10.5 ± 1.3 (range, 8–12 cm H_2O). In contrast, one patient breathed exclusively through the mouth. OSA was abolished at 17 cm H_2O of CPAP. Among the patients who breathed predominantly through the nose ($n = 11$), the percentage of oronasal plus oral breaths was similar during awake versus sleep (8.8% [1.0–17.4%] vs. 1.5% [0.2–4.5%]; $P = 0.11$] and non-REM versus REM sleep (1.9% [0.3–5.0] vs. 0% [0–0.9%]; $P = 0.08$]. Among patients who slept in both supine and lateral positions ($n = 8$), percentage of oronasal plus oral breaths was not significantly affected by position supine versus lateral while awake (10.1 [1.8–17.5] vs. 4.9 [1.3–23.8]; $P = 0.94$] and during sleep (0.8 [0–9.2] vs. 0.3 [0–2.4]; $P = 0.31$) (Figure 2).

Discussion

Our study reconciles previous physiological studies indicating that CPAP delivered by oronasal mask is less effective to treat OSA when the patient breathes predominantly through the mouth with the clinical observation that several patients are well adapted to oronasal CPAP (8). We confirmed the hypothesis that successful oronasal CPAP titration is associated with predominantly nasal breathing in 11 out of 12 patients. The only patient who breathed exclusively through the mouth required a CPAP of 17 cm H_2O, well above the remaining patients (8–12 cm H_2O). We speculate that in this patient, lung hyperinflation, induced by the high level of CPAP, was sufficient to stabilize airway patency owing to tracheal tug. The patient who breathed exclusively through the mouth only slept in the supine position. Unfortunately, he refused to return for a second study. We have recently reported one patient with OSA on oronasal mask for whom CPAP titration was successful in the lateral position but ineffective in the supine position. This observation raised the hypothesis that oral breathing may increase in the supine position, resulting in CPAP failure (9). In our study, breathing pattern was not significantly influenced by position and sleep stage. However, no reliable conclusion is possible because the number of observations was small, as the patients breathed predominantly through the nose at all times (Figure 2). We also showed that oral expiration, which can be associated with palatal prolapse, was rare (10). We are particularly concerned with widespread use of oronasal CPAP to treat OSA after the recent evidence that the acute transition from nasal CPAP to oronasal CPAP during flow limitation resulted in airway obstruction even in patients breathing exclusively through the nose (6). However, future studies are necessary to test the hypothesis that nasal-breathing patients benefit from switching from an oronasal to a nasal mask.

Conclusions

Patients with OSA who are well adapted to oronasal CPAP breathe predominantly through the nose. Our findings suggest that a nasal mask may be suitable for many patients using an oronasal mask. ■

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

Jeane Lima de Andrade Xavier, P.T.
Fernanda Madeiro Leite Viana Weaver, M.D.
George Lago Pinheiro, M.D.
Paulo Henrique Sousa Fernandes
Pedro R. Genta, M.D.
Geraldo Lorenzi-Filho, M.D.*
Universidade de São Paulo
São Paulo, Brazil

ORCID IDs: 0000-0002-3178-7235 (J.L.d.A.X.); 0000-0002-6764-165X (P.R.G.).

*Corresponding author (e-mail: geraldo.lorenzi@gmail.com).

References

1. Borker PV, Reid M, Sofer T, Butler MP, Azarbarzin A, Wang H, *et al.* Non-REM apnea and hypopnea duration varies across population groups and physiologic traits. *Am J Respir Crit Care Med* 2021;203: 1173–1182.
2. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981;1:862–865.
3. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. *J Appl Physiol (1985)* 1988;64:789–795.
4. Ebben MR, Milrad S, Dyke JP, Phillips CD, Krieger AC. Comparison of the upper airway dynamics of oronasal and nasal masks with positive airway pressure treatment using cine magnetic resonance imaging. *Sleep Breath* 2016;20:79–85.
5. Andrade RG, Madeiro F, Piccin VS, Moriya HT, Schorr F, Sardinha PS, *et al.* Impact of acute changes in CPAP flow route in sleep apnea treatment. *Chest* 2016;150:1194–1201.
6. Madeiro F, Andrade RGS, Piccin VS, Pinheiro GDL, Moriya HT, Genta PR, *et al.* Transmission of oral pressure compromises oronasal CPAP efficacy in the treatment of OSA. *Chest* 2019;156:1187–1194.
7. Andrade RGS, Viana FM, Nascimento JA, Drager LF, Moffa A, Brunoni AR, *et al.* Nasal vs oronasal CPAP for OSA treatment: a meta-analysis. *Chest* 2018;153:665–674.
8. Genta PR, Kaminska M, Edwards BA, Ebben MR, Krieger AC, Tamisier R, *et al.* The importance of mask selection on continuous positive airway pressure outcomes for obstructive sleep apnea. An official American Thoracic Society workshop report. *Ann Am Thorac Soc* 2020;17:1177–1185.
9. Nascimento JA, de Santana Carvalho T, Moriya HT, Fernandes PH, de Andrade RG, Genta PR, *et al.* Body position may influence oronasal CPAP effectiveness to treat OSA. *J Clin Sleep Med* 2016;12:447–448.
10. Azarbarzin A, Sands SA, Marques M, Genta PR, Taranto-Montemurro L, Messineo L, *et al.* Palatal prolapse as a signature of expiratory flow limitation and inspiratory palatal collapse in patients with obstructive sleep apnoea. *Eur Respir J* 2018;51:1701419.

circGSAP: A New Clinical Biomarker for Idiopathic Pulmonary Hypertension?

