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RDW、MPV与OSAHS-COPD重叠综合征相关性的研究进展

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摘　要

慢性阻塞性肺疾病(COPD)合并阻塞性睡眠呼吸暂停低通气综合征(OSAHS)称为重叠综合征(OS)。OS其病理生理学变化更复杂，两种疾病共同作用，互相影响，使得疾病发展更迅速。对OS患者的严重程度进行早期且准确评估对于有效的疾病管理和预防患者死亡具有重要意义。红细胞分布宽度(RDW)、平均血小板体积(MPV)是血常规的组成部分，检测简单、方便且价廉。本文对RDW、MPV与OS患者疾病严重程度进行综述。RDW、MPV可以作为综合评估慢性阻塞性肺疾病的新指标。

关键词

重叠综合征，慢性阻塞性肺疾病，阻塞性睡眠呼吸暂停低通气综合征，红细胞分布宽度，血小板平均体积

Research Progress on the Relationship between Red Cell Distribution Width, Mean Platelet Volume and OSAHS-COPD Overlap Syndrome

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Abstract

Chronic obstructive pulmonary disease (COPD) combined with obstructive sleep apnea hypopnea syndrome (OSAHS) is overlap syndrome (OS). The pathophysiology of OS is more complex, and the two diseases act together and influence each other, making the disease develop more rapidly. Early and accurate assessment of the severity of OS patients is important for effective disease management and prevention of patient death. Red blood cell distribution width (RDW) and mean platelet volume (MPV) are components of blood routine, which are simple, convenient and inexpensive to detect. This paper reviews disease severity in RDW, MPV, and OS patients. RDW and MPV can be used as new indexes for comprehensive evaluation of chronic obstructive pulmonary disease.

Keywords

Overlap Syndrome, Chronic Obstructive Pulmonary Disease, Obstructive Sleep Apnea Hypopnea Syndrome, Red Blood Cell Distribution Width, Mean Platelet Volume

1. OSAHS-COPD 重叠综合征(OS)的概述

阻塞性睡眠呼吸暂停低通气综合征(Obstructive sleep apnea hypopnea syndrome, OSAHS)是临床上常见的一种呼吸系统疾病，是以睡眠过程中周期性的出现上呼吸道塌陷，导致气流明显减少(低呼吸)或完全中断(呼吸暂停)，反复出现呼吸暂停，间歇性低氧血症和白天嗜睡[1]。OSAS 的严重程度由每小时睡眠中呼吸暂停/低通气发作的次数来估计，并用呼吸暂停－低通气指数(Apnea hypopnea index, AHI)来表示。根据 AHI 可分为轻度(AHI 5~15)、中度(AHI 15~30)和重度(AHI > 30) [2]。OSAHS 的患病率也很高。在 30~60 岁年龄段中，约 4%的男性和 2%的女性患有这种疾病[3]。

慢性阻塞性肺疾病(Chronic obstructive pulmonary diseases, COPD)是呼吸系统疾病中最常见的疾病之一，以慢性咳嗽、咳痰、气短或呼吸困难(COPD 标志性症状)为典型症，是一种常见且可预防和治疗的疾病，其特征是持续存在的肺气道阻塞和不完全可逆的气流减少，气流限制通常是进行性的，与肺部对有害颗粒或气体的异常炎症反应有关，主要由吸烟引起[4]。慢性阻塞性肺病是一种主要的全球性流行病，影响工业化国家 5%~15%的成年人[5]，通常出现在 50 岁以后。发病率随着年龄的增长而增加，例如 65 岁以上的吸烟者中有 50%受到影响[6]。Linberg 及其同事使用各种指南报告了 COPD 患病率在 7.6%至 12.2%之间[7]。

