左心疾病相关性肺动脉高压的研究进展

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【摘要】肺动脉高压（PH）是不良临床结局的独立危险因素，尤其是在左心疾病（LHD）患者中。LHD是PH最常见的病因。无论是由收缩或舒张功能障碍还是由瓣膜性心脏病引起的，伴发于左心疾病的肺动脉高压病死率高且预后差。本文对左心疾病相关性肺动脉高压（PH-LHD）的定义、分类、发病机制以及治疗研究进展等方面进行综述。

【关键词】左心疾病；肺动脉高压；诊断
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Progress on left heart associated pulmonary hypertension

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【Abstract】Pulmonary hypertension (PH) is an independent risk factor for adverse clinical outcomes, especially in patients with left heart disease (LHD). LHD is the most common cause of PH. Whether caused by systolic or diastolic dysfunction or valvular heart disease, pulmonary hypertension associated with left heart disease has a high mortality rate and poor prognosis. This paper reviewed the definition, hemodynamic diagnosis and classification, pathogenesis and therapeutic research progress of left heart disease associated pulmonary hypertension (PH-LHD).

【Key words】Left heart disease; Pulmonary hypertension; Diagnosis

肺动脉高压（pulmonary hypertension, PH）是一种高发病率和高病死率的疾病[1]，是由多种病因导致的进行性心血管疾病，通常因心力衰竭（heart failure, HF）而死亡[2]。PH的全球患病率约为1%，在65岁以上的人群中约为10%[3]。世界卫生组织将PH分为5组：（1）原发性肺动脉高压（pulmonary arterial hypertension, PAH）；（2）左心疾病相关性肺动脉高压（left heart disease associated pulmonary hypertension, PH-LHD）；（3）由肺部疾病引起和（或）缺氧状态相关的PH；（4）由肺动脉阻塞造成的PH，包含慢性血栓性PH；（5）尚未明确因素导致的PH[4-5]。其中，PH-LHD是临床上最常见的PH[6]。近几年研究表明，PH-LHD的发病率和病死率高，且预后不良。专门针对PH-LHD的治疗可以减缓其进展并可能改善疾病严重程度，从而带来更好的临床结局。因此，探索PH-LHD发病机制的研究具有重要意义。本研究对PH-LHD的定义、分类、发病机制以及治疗研究进展等方面进行综述。

1 PH-LHD的定义、分类

PH是一种经右心导管测量静息状态下的平均肺动脉压（mean pulmonary arterial hypertension, mPAH）＞20 mmHg(1 mmHg≈0.133 kPa)为特征的疾病[7]。PH增高可归为3种原因：（1）心输出量增强；（2）左心房压（left atrial pressure, LAP）增加；（3）肺动脉栓塞。肺动脉顺应性降低和肺动脉压力升高，导致左心室充盈压和肺毛细血管楔压升高[8]。PH-LHD可能由各种增加LAP的心脏疾病引起[9]。心功能不全、瓣膜性心脏病和其他导致LAP升高的先天性疾病是PH-LHD的原因[10]。

PH-LHD可分为2种：一种是孤立的毛细血管后PH（isolated post-capillary PH, IPCPH），另一种是毛细血管前和毛细血管后联合PH（combined pre-post-capillary PH, CPCPH）[11]。当mPAH≥20 mmHg且肺动脉楔压（pulmonary artery wedge pressure, PAWP）＞15 mmHg被定义为PH-LHD；当肺血管阻力（pulmonary vascular resistance, PVR）≤3 WU和（或）舒张期肺动脉压力梯度（diastolic pulmonary gradient, DPG）＜7 mmHg时，被定义为IPCPH；当PVR＞3 WU和（或）DPG≥7 mmHg时，被定义为CPCPH[12]。IPCPH和CPCPH的特征都是mPAH和PAWP升高。在大多数IPCPH患者中，mPAH升高可归因于左心室充盈压升高[13]。随着时间的流逝，潜在的LHD疾病可进一步引发血管收缩和血管重塑[14]。在组织学上，观察到肺动脉内膜增厚，导致远端肺动脉的病理性阻塞，随后PVR增加，转变为CPCPH[15]。过渡到该阶段标志着肺血管系统可能受到不可逆的损害[16]。

