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机械通气诱导气道塌陷中气道平滑肌细胞力学行为异常的研究进展

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摘要:机械通气为呼吸危重症患者提供生命支持,但也引起致命的肺损伤(ventilator induced lung injury, VILI),后者因病理机制不明一直是呼吸与危重症学科的重大难题。近年的研究发现,一方面 VILI 伴随同一气道多点塌陷现象,但这一现象很难用传统塌陷模型加以解释。另一方面,机械通气条件下气道平滑肌细胞(airway smooth muscle cells, ASMC)发生力学行为异常并伴随 Piezo1 表达变化和内质网应激等现象。这些现象显示,机械通气导致 ASMC 的力学行为异常与气道多点塌陷以及 VILI 密切相关。但要从细胞力学角度解释机械通气导致气道塌陷和 VILI 的机制,还需要系统深入地研究机械通气条件下 ASMC 力学行为变化规律与气道塌陷和肺损伤的相互关系及其力-化学信号耦合过程。本文综述了近期有关机械通气条件下气道塌陷现象、机械通气相关高拉伸对 ASMC 力学行为的调控及力-化学信号耦合机制等方面的研究进展,以期为进一步探索 ASMC 力学行为异常在 VILI 病理机制中的作用、有效防治 VILI 的新药干预靶点,以及临床优化的机械通气策略等提供重要的参考依据和启发性的研究思路。

关键词: 机械通气; 拉伸应变; 气道平滑肌细胞; 细胞力学响应; 细胞力学感受器
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Mechanical Ventilator-Induced Airway Collapse Due to Abnormal Mechanical Behaviors of Airway Smooth Muscle Cells: A Review

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Abstract: Mechanical ventilation (MV) provides life support for critically ill respiratory patients, but in the meantime can cause fatal ventilator-induced lung injury (VILI), and the latter remains a major challenge in respiratory and critical care medicine, because the pathological mechanism has not been fully elucidated. Recent studies show that on the one hand, in the lung with VILI, there exists airway collapse at multi-sites of an individual airway, which can not be explained by traditional airway collapse models. But on the other hand, under MV conditions, airway smooth muscle cells (ASMC) exhibit abnormal mechanical behaviors, accompanied by regulation of Piezo1 expression and endoplasmic reticulum stress. These phenomenons indicate that the MV-

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induced abnormal mechanical behavior of ASMC is closely related to multiple airway collapse and VILI. Therefore, by studying the MV-induced changes of ASMC mechanical behaviors and their relationship with airway collapse in lung injury, as well as the related mechanochemical signal coupling process, it is expected to reveal a novel mechanism of MV-associated airway collapse and lung injury from the perspective of cell mechanics. In this review, the recent research progress of airway collapse during MV, the regulation of ASMC mechanical behavior by MV-related high stretch, especially the related mechanochemical signal coupling mechanism is summarized. These advances may provide a novel insight for exploring the roles of ASMC abnormal mechanical behavior in the pathological mechanism of VILI, alternative targets of drug intervention for prevention and treatment of VILI, as well as for optimizing the ventilation mode in clinical practice.

Key words: mechanical ventilation; stretch strain; airway smooth muscle cells; cellular mechanical response; cellular mechanosensor

急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)等呼吸危重症患者依赖机械通气维持生命。但机械通气也会诱发致命的肺损伤(ventilator-induced lung injury, VILI),而且该类肺损伤的机制不甚明确,也无有效防治措施,一直是呼吸与危重症医学临床面临的重大难题[1-2]。

VILI 发生机制之一是机械通气导致的肺萎陷伤,肺泡塌陷被认为是肺萎陷的主要原因[3]。然而,随着成像等相关技术的发展,最新的证据显示,气道塌陷也是机械通气导致肺萎陷伤的重要问题之一[4-7]。近年来,呼吸与危重症医学的权威专家纷纷呼吁关注气道塌陷在 VILI 中的作用[8-17],并强调忽视气道塌陷问题会导致驱动压计算错误、呼气末正压(positive end-expiratory pressure,PEEP)设置不当等,是 VILI 发生的重要根源[18-20].

高精度成像观察进一步发现机械通气时,肺部同一气道出现多点塌陷[14]。更重要的是,这一现象不能用肺泡表面活性物质相关的液体桥或者顺应性塌陷等传统模型解释[21]。这些最新的发现提示,机械通气导致气道塌陷可能存在尚未认知的新机制[8]。另一方面,因气道平滑肌细胞(airway smooth muscle cell, ASMC)力学行为异常(如高反应性等)导致气道过度缩窄乃至多点塌陷的情况,多见于哮喘等慢性呼吸道疾病患者的气道[9,22-23]。已知 ASMC 对机械拉伸极为敏感,潮式呼吸或者深吸气等拉伸应变均会显著影响 ASMC 力学行为。但机械通气对 ASMC 高反应性、流态化等力学行为的影响及其在气道塌陷中的作用,目前鲜有深入探究。