OSAHS 和 COPD 在我国均为高发性呼吸道疾病，其发病及致死率均较高，当两种疾病并存时，其症状明显加重，这种改变被 Flenly 称为重叠综合征(Overlap syndrome, OS) [8]。而慢性阻塞性肺疾病诊治指南(2021 年修订版)再次提出 COPD 合并症 OSAHS，当二者并存时称为重叠综合征。有研究表明，需要长期家庭氧疗的 COPD 患者合并中到重度 OSAHS 患者占 16% [9]。重叠综合征在轻度 COPD 患者中的患病率为 14% [10]，在 OSAS 患者中的患病率为 11% [11]。国外曾报道 OS 患病率约为 11%~28.5% [12]。

2. OSAHS-COPD 重叠综合征(OS)发病机制

OSAHS 的发病机制十分复杂，目前国内外学者们仍在研究探讨中，但随着深入研究有些机制已被认

可。包括上呼吸道狭窄和梗阻，并伴有呼吸中枢神经调节的中断。例如存在于上呼吸道狭窄的解剖学结构异常，及上呼吸道扩张肌肉(咽扩张肌)的活动被认为是 OSA 的发病关键，而这些均被认为与遗传有关[13]。而非解剖性因素如气道发生狭窄时可导致胸内压的巨大变化、间歇性低氧血症和睡眠觉醒在 OSAHS 发病过程中也起到一定作用，所产生的影响随着病人的疾病严重程度的不同而变化[14]。此外，OSAHS 所导致的低氧血症通过增加外周化学感受器的敏感性连续激活交感神经系统，而其在使通气及循环适应间歇性低氧中起关键作用[15]。而交感神经活性的增高、氧化应激、炎症过程导致了心血管、神经、代谢等系统的改变[16]。由于大多数发生与肥胖患者，常伴有舌体肥厚、脖子短小以及颌面结构异常等情况，在睡眠状态下因上呼吸道狭窄等解剖异常而引起的气道阻塞，进而出现反复呼吸暂停和觉醒现象[17]。长期的睡眠呼吸暂停和低通气可导致患者出现夜间持续低氧血症及高碳酸血症。

COPD 通常是气道、肺泡和微血管的进行性炎症性疾病。气道上皮细胞损伤导致肺不同部位的中性粒细胞、巨噬细胞和 T-淋巴细胞($CD8^+$ T 细胞为主)等炎症细胞数量增加，进一步诱发炎症反应。而活化的炎症细胞通过释放内源性细胞因子或危险相关分子模式引发非特异性炎症反应。例如上皮细胞上的 toll 样受体(Toll-like receptors) 4 和 2，并导致细胞因子的释放，如肿瘤坏死因子-α (tumor necrosis factor, TNF-α)、和白细胞介素-1 (interleukin, IL-1)、白细胞介素-8 (interleukin-8, IL-8)，以及白三烯 B4 (leukotriene B4, LTB4)等，导致肺组织结构破坏，并持续刺激中性粒细胞，引起呼吸道炎症。而蛋白水解酶和活性氧对组织损伤有破坏性作用，特别是在抗蛋白酶不足、水解蛋白酶增多或抗氧化因子存在的情况下，均能导致肺组织结果的破坏[18]。最终产生两种重要病变包括小气道腔室的重塑和实质的肺气肿性破坏所导致的弹性回缩力的降低，共同造成持续气流受限。

OSAHS 和 COPD 均可引起低氧血症以及高碳酸血症，而 OS 患者同时合并 OSAHS 和 COPD 其病理生理学变化更加复杂，两种疾病共同作用及相互影响，使得疾病进展速度更快。

3. RDW、MPV 概述

红细胞分布宽度(Red blood cell distribution width, RDW)是常规血液学实验室检测中标准全血细胞计数的一个组成部分，是循环红细胞大小分化的测量和其异质性的指标。在贫血的鉴别诊断中，通常报告为全血细胞计数的组成部分。红细胞的标准尺寸约 6~8 μm，红细胞的正常参考范围为 11%~15%。无效的红细胞生成或增加破坏红细胞相关的疾病导致红细胞体积异质性升高，从而导致 RDW 显著增加[19] [20]。

