Cognitive dysfunction in patients with pulmonary hypertension

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To the Editor:

Pulmonary hypertension (PH) is a syndrome with an increased pulmonary vascular pressure from multiple etiology\(^1\). It is characterized by progressive shortness of breath, fatigue, and reduced quality of life, such as exercise intolerance, sleep disturbances, anxiety, and depression\(^2\). Growing evidence indicates that some chronic cardiovascular and pulmonary diseases (such as atherosclerosis, chronic obstructive pulmonary disease, hypertension) are linked to cognitive impairment due to inflammation, oxidative stress, and mitochondrial dysfunction\(^3,4\). Patients with PH have also been reported with inflammation and impaired cerebral hemodynamic regulation\(^5-7\).

However, whether these patients present with cognitive impairment remains uncertain. Therefore, to determine the relationship between cognitive impairment and PH risk, severity, and clinical events, we analyzed the patients’ cognitive function using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) questionnaires.

Methods

We recruited 315 incident patients with PH and 315 age- and gender-matched control subjects in a prospective cohort study conducted in Shanghai Pulmonary Hospital from October 2020 to January 2022. Median followed up was 273 ± 146 days for events (defined as cardiopulmonary death, hospitalization for right heart failure, addition of another therapy due to clinical worsening or a switch from oral PH therapy to parenteral for clinical worsening). All patients were diagnosed by right heart catheterization. Patients with previous or present cerebral hemorrhage, traumatic brain injury and other
neurological or psychiatric diseases, speech impairment, severe visual and hearing impairment, malignant tumors, alcoholism, drug abuse, and psychotropic substance abuse were excluded. A cohort of control individuals without the above diseases and PH was set up from the general Medical Examination Center in Shanghai Pulmonary Hospital. The Shanghai Pulmonary Hospital ethical committee approved and supervised this study, and the subjects provided written informed consent.

Cognitive function of subjects was measured by MMSE and MoCA. T-tests or one-way ANOVA was used to compare MMSE and MoCA scores. Logistic regression models were used to predict PH occurrence. Score-clinical parameter and outcome associations were determined using Spearman’s or Pearson’s correlation test, logistic and Cox regression models. The MMSE and MoCA score cut-off values were selected using Receiver Operative Characteristic (ROC) curves. Kaplan–Meier method was used to perform event-free survival analysis. A $P$-value < 0.05 was considered significant. Data were analyzed with SPSS 26.0.

Results

The demographic data showed no significant differences between patients with PH and control subjects (Table 1). PH classification, risk stratification, NT-proBNP, 6MWD, WHO-FC, mPAP, PVR and CI are presented in Table 1. Patients with PH demonstrated lower total scores of MoCA and MMSE than controls (all $P < 0.001$, Figure 1A). The total scores of MMSE and MoCA decreased as the risk stratification increased (all $P < 0.001$, Figure 1A). Patients with PH demonstrated lower scores for orientation,
registration, attention and calculation, recall, repetition, 3-stage command, reading, writing, copying and total scores of MMSE, and lower scores of visuoconstructional skills, naming, forward/backward digit span, serial 7s-administration, sentence repetition, verbal fluency, abstraction, delayed recall, orientation, and total scores of MoCA than controls (all \( P < 0.001 \), Figure 1B). The total scores of MMSE and MoCA significantly decreased in patients with events than event-free patients (both \( P < 0.05 \), data not shown). Age-, BMI-, education- and sex-adjusted logistic regression analyses revealed reduced scores of 3-stage command, writing, and total scores of MMSE, and that of abstraction, orientation, and total scores of MoCA could independently predict the risk of PH (all \( P < 0.05 \), Figure 1C).

The total scores of MMSE and MoCA correlated negatively with risk stratification, NT-proBNP, WHO-FC and PVR, and positively with 6MWD and CI in patients with PH (all \( P < 0.05 \), Figure 1D). The Cox regression analyses indicated that the total scores of MMSE and MoCA were the independently predicted the events of patients adjusted for age, sex, BMI, education, risk stratification, NT-proBNP, 6MWD, WHO-FC and hemodynamic parameter (\( P < 0.0001 \), Figure 1E). ROC analysis indicated that the total score for MMSE < 22.5 or MoCA < 19.5 distinguished patients with event from event-free patients (both \( P < 0.001 \)). Based on the ROC analyses, patients with lower MMSE and MoCA total scores demonstrated a higher rate of events (both \( P < 0.0001 \), Figure 1F).

