and on the market, are meant to impact one or more human physiological processes. In this context, the graphical primer on the physiological process of VO_2 and VCO_2 presented herein should facilitate the thought process on how pharmacology interacts with the factors that influence the capacity for physical exertion. Exercise is medicine and CRF is a vital sign and as such, the former should be prescribed to all capable individuals, and the latter should be considered a primary efficacy outcome measure in clinical and research settings. There is an opportunity to synergize and further enhance patient outcomes when pharmacologic and exercise interventions are considered integrated and in combination– a concept recently defined as pharma-cise – the graphical primer is proposed to facilitate application of this concept.

A human's ability to transfer oxygen from the environment to skeletal muscle and conversely remove carbon dioxide from skeletal muscle back to the environment during physical exertion is a critical representation of healthy longevity and functional capacity. Cardiorespiratory fitness (CRF) is the accepted construct for the assessment of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) – CRF is most accurately quantified through cardiopulmonary exercise testing (CPET) in the clinical setting.[1,2] The evidence supporting the ability of CRF assessment to: 1) predict risk for untoward events; 2) diagnose physiological dysfunction during physical exertion; and 3) quantify the ability to perform physical activities (e.g., activities of daily living, occupational requirements, athletic performance, etc.) is strongly supported by several decades of scientific evidence.[3] In fact, CRF is now considered a vital sign.[4] Moreover, the food and drug administration (FDA) now stresses the importance of clinical endpoints that capture improvements in how an individual *feels, functions and/or survives* to demonstrate therapeutic efficacy.[5]

However, the application of CRF assessment through CPET in the clinical and research settings, while justified by a robust evidence

* Corresponding author.
E-mail address: raarena@uic.edu (R. Arena).

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base as well as numerous scientific statements and clinical guidelines recommendations, remains suboptimal. A graphical primer on the physiological journey of VO_2 and VCO_2 has been previously published.[6,7] Herein, we present a revised version of this graphical primer (Fig. 1). The cardiovascular (i.e., right- and left-sided heart function and both central and peripheral vasculature), respiratory (i.e., respiratory muscle), pulmonary (i.e., gas exchange at the cardiopulmonary interface), and skeletal muscle are primary components of the physiological CRF chain. The autonomic nervous system, the integrity of the skeletal system (e.g., free from arthritis, scoliosis, etc.) and excess body mass (i.e., obesity) can also all have a significant peripheral impact on CRF. Of note, skeletal muscle strength, while not directly linked to CRF, has been shown to be correlated with VO_2 at peak exercise, including patients with obesity.[8] The following passages describe how this revised graphical primer may be employed alongside pharmacological interventions.

The rapidly emerging evidence surrounding the potential benefits associated with Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) is used here as an example of how the visual primary of CRF illustrated in Fig. 1 can be employed in the decision-making process. At this point, evidence suggests GLP-1 RAs may improve the function of the following gears and circuits illustrated in Fig. 1: 1) Respiratory system - respiratory muscle function in patients with COPD[9]; 2) Left Atrium -Ventricle – measures of left ventricular diastolic function in patients with and without diabetes[10]; 3) Systemic Arterial Circuit – improved systemic vascular function and reduced pressure in patients with diabetes.[11,12]; 4) Skeletal Muscle – Aerobic – potential improvement in mitochondrial function in animal models[13]; 5) Bone Health/Body Mass – improved obesity related joint inflammation and reduced body mass[14,15]; 6) Right Atrium – Ventricle – Reduced right ventricular hypertrophy in an animal model[16]; and 7) Pulmonary Arterial Circuit – improved pulmonary vascular function and potential reduction in pulmonary hypertension in diabetic patients.[17] Conversely, GLP-1 RAs has been associated with the following gears in Fig. 1 with potential negative implications for CRF: 1) Autonomic Nervous System – increase in resting heart rate in an animal model[18] and patients with diabetes[19], as well as increased resting heart rate and reduced heart rate variability in a human cohort where chronic conditions were not reported[20]; 2) Skeletal Muscle – Strength and Power – significant reductions in fat free mass[21-23] and potentially anorexia[24]; and 3) Bone Health/Body Mass – reduction in bone mineral density with GLP-1 RA use in isolation.[25]

As described in the previous section, driven by current available evidence, the potential impact on the drivers of CRF, as illustrated in Fig. 1, with GLP-1 RAs are numerous. As such, there is a strong rationale for CRF assessment across settings: 1) Clinicians should assess the effects of GLP-1 RA use on CRF as a primary measure of treatment efficacy given the vital sign status afforded CRF as a prognostic marker as well as indicator of functional capacity and quality of life. Clinicians should also view GLP-1 RA use as an opportunity to employ a *Pharma-cise*[26] program, synergizing pharmacotherapy and physical activity to further enhance functional