血小板是由巨核细胞产生，血小板平均体积(Mean platelet volume, MPV)是全血细胞分析中反映血小板大小的一个参数，是血小板活性的指标，MPV 可根据所使用的仪器而变化，每个实验室具有唯一的参考范围，其正常范围在 7.5~11.5 fL [21]。MPV 主要反映骨髓中巨核细胞的增殖、分化、代谢及血小板活化与功能[22]。

4. RDW、MPV 与 OSAHS-COPD 重叠综合征(OS)

4.1. RDW 与 OSAHS-COPD 重叠综合征(OS)关系的机制

RDW 是循环红细胞大小分化的测量和其异质性的指标，但与全身炎症、红细胞生成功能低下、营养缺乏、骨髓功能障碍或破坏增加相关的疾病会导致 RDW 升高[19]。

OSAHS 的主要表现为呼吸暂停和低通气，同时存在过度的氧化应激，这是 OSAHS 慢性炎症的简单机制。OSAHS 诱导的炎症反应是全身性的，炎症因子可以抑制红细胞的分化，进而抑制骨髓红细胞的成熟，从而增加 RDW。炎症因子 IL-6、TNF-a、C 反应蛋白、IL-8 与 RDW 升高显著相关。此外，IL-10 的降低也与 RDW 的增加相关[23] [24] [25]。可能是高水平的炎症细胞因子激活中性粒细胞或淋巴细胞，

以及其他侵袭性细胞，导致红细胞膜损伤和脆弱性增加。这会导致红细胞的病理性溶解和促红细胞生成素(EPO)基因的激活，从而增加骨髓中的红细胞产量。然而，过度的炎症抑制了红细胞在各个成熟阶段的分化，导致 RDW 显著增加[26]。EPO 促进干细胞增殖、分化和成熟进来增加红细胞数量。一些研究表明，严重 OSAHS 患者的 EPO 水平在夜间明显高于其他任何时间[27]。此外，EPO 增加导致大量不成熟红细胞的生成。这些细胞释放到血液循环中改变了层流，加速了红细胞在血管壁上的沉积，导致管腔狭窄或堵塞因此产生大量的活性氧(ROS)，这一过程会导致过度的氧化应激。而过度的氧化应激可导致红细胞的损伤进而使 RDW 进一步升高[28]。León Subías [29]等人则认为 OSAHS 患者的 RDW 增加与严重程度直接相关。

COPD 患者呼吸系统长期处于低血氧、过度氧化应激及炎症状态，而炎症细胞因子的释放可能影响骨髓功能，从而抑制促红细胞生成素诱导的红细胞成熟，导致 RDW 值升高。有研究表明，较高 RDW 水平可能是由于慢性炎症引起的红细胞生成功能低下所致。炎性细胞因子可抑制红细胞成熟，使幼红细胞进入循环，导致 RDW 升高[30]。在 COPD 患者中，低氧血症、氧化应激也被认为是导致 RDW 的原因[31]。而 COPD 与慢性炎性状态和炎性细胞因子水平升高有关[32] [33]。

4.2. MPV 与 OSAHS-COPD 重叠综合征(OS)关系的机制

MPV 是全血细胞分析中反映血小板大小的一个参数，是血小板活化的标志[34] [35]。10，11 MPV 升高可预测心血管疾病，包括外周、脑血管和冠状动脉疾病，并与肥胖、糖尿病和代谢综合征有关[36] [37]。

