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VIEWPOINT |

The ongoing need for good physiological investigation: obstructive sleep apnea in HIV patients as a paradigm

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IMPROVEMENTS IN TREATMENT of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) have extended longevity such that >50% of those living with HIV in United States will be ≥ 50 yr by 2015 (6). The remarkable success of antiretroviral therapy (ART) has not been without costs, as non-AIDS conditions account for an increasing proportion of complications, including coronary disease, diabetes mellitus, and various malignancies. Other disorders including obstructive sleep apnea (OSA) have been identified commonly in HIV-infected persons (17).

Considerable research has been ongoing in the field of OSA (9). Investigators have developed and applied physiological methods to assess various aspects of OSA pathogenesis (2, 24). OSA is a common disease with major neurocognitive and cardiovascular consequences. Although existing therapies can be transformative for some patients (29), many have advocated for further mechanistic research for new therapies to be developed (15, 20). Nasal continuous positive airway pressure is the treatment of choice for OSA based on randomized trials, but alternative therapies such as oral appliances and upper airway surgery also have a role for selected patients (9, 15). OSA is characterized by repetitive collapse of the pharyngeal airway during sleep leading to disturbances in gas exchange, sleep architecture, and autonomic function (18). OSA involves a complex interplay of anatomical predisposition to upper airway collapse, dysfunction, or dysregulation in upper airway dilator muscles and instability in ventilatory control (high loop gain) (9, 21, 22). Pharyngeal anatomy, as assessed by the passive critical closing pressure (P_{crit}), explains only a fraction of the variance in the occurrence of OSA, emphasizing the importance of other pathophysiological variables. The arousal threshold (propensity to wake up from sleep) is also an important variable in some patients (1). A mechanistic approach to OSA therapy has been proposed such that agents could be provided to treat OSA based on underlying pathophysiological abnormality (20, 27). Recent data have suggested that integrative models are required to understand the interactions between key pathophysiological variables to determine why a given individual does or does not develop OSA (5, 30). Such approaches are crucial to a personalized medicine approach to OSA, because manipulation of a given variable in isolation may be beneficial for some patients but ineffective or even

deleterious for other patients depending on underlying mechanisms (15).

Major risk factors for OSA include aging and obesity, and thus the prevalence of OSA has been increasing in recent years based on societal trends. These same general population trends are occurring in HIV-infected persons, perhaps explaining >70% prevalence of OSA in this group (17). Interestingly, however, the prevalence of OSA among HIV-infected persons has been high even among those who are not overweight/obese. Several possibilities may underlie this finding. First, ART-induced adverse events could predispose to OSA as discussed below. Second, ART could simply be facilitating restoration of health and concomitant weight gain such that obesity occurs via the natural history of current diet and exercise patterns (10). Third, the prolonged survival of contemporary HIV-infected patients with improved ART may extend the effects of HIV viremia and immune activation/inflammation over time. Indeed, systemic inflammation could affect OSA risk via impaired pharyngeal mechanics and/or could affect the risk of OSA cardiometabolic complications via inflammatory pathways (26). Finally, ART may be prolonging survival such that aging effects on the upper airway may have time to manifest. A variety of factors likely contribute to the observed link between HIV infection and OSA.

We have followed with interest the recent literature on chronic complications of HIV infection (11–13, 17). Fatigue is a common symptom in persons living with HIV, and thus OSA may contribute via sleep disruption in these individuals (17). However, the mechanism(s) underlying this potential association remain unclear. Lipohypertrophy associated with antiretroviral therapy is an increasingly well-recognized problem that may have a range of deleterious effects (14). In theory, HIV-associated lipohypertrophy could be affecting fat deposition around the pharyngeal airway, adversely affecting pharyngeal mechanics. HIV patients could also experience upper airway neuromuscular dysfunction and/or instability in ventilatory control, although rigorous data remain sparse. For example, leptin has an important role in ventilatory control and pharyngeal mechanics in some studies, although the importance of these findings in people with HIV is unclear (28). Because both HIV infection and OSA are independently linked to increased cardiovascular disease risk, we believe that a thorough analysis of upper airway structure and function in persons living with HIV is important to determine potential mechanisms for OSA in this population (7, 19, 32). Such findings might have major clinical relevance, because therapeutic or preventive strategies may be guided by these insights.

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We have chosen three examples to illustrate the potential importance of pathophysiological considerations with ART.

1) If certain populations of HIV-infected patients were known to be at increased risk of OSA due to lipohypertrophy based on their upper airway dilator muscle function, treating these groups with alternative ART regimens less likely to induce fat gain may be preferred. Alternatively, mechanical or pharmacological approaches to altering fat distribution could be considered (4). Improved understanding of which individuals may be susceptible to lipohypertrophy would inform ART treatment decisions.

2) Some antiretroviral drugs (i.e., dideoxynucleoside reverse transcription inhibitors) have been associated with neuromyopathy, and thus at least in theory these drugs should be avoided in patients reliant on upper airway dilator muscle reflexes for the maintenance of pharyngeal airway patency (16, 21). Although infrequently prescribed in the United States, these drugs remain a major part of ART in low- and middle-income countries.

3) Certain therapeutic agents commonly used in persons living with HIV infection (antidepressants, anxiolytics, analgesics, etc.) have sedating properties and as such would be predicted to raise arousal threshold (i.e., harder to wake up). Elevating the arousal threshold may be beneficial for some patients with OSA because it may allow the accumulation of respiratory stimuli to activate the pharyngeal dilator muscles and protect pharyngeal patency (3). On the other hand, raising the arousal threshold may be problematic for patients with profound hypoxemia in whom end organs may be impacted by deteriorating gas exchange. As such, sedating medications may have to be used cautiously in HIV-infected patients, particularly in those with underlying OSA.

These observations allow us to draw several conclusions. First, assessment of a single variable in isolation is unlikely to provide much insight into the cause of OSA in any particular HIV-infected individual. Studies of upper airway imaging, pharyngeal collapsibility, or upper airway muscle electromyography show considerable overlap between patients with and without OSA (23, 25). For example, the size of the upper airway lumen may be more of an issue in patients with upper airway dilator muscle dysfunction rather than those with robust protective reflexes. As such, simple static imaging—"photography"—without any functional assessment will likely provide minimal mechanistic insight. Similarly, unstable ventilatory control may not be a major issue in those who are anatomically protected from OSA or who have severe anatomical compromise (31). Second, interactions between variables can only be assessed using sophisticated modeling or integrative physiology approaches (8). For example, an elevated arousal threshold in isolation may be either protective or harmful depending on the responsiveness of the upper airway dilator muscle reflexes and prevailing pharyngeal mechanics. As such, a randomized trial giving an unselected population of patients an agent to raise the arousal threshold would likely yield heterogeneous results and fail to achieve overall positive benefits. Third, progress in HIV therapy has been transformative, but the "price of success" has been the development of apparently increased rates of a variety of long-term chronic disease conditions. Sophisticated analyses of the effects of antiretroviral therapy on an individual's physiology are likely to be fruitful given the high prevalence of OSA in HIV. We strongly support the

importance of integrative physiology to understand chronic diseases with a view toward improving the lives of persons living with HIV.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: C.D., C.B.H., and A.M. conception and design of research; C.D., C.B.H., and A.M. drafted manuscript; C.D., C.B.H., and A.M. edited and revised manuscript; C.D., C.B.H., and A.M. approved final version of manuscript.

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