**Discussion**
Our study reports PH patients with significantly impaired cognitive functions associated with a higher occurrence risk and worse outcomes in patients with PH. Cognitive impairment is induced by various pathological changes including cerebrovascular abnormalities, neuroinflammation, and dysregulation of neurodegenerative factors\textsuperscript{8-10}. A reduced of cerebral blood flow (CBF) in patients with PH has been reported, suggesting compromised cerebrovascular regulation in PH\textsuperscript{8}. Since reduced CBF correlates with cognitive dysfunction in type 2 diabetes\textsuperscript{9}, cerebrovascular dysregulation may be one mechanism for cognitive impairment in PH.

However, the MRI data of 10 patients and 10 controls in our study (data not shown) showed no difference in Fazekas scores. Cognitive performances can be influenced by comorbidities in patients. We excluded patients with severe comorbidities; however, some recruited individuals presented with hypertension, diabetes, and coronary artery disease. Since the prevalence rates of these diseases in patients with PH and control individuals are comparable, comorbidities were not the main contributors to our conclusions. Most recruited individuals are/were unemployed due to old age; thus, the occupational status could also contribute to the cognitive performance differences between patients with PH and control individuals, especially in the young population, which needs to be clarified in the future studies.

This study is limited by the small sample size. However, the cohort includes all five PH subtypes. Hence, these results sufficient indicate the abnormal cognitive impairment and their potential predictive value in PH. The effect of MMSE and MoCA
on the prognosis of all-cause death in PH have not been assessed due to the limited followed-up time. Although patients received PH therapy after diagnosis, we did not analyze the impacts of PH medications on cognitive function as this clinical trial is still in progress. Therefore, to assess the impact of PH therapy on cognitive function, we plan to perform a multi-centered, long-term, prospective study. Additionally, extensive investigations are also required to clarify the mechanism of cognitive dysfunction in PH using both animal and cell models.

Conclusions

We identified cognitive impairment in patients with PH and found that lower MMSE and MoCA total scores were associated with higher occurrence risk and worse outcomes. Our study indicates the importance of examining the cognitive function in patients with PH during diagnosis and treatment.
References

1. Frid MG, McKeon BA, Thurman JM, Maron BA, Li M, Zhang H, Kumar S, Sullivan T, Laskowsky J, Fini MA, Hu S, Tuder RM, Gandjeva A, Wilkins MR, Rhodes CJ, Ghataorhe P, Leopold JA, Wang RS, Holers VM, Stenmark KR. Immunoglobulin-driven complement activation regulates proinflammatory remodeling in pulmonary hypertension. Am J Respir Crit Care Med 2020;201:224-239.

2. Dauriat G, Reynaud-Gaubert M, Cottin V, Lamia B, Montani D, Canuet M, Boissin C, Tromeur C, Chaouat A, Degano B, Bergot E, Sanchez O, Prevot G, Sitbon O, Thabut G, Belhadi D, de Beauregard YC, Bencherif A, Humbert M, Simonneau G, Laouenan C, Mal H. Severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A prospective French multicenter cohort. J Heart Lung Transplant 2021;40:1009-1018.

3. Brummel NE, Hughes CG, Thompson JL, Jackson JC, Pandharipande P, McNeil JB, Raman R, Orun OM, Ware LB, Bernard GR, Ely EW, Girard TD. Inflammation and coagulation during critical illness and long-term cognitive impairment and disability. Am J Respir Crit Care Med 2021;203:699-706.

4. Faraco G, Hochrainer K, Segarra SG, Schaeffer S, Santisteban MM, Menon A, Jiang H, Holtzman DM, Anrather J, Iadecola C. Dietary salt promotes cognitive impairment through tau phosphorylation. Nature 2019;574:686-690.
5. Malenfant S, Brassard P, Paquette M, Le Blanc O, Chouinard A, Nadeau V, Allan PD, Tzeng YC, Simard S, Bonnet S, Provencher S. Compromised Cerebrovascular Regulation and Cerebral Oxygenation in Pulmonary Arterial Hypertension. J Am Heart Assoc 2017;6:e006126.

6. Cunningham CM, Li M, Ruffenach G, Doshi M, Aryan L, Hong J, Park J, Hrncir H, Medzikovic L, Umar S, Arnold AP, Eghbali M. Y-chromosome gene, Uty, protects against pulmonary hypertension by reducing proinflammatory chemokines. Am J Respir Crit Care Med 2022;206:186-196.

7. Hu L, Wang J, Huang H, Yu Y, Ding J, Yu Y, Li K, Wei D, Ye Q, Wang F, Shen B, Chen J, Fulton DJR, Chen F. YTHDF1 regulates pulmonary hypertension through translational control of MAGED1. Am J Respir Crit Care Med 2021;203:1158-1172.