在 OS 患者中，有以下几种机制与血小板活化有关。事实上，交感神经激活的增加是 OSAS 的一个基本特征，增加了循环儿茶酚胺，而儿茶酚胺又以剂量依赖性的方式激活血小板[38]。此外，急慢性间歇性缺氧，伴随呼吸暂停，这一特征也存在于 COPD 患者中，直接触发血小板活化，进而导致 MPV 值增高[39]。在 COPD 患者中，肺血管的局部血小板活化、凝血级联和纤维蛋白溶解系统的局部活化也可能对血小板功能障碍的全身性影响起重要作用[40] [41]。吸烟是慢性阻塞性肺病的主要原因，已被证明可以直接影响血小板的大小，导致 MPV 值比不吸烟者增加[42]。此外，肺功能下降与持续的炎症状态有关，这会导致内皮功能受损，暴露内皮下胶原，使得血小板活化，从而导致 MPV 升高[40] [41]。慢性炎症和缺氧可诱导血小板活化[43]。OSAS 和 COPD 现在都被认为会增加全身性炎症[44] [45] [46]。33~35 这两种情况的共同点可能是促使炎细胞因子(如白细胞介素-6)的分泌增加，或在血小板活化中起重要作用的粘附分子的过度表达，使得 MPV 水平发生高表达[44] [47] [48]。由于 OSAHS 和 COPD 分别引起上、下气道阻塞，因此 OS 患者低氧血症和高碳酸血症会加重，进而导致 OS 的系统性炎症反应。而 RDW 及 MPV 的升高与炎症反应相关。故而提示外周血 RDW、MPV 与重叠综合征的严重程度关系密切。

5. 展望

OS 的早期诊断和预测是治疗的关键，生物学标志物检测是 OS 严重程度预测的重要手段，而 RDW、MPV 是各级医疗机构常规检查项目，具有简单、经济、快捷、可反复操作等优点，能够为临床早期评估 OS 患者疾病严重程度提供帮助，从而进行早期干预，积极治疗，改善患者预后。但该指标较为粗略，对于 RDW、MPV 升高的 OS 患者需完善进一步的检查。

参考文献

[1] Bednarek, M., Plywaczewski, R., Jonczak, L. and Zielinski, J. (2005) There Is No Relationship between Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea Syndrome: A Population Study. *Respiration*, **72**, 142-149. https://doi.org/10.1159/000084044

[2] Kapur, V.K., *et al*. (2017) Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine*, **13**, 479-504.

https://doi.org/10.5664/jcsm.6506

[3] Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S. and Badr, S. (1993) The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults. *The New England Journal of Medicine*, **328**, 1230-1235. https://doi.org/10.1056/NEJM199304293281704

[4] Celli, B.R. and MacNee, W. (2004) Standards for the Diagnosis and Treatment of Patients with COPD: A Summary of the ATS/ERS Position Paper. *The European Respiratory Journal*, **23**, 932-946. https://doi.org/10.1183/09031936.04.00014304

[5] Pauwels, R.A., Buist, A.S., Ma, P., Jenkins, C.R. and Hurd, S.S. (2001) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): Executive Summary. *Respiratory Care*, **46**, 798-825.

[6] Louw, S.J., Goldin, J.G. and Joubert, G. (1996) Spirometry of Healthy Adult South African Men. Part I. Normative Values. *South African Medical Journal*, **86**, 814-819.

[7] Lindberg, A., Jonsson, A.C., Rönmark, E., Lundgren, R., Larsson, L.G. and Lundbäck, B. (2005) Prevalence of Chronic Obstructive Pulmonary Disease According to BTS, ERS, GOLD and ATS Criteria in Relation to Doctor's Diagnosis, Symptoms, Age, Gender, and Smoking Habits. *Respiration*, **72**, 471-479. https://doi.org/10.1159/000087670

[8] Flenley, D.C. (1985) Sleep in Chronic Obstructive Lung Disease. *Clinics in Chest Medicine*, **6**, 651-661. https://doi.org/10.1016/S0272-5231(21)00402-0

[9] Machado, M., Vollmer, W.M., Togeiro, S.M., *et al*. (2010) CPAP and Survival in Moderate-to-Severe Obstructive Sleep Apnoea Syndrome and Hypoxaemic COPD. *European Respiratory Journal*, **35**, 132-137. https://doi.org/10.1183/09031936.00192008