PH-LHD的诊断和正确分类具有挑战性，准确诊断和区分IPCPH和CPCPH对预后和治疗管理至关重要[17]。

2 PH-LHD的发病机制

2.1 肺血管的病理改变

肺动脉顺应性降低和肺动脉压力升高，发生左心室充盈压和肺毛细血管楔压升高[8]。肺毛细血管壁应力增加会引起“毛细血管应力衰竭”状态，毛细血管内皮和

肺泡上皮层破裂会导致肺水肿和肺泡出血，并进一步释放炎症因子和血管收缩介质[18]。这些反应的相互作用引发了细胞外基质的重塑和成纤维细胞/肌成纤维细胞的增殖[19]。这表现为CPCPH患者的气体扩散能力降低和死腔通气增加[20]。肺血管的长期压力负荷导致肺泡毛细血管重构、内皮功能障碍、NO可用性降低和肺血管重构[21]。

2.2　心房心室结构和功能的改变

由于左心房在左心室充盈和心脏输出的调节中起着重要作用，增加的左心室充盈压力被传回左心房并增加左心房压力和壁压力，最终导致左心房功能障碍[22]。左心房功能下降进一步加重左心室充盈压力，不能代偿左心室舒张功能障碍，还可能导致心房利钠肽合成和调节不足，导致左心室压力进一步升高和肺循环压力升高[23]。

HF患者的LAP慢性升高，或左侧瓣膜性心脏病，导致左室重塑和纤维化，压力过度传递到肺循环[19]。左心房对容量和压力比较敏感，长期压力和容量负荷过重，导致心房失代偿，表现为心房心室失偶联，心输出量下降[24]。左心房僵硬度增加，为左心室和肺动脉之间提供容量和压力缓冲的功能受损，肺动脉顺应性降低和肺血管阻力增加，导致右心功能不全[24]。与IPCPH相比，CPCPH的右心室衰竭风险更高，预后更差[16]。

2.3　血管壁切应力改变

血管壁切应力指的是血流在接触血管内皮时产生的横向摩擦力[25]。血管壁切应力刺激内皮细胞产生NO，可反映内皮功能。NO作为一种重要的保护剂，通过调节血管壁力学来维持血流动力学稳态[26]。血管内皮细胞信号对血管壁切应力改变的反应与血管重塑有关，这可能导致PH-LHD恶化[27]。

2.4　WNT抑制因子1（WNT inhibitory factor 1, WIF-1）重组蛋白

WIF-1是一种结合并抑制WNT蛋白的分泌蛋白，是内源性WNT拮抗剂之一[28]。研究表明，WNT信号传导在调节血管重构中发挥重要作用。由于血管重塑可能在所有PH组的进展中发挥作用，这可能暗示WNT信号是PH的病理生理和进展的一部分[29]。研究表明，毛细血管前PH中WIF-1水平升高，高WIF-1水平也与毛细血管前PH预后较差相关[28]。另外一项研究表明，WIF-1水平与LHD-PH有关，并可能有助于判断其预后[29]。

2.5　醛脱氢酶-2（aldehyde dehydrogenase-2, ALDH2）突变

ALDH2作为线粒体内的一类醛氧化酶，其功能在于催化代谢乙醛以及身体内源性醛类物质的解毒。当ALDH2 rs671位点的G核苷酸由G变为A时，人体内ALDH2的表达水平显著降低，从而增加心血管疾病的风险[30]。一项动物模型研究发现，ALDH2通过调节肺血管平滑肌细胞的线粒体裂变和增殖，减少缺氧所致PH的发生[31]。对比HF合并和不合并PH-LHD组，发现HF合并PH-LHD组ALDH2突变比例更高，ALDH2突变增加了HF患者发生PH-LHD的风险[30]。突变ALDH2可能是PH-LHD临床治疗的潜在新靶点[32]。

