The Controversies and Difficulties of Diagnosing Primary Ciliary Dyskinesia

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Published in:
American Journal of Respiratory and Critical Care Medicine

DOI:
10.1164/rccm.201907-1334LE

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

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Reply to Gagnon *et al.*

From the Authors:

We thank Dr. Gagnon and colleagues for their interest and comments. Because of the constraints of a research letter, we were not able to provide all the details of the telehealth intervention. Briefly, each video session was designed to mimic the components of center-based pulmonary rehabilitation (PR) and lasted 45 to 60 minutes. The sessions included stretching and breathing exercises for approximately 10 minutes; aerobic exercises using a foot peddler or walking for 10 and 20 minutes in those with low and high baseline functional capacity, respectively; and strength training with stretch bands for 10 minutes. Educational sessions were interspersed between these exercise periods. We agree with Dr. Gagnon and colleagues that the interval between the initiation of PR and 30 days is short, and thus we may not see meaningful changes in functional capacity. The 30-day time point was chosen based on our primary outcome of hospital readmission (1). We disagree that the higher proportion of patients on domiciliary oxygen in the group exposed to PR may have contributed to improved outcomes, as this suggests more severe and perhaps less-responsive disease. We acknowledge that the study was not randomized and that we did not collect data on the number of patients approached and reasons for patient refusal to participate. These limitations in part underlie our call for well-conducted randomized trials to test the efficacy of our intervention. They also make a case that behavioral changes could have had a significant impact. Although we did not systematically study this in both groups, the emotional guardedness domain of the psychosocial risk factor survey did improve with telehealth PR (2). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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The Controversies and Difficulties of Diagnosing Primary Ciliary Dyskinesia

To the Editor:

We welcome the correspondence from Lavie and Amirav (1), highlighting the difficulties diagnosing primary ciliary dyskinesia (PCD) and the role of high-speed video analysis (HSVA). As members of the European Respiratory Society (ERS) PCD Diagnostic Task Force (2) and/or large PCD Centres, we agree that HSVA has an important role that is not recognized by the American Thoracic Society (ATS) PCD Diagnostic Guideline (3). This risks a large

Supported by NIH grant K23HL133438 (S.P.B.).

Originally Published in Press as DOI: 10.1164/rccm.201907-1486LE on August 6, 2019

Author Contributions: A.S. and J.S.L. provided the concept and drafted the correspondence; all authors commented and approved the manuscript.

The authors are members of European Respiratory Society Task Force (TF-2014-04) and BEAT-PCD network (COST Action BM 1407).

Originally Published in Press as DOI: 10.1164/rccm.201907-1334LE on August 21, 2019

proportion of false-negative "missed" diagnoses and a sizable number of false-positive cases; we make additional important observations.

We agree with Lavie and Amirav that nasal nitric oxide (nNO) should not be used in isolation to make a diagnosis or to exclude PCD. The risk for false-negatives is clearly described in the literature (reviewed in Reference 2). The ERS Guidelines therefore suggest that both nNO and HSVA should be entirely normal before deciding that further investigation is not warranted (2). We all have patients who proceeded to further testing because clinical history was strong or HSVA was abnormal despite normal nNO, and then had a diagnosis confirmed by transmission electron microscopy (TEM) or genetics (e.g., *CCDC103*, *DNAH9*, or *RSPH1* mutations). Contrary to Lavie and Amirav, neither ATS nor ERS guidelines would exclude the diagnosis of PCD in patients with a compatible history and diagnostically low nNO despite normal HSVA, without proceeding to further tests including TEM and genetics.

Similarly to Lavie and Amirav, we were surprised that the ATS guideline specifically suggests not assessing ciliary beat pattern. Dyskinesia is a key feature of the condition and can be accurately detected by HSVA (4). According to the ERS Guidelines, repeatedly dyskinetic cilia or abnormal beat pattern following reanalysis after culture, with normal genetics and TEM, indicates PCD is "highly likely" (2), and patients should follow a PCD treatment plan (2). This recognizes that TEM and genetics will each be normal in 20–30% (2) of patients who truly have PCD (false negative), and that HSVA will detect most of these patients who require specialist PCD care. Until *HYDIN*, *DNAH11*, and *GAS8* were discovered as PCD genes, the patients were recognized by abnormal HSVA, and until all genetic causes are identified, HSVA is needed. It also acknowledges that even repeatedly abnormal HSVA may be falsely positive, and therefore the ERS Guidelines recommend that patients are not labeled as definitely having PCD based on HSVA alone (2, 4). Importantly, HSVA provides an accurate result on the day of testing that can be used to counsel patients and commence treatment while awaiting confirmatory TEM and genetics (4). HSVA also has an important research value, assessing the ability of novel treatments to restore function.