To the Editor:

We read with interest the recent paper published by Yuan and colleagues (1). They find that lower circGSAP (circular

Supported by the Science and Technology Special Fund of Guangdong Province in 2019 ("Major Projects + Task List") (Special Project for Major Science and Technology Innovation Platform and Project Introduction) (No. 2019A201).

Author Contributions: All authors contributed to the writing, review, and approval of the final copy of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202108-1868LE on November 5, 2021

γ-secretase activating protein) level is associated with the occurrence and poor prognosis of idiopathic pulmonary hypertension (IPAH). circGSAP may be an emerging biomarker for the diagnosis and prognosis of IPAH. We first congratulate the authors for clarifying the correlation between them for the first time, which provides a new direction for our diagnosis and treatment of IPAH. This is an important field, but the relationship between them has not yet been fully studied.

As we all know, patients with PAH have a poor prognosis if they do not receive an early diagnosis and adequate treatment (2). However, the current main approach for the diagnosis and treatment of IPAH is based on invasive hemodynamics and subjective parameters (3). This brings great inconvenience to the diagnosis and treatment of IPAH in many places and even delays the condition of IPAH. In addition, in current clinical practice, there are only three drugs for PAH, including nitric oxide–cyclic guanosine monophosphate pathway, prostacyclin pathway, and endothelin pathway, and the efficacy is not ideal (2). The research results of Yuan and colleagues provide a new direction for solving this problem, and we affirm the authors' contribution in this regard (1). With the development of high-throughput sequencing technology and bioinformatics, more and more data show that circular RNA (circRNA) plays an important role in regulating gene expression (3). The expression profile of circRNA has been analyzed in the context of many diseases such as tumors, hypertension, cardiovascular disease, pulmonary fibrosis, pulmonary tuberculosis, and acute lung injury, which has a great impact on the diagnosis and treatment of these diseases (3). As far as we know, circRNA is a kind of epigenetic modifier, and their disorder is related to the pathogenesis of the disease. It has attracted extensive attention as a biomarker or therapeutic target (3–5). From the experimental results at the clinical, cellular, and animal levels, the studies of Yuan and colleagues have well proved that the lower circGSAP level is related to the occurrence and poor prognosis of IPAH (1). Therefore, the relationship between circRNA and IPAH is worthy of further study.

However, there are still some problems in the research of Yuan and colleagues (1). The comparison between the control group and the experimental group in the clinical baseline of the patient did not list the *P* value, and it is not known whether the statistical difference is significant. To minimize the influence of other factors, we should try to match common demographic characteristics, and even control related covariates in multivariate regression analysis.

In a word, although the research of Yuan and colleagues still has some limitations, it is undeniable that their research has opened a new situation for our diagnosis and treatment of IPAH (1). We suggest that the authors perform enrichment analysis on the differential expression screened in the article to provide relevant signal pathways, which will provide great convenience for the subsequent research on mechanisms and therapeutic targets. In addition, the authors have calculated the receiver operating curve area of circGSAP, but its predictive value is not very high. It can be combined with other meaningful indicators to build a model, and even machine learning methods can be used to analyze and choose a more appropriate model to predict IPAH, which may make this research more meaningful. Finally, we suggest expanding the sample size and conducting a multicenter study to provide further evidence for clinical practice. ■

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

Acknowledgment: The authors thank Prof. Nanshan Zhong from State Key Laboratory of Respiratory Disease for the constructive advice he gave.

Xishi Sun, M.M.*
Affiliated Hospital of Guangdong Medical University
Zhanjiang, Guangdong, China
and
The Second Affiliated Hospital of Guangdong Medical University
Zhanjiang, Guangdong, China

Riken Chen, M.D.*
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou, Guangdong, China

Xiaoyun Yao, M.B.*
Guangdong Provincial Agricultural Reclamation Central Hospital
Zhanjiang, Guangdong, China

Zhenzhen Zheng, M.M.*
The Second Affiliated Hospital of Guangdong Medical University
Zhanjiang, Guangdong, China

Chaoyu Wang, M.M.*
Taishan Hospital of Traditional Chinese Medicine
Jiangmen, Guangdong, China

Jiahui Chen, M.M.*
Guangdong Provincial Agricultural Reclamation Central Hospital
Zhanjiang, Guangdong, China

Junfen Cheng, M.B.‡
The Second Affiliated Hospital of Guangdong Medical University
Zhanjiang, Guangdong, China

ORCID ID: 0000-0003-3841-4789 (X.S.).

*These authors contributed equally to this work.
‡Corresponding author (e-mail: 13729063939@139.com).

References

1. Yuan P, Wu WH, Gong SG, Jiang R, Zhao QH, Pudasaini B, *et al.* Impact of circGSAP in peripheral blood mononuclear cells on idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2021;203:1579–1583.
2. Chen L, Liu C, Lu W, Wang T. BET signaling: a novel therapeutic target for pulmonary hypertension? *Am J Respir Crit Care Med* 2020;201:1313.
3. Zhang Y, Chen Y, Yao H, Lie Z, Chen G, Tan H, *et al.* Elevated serum circ_0068481 levels as a potential diagnostic and prognostic indicator in idiopathic pulmonary arterial hypertension. *Pulm Circ* 2019;9: 2045894019888416.
4. Wang J, Zhao X, Wang Y, Ren F, Sun D, Yan Y, *et al.* circRNA-002178 act as a ceRNA to promote PDL1/PD1 expression in lung adenocarcinoma. *Cell Death Dis* 2020;11:32.
5. Jacky Lam WK, Dennis Lo YM. Circular RNAs as urinary biomarkers. *Clin Chem* 2019;65:1196–1198.