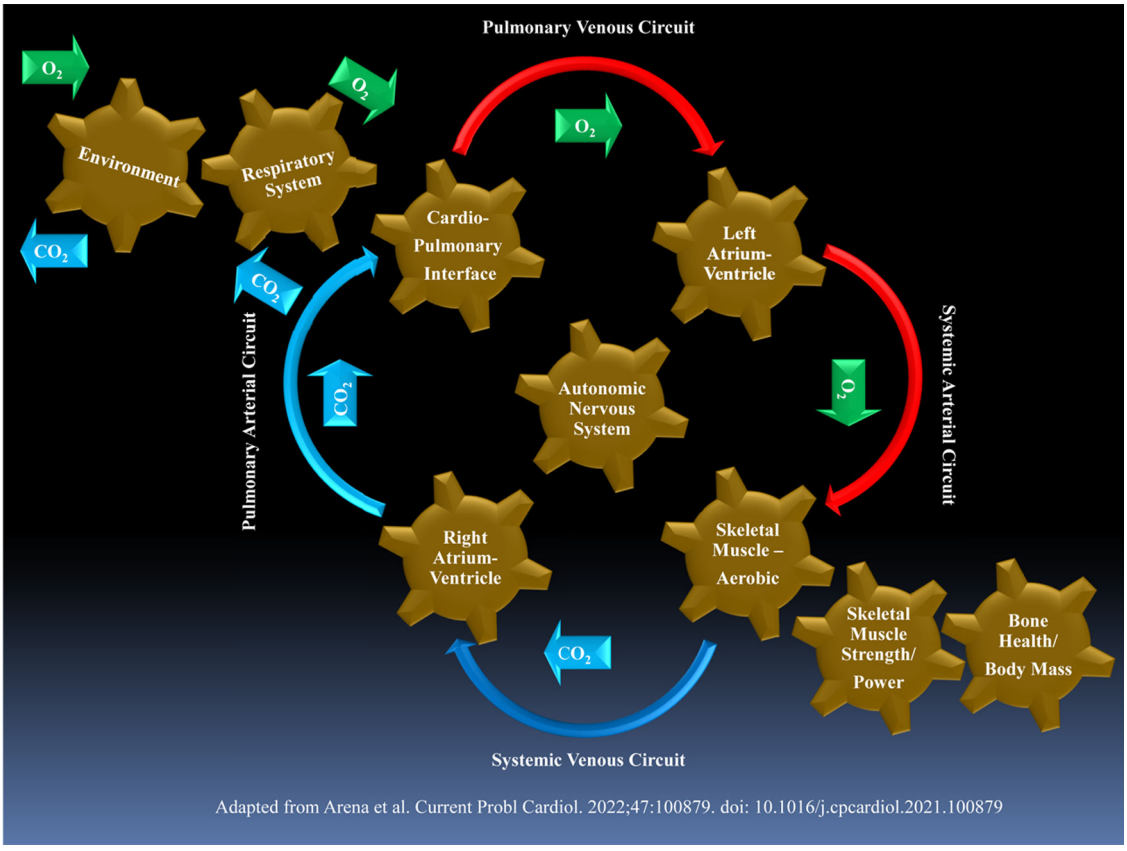

Fig. 1. Gears and Circuits Impacting Cardiorespiratory Fitness and Physical Function.

capacity and CRF. Exercise training is also critical in diminishing the side effect profile, particularly related to preserving muscle mass[24]; 2) Researchers studying the effects of GLP-1 RAs should incorporate CRF as a primary or secondary endpoint in all studies involving this drug class given the broad impact its use has on the CRF components in Fig. 1. Pharmacologic companies that conduct GLP-1 RA clinical trials should likewise incorporate CRF assessment as a primary or secondary endpoint.

The graphical primer presented herein, in the context of GLP-1 RAs, serves as one strong example of its potential utility. All pharmacological interventions, from experimental to approved and on the market, are meant to impact one or more human physiological processes. In this context, the graphical primer on VO_2 and VCO_2 should facilitate the thought process on how pharmacology interacts with the factors that influence the capacity for physical exertion. There are numerous positive synergies with parallel pharmacologic and exercise enhancements to the human physiological process. Exercise may also counteract some negative consequences associated with pharmacologic interventions. In the case of GLP-1 RAs, exercise training in parallel to this pharmacologic intervention has been shown to counteract drug-related reductions in bone mineral density[25] and increase in resting heart rate[20]. Exercise is medicine[27] and CRF is a vital sign[4] and as such, the former should be prescribed to all capable individuals and the latter should be considered a primary efficacy outcome measure in clinical and research settings. There is an opportunity to synergize and further enhance patient outcomes when pharmacologic and exercise interventions are considered in parallel – a concept recently defined as pharma-cise[26] – the revised graphical primer is proposed to facilitate application of this concept.

Declaration of competing interest

The authors have no disclosures or conflicts regarding this submission

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