3　PH-LHD的治疗

大量研究表明，用于HF治疗的新药在减少PH-LHD方面具有潜在影响，PH-LHD的治疗取决于LHD的病因。

3.1　血管紧张素受体脑啡肽酶抑制剂（angiotensin receptor neprilysin inhibitor,ARNI）

沙库巴曲缬沙坦属于ARNI，通过抑制脑啡肽酶和血管紧张素AT1受体起作用，可抑制血管壁增厚，同时促进血管壁抗纤维化，在LHD中表现出显著的疗效[33]。一项研究表明，射血分数降低的HF患者在早期开始ARNI治疗6个月后，肺动脉收缩压显著降低，预后较好[34]。也有研究提示ARNI可以防止右心室不良重塑[35]。

3.2　左旋西孟旦

左旋西孟旦是一种钙增敏剂、钾ATP通道激活剂和磷酸二酯酶-3抑制剂，具有正性肌力、舒张血管和抑制心脏活性作用[18]。研究表明接受左旋西孟旦治疗的患者在6 min步行试验有明显改善，这与已获批的肺血管扩张剂治疗PH药物的作用相当[36]，证实了左旋西孟旦在降低射血分数降低的HF患者肺动脉压和改善右心室功能方面的积极作用[37]。

3.3　钠－葡萄糖共同转运蛋白-2（sodium-glucose cotransporter-2, SGLT-2）抑制剂

一项随机试验中，在2型糖尿病和运动诱导的PH-LDH患者中，SGLT-2抑制剂达格列净治疗与安慰剂相比，6个月后重复运动试验时，经超声心动图评估，左室收缩压和左室充血压有所改善[38]。研究结果表明SGLT-2抑制剂可以为控制HF患者的肺动脉压力提供新的可能[39]。

此外，近期一项研究证实肾上腺素能受体（adrenergic receptor, AR）激动剂在心血管系统中，刺激促进NO依赖性信号转导，并间接激活心肌细胞Na^+/K^+-ATP酶[40]。研究表明，AR激动剂可改善HF患者的心脏功能，并诱导动物和人类肺血管的舒张[41]。此外，前列环素是一种前列腺素类化合物，作用于血小板和内皮细胞中的特异性受体。它被证实具有扩血管，降低肺血管和全身血管阻力的作用[42]。

综上所述，PH-LHD是死亡和HF住院的预测指标，并可能成为未来研究的重点。优化HF治疗是目前推荐的PH-LHD治疗方法。以上结果表明治疗PH-LHD的关键是优化基础心脏病的管理。PH-LHD患病率高且治疗选择有限。积极开展相关研究进一步明确肺血管重塑的分子机制，有利于寻求新型特异性靶向疗法，为PH-LHD患者提供新的治疗选择。

参考文献

[1] FUNK-HILSDORF T C, BEHRENS F, GRUNE J, et al. Dysregulated immunity in pulmonary hypertension: from companion to composer [J]. Front Physiol, 2022,13: 819145.

[2] LIU S F, YAN Y. Animal models of pulmonary hypertension due to left heart disease [J]. Animal Model Exp Med, 2022,5(3): 197-206.

[3] AHMAD A, ZHANG P, LI L, et al. Editorial: advances in understanding the mechanisms of pulmonary hypertension[J]. Front Cardiovasc Med, 2023,10:1249889.

[4] TITZ A, MAYER L, APPENZELLER P, et al. Long-term outcome of patients with combined post-and pre-capillary pulmonary hypertension [J]. Eur Heart J Open, 2023,3(4): oead069.

[5] QAISER K N, ALMOUSHREF A, MEHTA A K, et al. Fluid loading during the hemodynamic evaluation of pulmonary hypertension: a cross-sectional study [J]. Cardiovasc Diagn Ther, 2023,13(5): 833-842.

[6] BABU G, ANNIS J S, GARRY J D, et al. Clinical features do not identify risk of progression from isolated postcapillary pulmonary hypertension to combined pre-and postcapillary pulmonary hypertension [J]. Pulm Circ, 2023,13(2): e12249.

[7] SIMONNEAU G, MONTANI D, CELERMAJER D S, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension [J]. Eur Respir J, 2019,53(1): 1801913.