[10] Chaouat, A., Weitzenblum, E., Krieger, J., Ifoundza, T., Oswald, M. and Kessler, R. (1995) Association of Chronic Obstructive Pulmonary Disease and Sleep Apnea Syndrome. *American Journal of Respiratory and Critical Care Medicine*, **151**, 82-86. https://doi.org/10.1164/ajrccm.151.1.7812577

[11] Sanders, M.H., Newman, A.B., Haggerty, C.L., *et al*. (2003) Sleep and Sleep-Disordered Breathing in Adults with Predominantly Mild Obstructive Airway Disease. *American Journal of Respiratory and Critical Care Medicine*, **167**, 7-14. https://doi.org/10.1164/rccm.2203046

[12] Zamarron, C. (2008) Association of Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea Consequences. *International Journal of Chronic Obstructive Pulmonary Disease*, **3**, 671-682. https://doi.org/10.2147/COPD.S4950

[13] Chi, L., Comyn, F.L., Keenan, B.T., *et al*. (2014) Heritability of Craniofacial Structures in Normal Subjects and Patients with Sleep Apnea. *Sleep*, **37**, 1689-1698. https://doi.org/10.5665/sleep.4082

[14] Eckert, D.J., White, D.P., Jordan, A.S., Malhotra, A. and Wellman, A. (2013) Defining Phenotypic Causes of Obstructive Sleep Apnea. Identification of Novel Therapeutic Targets. *American Journal of Respiratory & Critical Care Medicine*, **188**, 996-1004. https://doi.org/10.1164/rccm.201303-0448OC

[15] Prabhakar, N.R., Peng, Y.J., Kumar, G.K. and Nanduri, J. (2015) Peripheral Chemoreception and Arterial Pressure Responses to Intermittent Hypoxia. *Comprehensive Physiology*, **5**, 561-577. https://doi.org/10.1002/cphy.c140039

[16] Ayas, N., Hirsch, A.J., Laher, I., *et al*. (2014) New Frontiers in Obstructive Sleep Apnoea. *Clinical Science*, **127**, 209-216. https://doi.org/10.1042/CS20140070

[17] Verse, T. and Pirsig, W. (2003) Impact of Impaired Nasal Breathing on Sleep-Disordered Breathing. *Sleep Breath*, **7**, 63-76. https://doi.org/10.1007/s11325-003-0063-2

[18] Rabe, K.F. and Watz, H. (2017) Chronic Obstructive Pulmonary Disease. *The Lancet*, **389**, 1931-1940. https://doi.org/10.1016/S0140-6736(17)31222-9

[19] Romero Artaza, J., Carbia, C.D., Ceballo, M.F. and Díaz, N.B. (1999) Red Cell Distribution Width (RDW): Its Use in the Characterization of Microcytic and Hypochromic Anemias. *Medicina*, **59**, 17-22.

[20] Tonelli, M., Sacks, F., Arnold, M., Moye, L., Davis, B. and Pfeffer, M. (2008) Relation between Red Blood Cell Distribution Width and Cardiovascular Event Rate in People With Coronary Disease. *Circulation*, **117**, 163-168. https://doi.org/10.1161/CIRCULATIONAHA.107.727545

[21] Schmoeller, D., Picarelli, M.M., Paz Munhoz, T., Poli de Figueiredo, C.E. and Staub, H.L. (2017) Mean Platelet Volume and Immature Platelet Fraction in Autoimmune Disorders. *Frontiers in Medicine*, **4**, Article 146. https://doi.org/10.3389/fmed.2017.00146

[22] Harrison, P. and Goodall, A.H. (2016) Studies on Mean Platelet Volume (MPV)—New Editorial Policy. *Platelets*, **27**, 605-606. https://doi.org/10.1080/09537104.2016.1225467

[23] Arnardottir, E.S., Mackiewicz, M., Gislason, T., Teff, K.L. and Pack, A.I. (2009) Molecular Signatures of Obstructive

Sleep Apnea in Adults: A Review and Perspective. *Sleep*, **32**, 447-470. https://doi.org/10.1093/sleep/32.4.447