There are a large number of PCD genes, and because of their size, variants are common; not infrequently, patients without PCD have biallelic variants of unknown significance in PCD-related genes. The specificity of genetic testing is severely reduced, and many individuals could be incorrectly diagnosed with PCD (false positive) unless the mutations are confirmed pathogenic. It is therefore essential to ensure that the genotype is compatible with the ciliary phenotype using HSVA, TEM, and/or immunofluorescence labeling, as well as with the clinical phenotype (2).

Importantly, there is no perfect way to identify patients for diagnostic testing based on clinical assessment. Lavie and Amirav outline the approach proposed by the ATS Guideline, using a four-point clinical symptoms score. Having two of four clinical features provides specificity (0.72), ensuring that the diagnostic service only sees the most likely cases, but we suggest it has insufficient sensitivity for screening (0.8), meaning that 20% of patients with PCD are not tested and will therefore never be correctly diagnosed (5). The ERS Guideline provides a flexible approach ("patients with several typical features" [2]), or suggests a clinical predictive score called Primary Ciliary Dyskinesia Rule (PICADAR), which has good sensitivity and specificity (cutoff, 4; 0.97, specificity, 0.48) (6). Therefore, PICADAR may correctly identify 97% of patients who require further testing, while not inappropriately overwhelming diagnostic services, as approximately 50% of patients will turn out to have PCD. Both scores need validating in primary care settings. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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High-Speed Videomicroscopy Analysis Presents Limitations in Diagnosis of Primary Ciliary Dyskinesia

To the Editor:

In response to the letter by Dr. Lavie and Dr. Amirav highlighting the use of high-speed videomicroscopy analysis (HSVA) in a patient with suspected primary ciliary dyskinesia (PCD) (1), we stand by the American Thoracic Society (ATS) PCD diagnostic guideline recommendation. This recommendation specifically states that clinicians should avoid using HSVA as a replacement diagnostic test for transmission electron microscopy (TEM) and/or extended genetic panel testing (2). Although we appreciate the authors' opinion and argument for the use of HSVA as a diagnostic tool in PCD, we have concerns about their anecdotal evidence and reference to publications with methodologic bias.

First, they reference a publication reporting near-perfect sensitivity and specificity of HSVA testing for PCD (3). In this article, randomly selected HSVA case interpretations from blinded experts, at three separate centers in England, are retrospectively analyzed for diagnostic accuracy. This publication has numerous methodologic biases (explained in a recently published letter [4]) that affect data interpretation and likely inflate the diagnostic accuracy. No other publication has examined the diagnostic accuracy of HSVA against PCD genetic testing. Thus, the true diagnostic accuracy of HSVA in the era of PCD genomics remains unclear, but it is likely lower than the values described in that article.

No single diagnostic test can exclude PCD. TEM and genetic testing individually miss approximately 30% of PCD diagnoses. The authors claim that in one case, normal HSVA "helped to determine a diagnosis of PCD in this patient as being highly unlikely," even though the patient had a strong PCD phenotype and repeatedly low nasal nitric oxide (nNO) values. Defects in at least six known PCD-associated genes (*HYDIN*, *CCDC164*, *DNAH9*, *GAS8*, *CCNO*, and *MCIDAS*) result in normal or nondiagnostic HSVA, and more common genes (*DYX1C1*, *RSPH1*, and *RSPH4A*) have unexpected beat patterns for their corresponding axonemal defects, making HSVA nondiagnostic in these cases as well. Despite the well-recognized possibility of PCD with normal HSVA, the authors do not present any TEM or genetic testing results in their case and dismiss this patient from further PCD therapies. Their decision to ignore the repeatedly low nNO values as a consequence of sinus surgeries is concerning, as nNO levels typically increase in non-PCD patients after sinus surgery (5). The ATS PCD guidelines were prioritized to avoid this scenario, in which patients with PCD are dismissed because of false-negative results on a single diagnostic test.

Finally, the authors claim the "simplicity of use and expeditious results" of HSVA should prompt the ATS to reconsider its PCD diagnostic guidelines. However, there is nothing simple about HSVA studies, as they remain nonstandardized in both sample preparation and beat pattern interpretation. Moreover, to avoid secondary causes of dyskinesia giving false-positive results, the European Respiratory Society PCD guidelines also strongly recommend regrowth of ciliary samples at the air–liquid interface before HSVA analysis (6). This arduous, weeks-long regrowth process requires highly specialized laboratory expertise and refutes the claim of "expeditious results," leading to an immediate PCD diagnosis. Most important, no studies have shown that HSVA can be reliably and accurately performed outside of a few expert centers (2).

The ATS PCD diagnostic guidelines are rooted in science with rigorous methodology. Although not perfect, they represent the most rigorous review and analysis of scientific publications on PCD diagnosis and prioritize limiting false-negative diagnoses in which patients will suffer without proper, long-term PCD therapies. Until prospective, well-designed, multicenter studies are completed, the ATS guideline committee cannot recommend HSVA as a clinical diagnostic test for PCD. ■

Author Contribution: All authors created and edited the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201907-1366LE on August 21, 2019