[8] CAMELI M, PASTORE M C, HENEIN M Y, et al. The left atrium and the right ventricle: two supporting chambers to the failing left ventricle [J]. Heart Fail Rev, 2019,24(5): 661-669.

[9] VACHIÉRY J L, TEDFORD R J, ROSENKRANZ S, et al. Pulmonary hypertension due to left heartdisease [J]. Eur Respir J, 2019,53(1): 1801897.

[10] HUMBERT M, KOVACS G, HOEPER M M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [J]. Eur Heart J, 2022,43(38): 3618-3731.

[11] LEE F, MIELNICZUK L M. Pulmonary hypertension due to left heart disease-a practical approach to diagnosis and management [J]. Can J Cardiol, 2021,37(4): 572-584.

[12] SÄLLBERG A E, HELLEBERG S, AHMED S, et al. Plasma tumour necrosis factor-alpha-related proteins in prognosis of heart failure with pulmonary hypertension [J]. ESC Heart Fail, 2023,10(6): 3582-3591.

[13] XIAO M Z, LAI D S, YU Y M, et al. Pathogenesis of pulmonary hypertension caused by left heart disease [J]. Front Cardiovasc Med, 2023,10: 1079142.

[14] FERNÁNDEZ A I, YOTTI R, GONZÁLEZ-MANSILLA A, et al. The biological bases of group 2 pulmonary hypertension [J]. Int J Mol Sci, 2019,20(23): 5884.

[15] JANG A Y, PARK S J, CHUNG W J. Pulmonary hypertension in heart failure [J]. Int J Heart Fail, 2021,3(3): 147-159.

[16] VAN DE VEERDONK M C, ROOSMA L, TRIP P, et al. Clinical-imaging-pathological correlation in pulmonary hypertension associated with left heart disease [J]. Eur Respir Rev, 2024,33(171): 230144.

[17] ADLER J, GERHARDT F, WISSMÜLLER M, et al. Pulmonary hypertension associated with left-sided heart failure [J]. Curr Opin Cardiol, 2020,35(6): 610-619.

[18] LTAIEF Z, YERLY P, LIAUDET L. Pulmonary hypertension in left heart diseases: pathophysiology, hemodynamic assessment and therapeutic management [J]. Int J Mol Sci, 2023,24(12): 9971.

[19] GUAZZI M, GHIO S, ADIR Y. Pulmonary hypertension in HFpEFandHFrEF [J]. J Am Coll Cardiol, 2020,76(9): 1102-1111.

[20] OMOTE K, SORIMACHI H, OBOKATA M, et al. Pulmonary vascular disease in pulmonary hypertension due to left heart disease: pathophysiologic implications [J]. Eur Heart J, 2022,43(36): 3417-3431.

[21] AL-OMARY M S, SUGITO S, BOYLE A J, et al. Pulmonary hypertension due to left heart disease: diagnosis, pathophysiology, and therapy [J]. Hypertension, 2020,75(6): 1397-1408.

[22] LEE J H, PARK J H, HWANG I C, et al. Decreased peak left atrial longitudinal strain is associated with persistent pulmonary hypertension associated with left heart disease [J]. J Clin Med, 2022,11(12): 3510.

[23] XU Y, YANG B W, HUI J J, et al. The emerging role of sacubitril/valsartan in pulmonary hypertension with heart failure [J]. Front Cardiovasc Med, 2023,10: 1125014.

[24] 郑舒文，王喆，翟振国，等. 左心衰竭相关肺动脉高压的研究进展[J]. 中华内科杂志，2024,63(1): 113-120.

[25] GOUDOT G, VAN KAMPEN A. Wall shear stress: the challenges of a rising imaging marker in current clinical practice [J]. J Thorac Dis, 2023,15(5): 2371-2373.

[26] BARTOLO M A, QURESHI M U, COLEBANK M J, et al. Numerical predictions of shear stress and cyclic stretch in pulmonary hypertension due to left heart failure [J]. Biomech Model Mechanobiol, 2022,21(1): 363-381.