8. Livingston G, Sommerlad A, Orgeta V, Costa Freda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care. Lancet 2017;390:2673-2734.

9. Dai W, Duan W, Alfaro FJ, Gavrieli A, Kourtelidis F, Novak V. The resting perfusion pattern associates with functional decline in type 2 diabetes. Neurobiol Aging 2017;60:192-202.
10. Honarmand K, Lalli RS, Priestap F, Chen JL, McIntyre CW, Owen AM, Slessarev M. Natural history of cognitive impairment in critical illness survivors. a systematic review. Am J Respir Crit Care Med 2020;202:193-201.
### Tables

**Table 1. Baseline characteristics in patients with PH and control individuals.**

|                      | **PH** (n=315) | **Control** (n=315) | **P-value** |
|----------------------|----------------|---------------------|-------------|
| Age, yrs             | 66.4 ± 9.1     | 67.1 ± 8.6          | 0.277       |
| Male/Female, n       | 137/178        | 156/159             | 0.129       |
| BMI, kg/m²           | 24.3 ± 4.0     | 24.2 ± 4.1          | 0.783       |
| Education level*     | 3.2 ± 1.4      | 3.3 ± 1.3           | 0.406       |
| Comorbidities†, n    |                |                     |             |
| Hypertension         | 32             | 40                  | 0.372       |
| Diabetes             | 13             | 20                  | 0.235       |
| Coronary artery disease | 14             | 13                  | 0.851       |
| PH Classification    |                |                     |             |
| Group 1/2/3/4/5, n   | 90/29/82/93/21 | -                   | -           |
| Risk stratification‡ |                |                     |             |
| Low/Intermediate/High| 172/112/31     | -                   | -           |
| NT-proBNP, pg/mL     | 480(135, 1591) | -                   | -           |
| 6MWD, m              | 343 ± 122      | -                   | -           |
| WHO-FC, II-III, n (%)| 209 (86.0)     | -                   | -           |
| mPAP, mm Hg          | 40.8 ± 15.3    | -                   | -           |
| PVR, Wood units      | 6.9 ± 4.3      | -                   | -           |
| CI, L/min/m²         | 3.1 ± 0.9      | -                   | -           |

Values are means (±SD), medians (interquartile range), or n (%). *The levels of education, 1 = Illiteracy; 2 = Primary school; 3 = Junior middle school; 4 = High school or technical secondary school; 5 = Junior college; 6 = University; 7 = Master’s degree or above; †Comorbidities only include hypertension, diabetes, and coronary artery disease. Group 1-PH, PAH; Group 2-PH, PH associated with left ventricular disease; Group 3-PH, PH associated with chronic lung disease; Group 4-PH, PH associated with pulmonary arterial obstruction; Group 5-PH, PH associated with unclear and/or multifactorial mechanisms. ‡Low, intermediate, and high-risk points of the European Society of Cardiology/European
Respiratory Society were assigned to WHO-FC I/II, III, and IV, 6MWD > 440 m, 165 to 440 m, and < 165 m, and NT-proBNP < 300 ng/L, 300–1,400 ng/L, and > 1400 ng/L, respectively, followed by calculation of the rounded average value to determine individual risk. 6MWD, 6-minute walk distance; BMI, body mass index; CI, cardiac index; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization Functional Class.
Figure Legends

**Figure 1. Cognitive dysfunction in patients with PH and controls.** A, MMSE and MoCA total scores in patients with PH (including the different risk stratification) and controls; B, The details of MMSE and MoCA in patients with PH and controls; C, Logistic regression analyses of MMSE and MoCA total scores in patients with PH versus controls; D, The correlations between the two questionnaire total scores and the baseline clinical parameters in patients with PH; E, The Cox regression analyses of MMSE and MoCA total scores in patients with event versus event-free; F, Kaplan–Meier curve of patients with higher and lower MMSE and MoCA total scores. The upper right area of the correlation matrix is the correlation coefficient, and the lower left area is the P-value. * P < 0.05, *** P < 0.001 vs. controls, ns means p > 0.05. 3-S Command, 3-Stage Command; 6MWD, 6-minute walk distance; A & C, Attention and Calculation; CI, cardiac index; F/B Digit Span, Forward/Backward Digit Span; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; ROC, Receiver Operative Characteristic; Serial 7s: A, Serial 7s: Administration; S R, Sentence Repetition; V S-Total, Visuoconstructional Skills-Total; Vigilance: A, Vigilance: Administration; WHO-FC, World Health Organization Functional Class.
Figure One - Cognitive dysfunction in patients with PH and controls.