[24] Arnardottir, E.S., Maislin, G., Schwab, R.J., *et al*. (2012) The Interaction of Obstructive Sleep Apnea and Obesity on the Inflammatory Markers C-Reactive Protein and Interleukin-6: The Icelandic Sleep Apnea Cohort. *Sleep*, **35**, 921-932. https://doi.org/10.5665/sleep.1952

[25] Bouloukaki, I., Mermigkis, C., Kallergis, E.M., Moniaki, V., Mauroudi, E. and Schiza, S.E. (2015) Obstructive Sleep Apnea Syndrome and Cardiovascular Disease: The Influence of C-Reactive Protein. *World Journal of Experimental Medicine*, **5**, 77-83. https://doi.org/10.5493/wjem.v5.i2.77

[26] Szygula, Z., Lubkowska, A., Giemza, C., Skrzek, A., Bryczkowska, I. and Dołęgowska, B. (2014) Hematological Parameters, and Hematopoietic Growth Factors: EPO and IL-3 in Response to Whole-Body Cryostimulation (WBC) in Military Academy Students. *PLOS ONE*, **9**, e93096. https://doi.org/10.1371/journal.pone.0093096

[27] Dayyat, E.A., Zhang, S.X., Wang, Y., Cheng, Z.J. and Gozal, D. (2012) Exogenous Erythropoietin Administration Attenuates Intermittent Hypoxia-Induced Cognitive Deficits in a Murine Model of Sleep Apnea. *BMC Neuroscience*, **13**, Article No. 77. https://doi.org/10.1186/1471-2202-13-77

[28] Almendros, I., Farré, R., Planas, A.M., *et al*. (2011) Tissue Oxygenation in Brain, Muscle, and Fat in a Rat Model of Sleep Apnea: Differential Effect of Obstructive Apneas and Intermittent Hypoxia. *Sleep*, **34**, 1127-1133. https://doi.org/10.5665/SLEEP.1176

[29] León Subías, E., Gómara de la Cal, S. and Marin Trigo, J.M. (2017) Red Cell Distribution Width in Obstructive Sleep Apnea. *Archivos de Bronconeumología* (*English Edition*), **53**, 114-119. https://doi.org/10.1016/j.arbr.2016.12.003

[30] Pierce, C.N. and Larson, D.F. (2005) Inflammatory Cytokine Inhibition of Erythropoiesis in Patients Implanted with a Mechanical Circulatory Assist Device. *Perfusion*, **20**, 83-90. https://doi.org/10.1191/0267659105pf793oa

[31] Maclay, J.D., Mcallister, D.A. and Macnee, W. (2007) Cardiovascular Risk in Chronic Obstructive Pulmonary Disease. *Official Journal of the Asian Pacific Society of Respirology*, **12**, 634-641. https://doi.org/10.1111/j.1440-1843.2007.01136.x

[32] Palange, P., Testa, U., Huertas, A., *et al*. (2006) Circulating Haemopoietic and Endothelial Progenitor Cells Are Decreased in COPD. *European Respiratory Journal*, **27**, 529-541. https://doi.org/10.1183/09031936.06.00120604

[33] Schols, A.M., Buurman, W.A., Staal van den Brekel, A.J., Dentener, M.A. and Wouters, E.F. (1996) Evidence for a Relation between Metabolic Derangements and Increased Levels of Inflammatory Mediators in a Subgroup of Patients with Chronic Obstructive Pulmonary Disease. *Thorax*, **51**, 819-824. https://doi.org/10.1136/thx.51.8.819

[34] Park, Y., Schoene, N. and Harris, W. (2002) Mean Platelet Volume as an Indicator of Platelet Activation: Methodological Issues. *Platelets*, **13**, 301-306. https://doi.org/10.1080/095371002220148332

[35] Vagdatli, E., Gounari, E., Lazaridou, E., Katsibourlia, E., Tsikopoulou, F. and Labrianou, I. (2010) Platelet Distribution Width: A Simple, Practical and Specific Marker of Activation of Coagulation. *Hippokratia*, **14**, 28-32.