[27] YAN Y Z, XIONG J C, XU F F, et al. SDF-1α/CXCR4 pathway mediates hemodynamics-induced formation of intracranial aneurysm by modulating the phenotypic transformation of vascular smooth muscle cells [J]. Transl Stroke Res, 2022,13(2): 276-286.

[28] UELAND T, ABRAITYTE A, NORUM H, et al. Circulating regulators of the wingless pathway in precapillary pulmonary hypertension [J]. Respirology, 2021,26(6): 574-581.

[29] KANIA K, AHMED A, AHMED S, et al. Elevated plasma WIF-1 levels are associated with worse prognosis in heart failure with pulmonary hypertension [J]. ESC Heart Fail, 2022,9(6): 4139-4149.

[30] ZHANG J, GUO Y Y, ZHAO X K, et al. The role of aldehyde dehydrogenase 2 in cardiovascular disease [J]. Nat Rev Cardiol, 2023,20(7): 495-509.

[31] ZHAO Y, WANG B L, ZHANG J, et al. ALDH2 (aldehyde dehydrogenase 2) protects against hypoxia-induced pulmonary hypertension [J]. Arterioscler Thromb Vasc Biol, 2019,39(11): 2303-2319.

[32] CHANG S C, WU J, JIN J F, et al. Aldehyde dehydrogenase 2 (ALDH2) elicits protection against pulmonary hypertension via inhibition of ERK1/2-mediated autophagy [J]. Oxid Med Cell Longev, 2022,2022: 2555476.

[33] ABUMAYYALEH M, EL-BATTRAWY I, BEHNES M, et al. Current evidence of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction [J]. Future Cardiol, 2020,16(4): 227-236.

[34] MOON M G, HWANG I C, CHOI W, et al. Reverse remodelling by sacubitril/valsartan predicts the prognosis in heart failure with reduced ejection fraction [J]. ESC Heart Fail, 2021,8(3): 2058-2069.

[35] SHARIFI KIA D, BENZA E, BACHMAN T N, et al. Angiotensin receptor-neprilysin inhibition attenuates right ventricular remodeling in pulmonary hypertension [J]. J Am Heart Assoc, 2020,9(13): e015708.

[36] BURKHOFF D, BORLAUG B A, SHAH S J, et al. Levosimendan improves hemodynamics and exercise tolerance in PH-HFpEF: results of the randomized placebo-controlled HELP trial [J]. JACC Heart Fail, 2021,9(5): 360-370.

[37] HU Y S, WEI Z, ZHANG C Y, et al. The effect of levosimendan on right ventricular function in patients with heart dysfunction: a systematic review and meta-analysis [J]. Sci Rep, 2021,11: 24097.

[38] KAYANO H, KOBA S, HIRANO T, et al. Dapagliflozin influences ventricular hemodynamics and exercise-induced pulmonary hypertension in type 2 diabetes patients: a randomized controlled trial [J]. Circ J, 2020,84(10): 1807-1817.

[39] KING N E, BRITTAIN E. Emerging therapies: the potential roles SGLT2 inhibitors, GLP1 agonists, and ARNI therapy for ARNI pulmonary hypertension [J]. Pulm Circ, 2022,12(1): e12028.

[40] BUNDGAARD H, AXELSSON RAJA A, IVERSEN K, et al. Hemodynamic effects of cyclic guanosine monophosphate-dependent signaling through β3 adrenoceptor stimulation in patients with advanced heart failure: a randomized invasive clinical trial [J]. Circ Heart Fail, 2022,15(7): e009120.

[41] GARCÍA-ÁLVAREZ A, BLANCO I, GARCÍA-LUNAR I, et al. β3 adrenergic agonist treatment in chronic pulmonary hypertension associated with heart failure (SPHERE-HF): a double blind, placebo-controlled, randomized clinical trial [J]. Eur J Heart Fail, 2023,25(3): 373-385.

[42] WANG P W, DENG J X, ZHANG Q Y, et al. Additional use of prostacyclin analogs in patients with pulmonary arterial hypertension: a meta-analysis [J]. Front Pharmacol, 2022,13: 817119.