[36] Papanas, N., Symeonidis, G., Maltezos, E., *et al*. (2004) Mean Platelet Volume in Patients with Type 2 Diabetes Mellitus. *Platelets*, **15**, 475-478. https://doi.org/10.1080/09537100420002677O7

[37] Vizioli, L., Muscari, S. and Muscari, A. (2009) The Relationship of Mean Platelet Volume with the Risk and Prognosis of Cardiovascular Diseases. *International Journal of Clinical Practice*, **63**, 1509-1515. https://doi.org/10.1111/j.1742-1241.2009.02070.x

[38] Anfossi, G. and Trovati, M. (1996) Role of Catecholamines in Platelet Function: Pathophysiological and Clinical Significance. *European Journal of Clinical Investigation*, **26**, 353-370. https://doi.org/10.1046/j.1365-2362.1996.150293.x

[39] Rahangdale, S., Yeh, S.Y., Novack, V., *et al*. (2011) The Influence of Intermittent Hypoxemia on Platelet Activation in Obese Patients with Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine*, **7**, 172-178. https://doi.org/10.5664/jcsm.28105

[40] Nakstad, B., Lyberg, T., Skjønsberg, O.H. and Boye, N.P. (1990) Local Activation of the Coagulation and Fibrinolysis Systems in Lung Disease. *Thrombosis Research*, **57**, 827-838. https://doi.org/10.1016/0049-3848(90)90150-B

[41] Rostagno, C., Prisco, D., Boddi, M. and Poggesi, L. (1991) Evidence for Local Platelet Activation in Pulmonary Vessels in Patients with Pulmonary Hypertension Secondary to Chronic Obstructive Pulmonary Disease. *European Respiratory Journal*, **4**, 147-151. https://doi.org/10.1183/09031936.93.04020147

[42] Kario, K., Matsuo, T. and Nakao, K. (1992) Cigarette Smoking Increases the Mean Platelet Volume in Elderly Patients with Risk Factors for Atherosclerosis. *Clinical & Laboratory Haematology*, **14**, 281-287. https://doi.org/10.1111/j.1365-2257.1992.tb00103.x

[43] Onder, I., Topcu, S., Dökmetas, H.S., Türkay, C. and Seyfikli, Z. (1997) Platelet Aggregation Size and Volume in Chronic Obstructive Pulmonary Disease. *Materia Medica Polona*, **29**, 11-13.

[44] Archontogeorgis, K., Nena, E., Papanas, N. and Steiropoulos, P. (2014) Biomarkers to Improve Diagnosis and Moni-

toring of Obstructive Sleep Apnea Syndrome: Current Status and Future Perspectives. *Pulmonary Medicine*, **2014**, Article ID: 930535. https://doi.org/10.1155/2014/930535

[45] Barnes, P.J. and Celli, B.R. (2009) Systemic Manifestations and Comorbidities of COPD. *European Respiratory Journal*, **33**, 1165-1185. https://doi.org/10.1183/09031936.00128008

[46] Gasparyan, A.Y., Ayvazyan, L., Mikhailidis, D.P. and Kitas, G.D. (2011) Mean Platelet Volume: A Link between Thrombosis and Inflammation. *Current Pharmaceutical Design*, **17**, 47-58.

[47] Wei, J., Xiong, X.F., Lin, Y.H., Zheng, B.X. and Cheng, D.Y. (2015) Association between Serum Interleukin-6 Concentrations and Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *PeerJ*, **3**, e1199. https://doi.org/10.7717/peerj.1199

[48] Oelsner, E.C., Pottinger, T.D., Burkart, K.M., *et al*. (2013) Adhesion Molecules, Endothelin-1 and Lung Function in Seven Population-Based Cohorts. *Biomarkers*, **18**, 196-203. https://doi.org/10.3109/1354750X.2012.762805