因此,需要系统探究机械通气对 ASMC 高反应性等力学行为的影响规律及其与气道塌陷和肺损伤的关系,以及力-化学信号耦合过程在其中的调控作用,最终从 ASMC 力学角度揭示机械通气诱导气道塌陷和肺损伤的内在机制,为探索防治 VILI 的新药干预靶点以及优化临床通气模式提供科学依据。

1 机械通气导致肺损伤中气道塌陷的现象

呼吸道病毒(如严重急性呼吸综合征冠状病毒 2, SARS-CoV-2)感染的危重症患者会表现为 ARDS,需要机械通气才能维持生命[24]。但临床发现机械通气患者会发生肺萎陷伤,是 VILI 发生的一种重要机制(见图 1)。

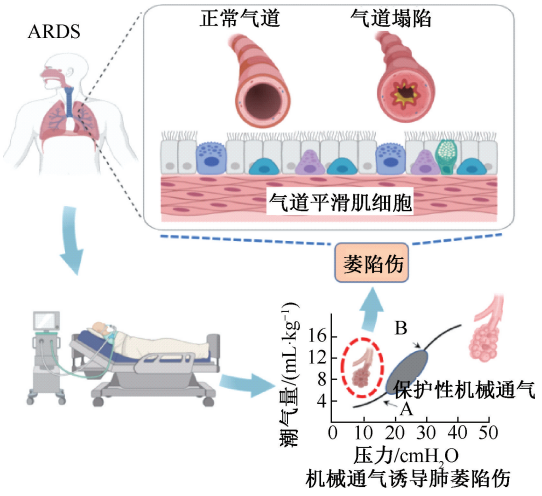

图 1 危重症 ARDS 患者机械通气后出现肺萎陷伤

Fig. 1 Atelectasis in critically ill acute ARDS patients after mechanical ventilation

为避免发生肺萎陷伤,临床采用“保护性通气”策略(图 1 灰色区域)中的 PEEP 防止气道和肺泡

塌陷[25]。遗憾的是,临床操作中 PEEP 的设置大多凭借经验,缺乏可靠的科学依据,往往因设置不当不能防止肺萎陷,甚至引发肺损伤[26-27]。

早期的研究主要关注肺泡塌陷在 VILI 中的作用,虽然也认识到气道塌陷的可能性,但技术上难以对其进行研究[28]。随着技术的进步,精细的呼吸力学分析发现,机械通气时存在气道阻力升高、内源性 PEEP、气体陷闭或压力-体积曲线上的低拐点等,这些现象均反映小气道塌陷[17,29-30]。高精度电子计算机断层扫描(computed tomography, CT)技术和电阻抗成像分析的发展也为直观评估机械通气时小气道塌陷提供了可能[31]。Chen 等[10]通过分析中重度 ARDS 患者机械通气时压力-体积曲线发现,大约 25% 患者出现严重气道塌陷。该研究结果引起了呼吸与危重症医学领域专家的广泛关注,并提出"支气管损伤"的新概念,但也提出需要直接观察气道塌陷[11-12]。Broche 等[14]利用高精度 CT 技术观察兔 ARDS 模型机械通气后肺组织影像,首次观察到机械通气时气道塌陷的存在,并发现在同一气道有多点塌陷。后续的研究显示,时间控制自适应通气模式通过缩短呼气时间先稳定肺,然后延长吸气时间恢复塌陷的气道,有助于降低机械通气 ARDS 患者的死亡率[32]。这些动物和人体研究明确了机械通气时气道塌陷的存在,并揭示气道塌陷是 VILI 的重要根源[9,33-36]。

传统的理论认为,机械通气导致气道表面活性物质失活而损害气道力学行为,进而导致气道发生液体桥塌陷或者顺应性塌陷[21]。但这些理论只能解释同一气道发生一处塌陷的情况,而不能解释最新观察到的同一气道多点塌陷现象[15];且即使输注表面活性物质也不能显著改善这类气道塌陷,提示气道塌陷存在新的机制[8]。

有意思的是,多点气道塌陷多见于哮喘和慢性阻塞性肺部疾病患者,且 ASMC 是导致这些气道塌陷的终极效应器[37]。早期已有针对 ASMC 是否参与机械通气 ARDS 患者气道阻力增加而开展的研究,但相关研究没有形成一致的结果。研究显示,机械通气 ARDS 患者气道阻力显著增加,且 ASMC 舒张剂显著降低气道阻力[38]。也有研究显示,舒张剂不能改善机械通气 ARDS 患者的呼出气流受限现象[39]。短期临床试验显示,靶向 β2 受体舒张剂有一定疗效;但长时间多中心随机双盲临床观察则发现,其作用效果不明显、副作用过大[40]。这些研究虽然关注了 ASMC 收缩在机械通气诱导气道塌陷中的作用,但忽略了 ASMC 力学行为的复杂性及其对外部力学刺激的敏感性,如力学刺激导致的 ASMC 高反应性、流态化等力学行为变化都可能导致气道塌陷(见图 2)。

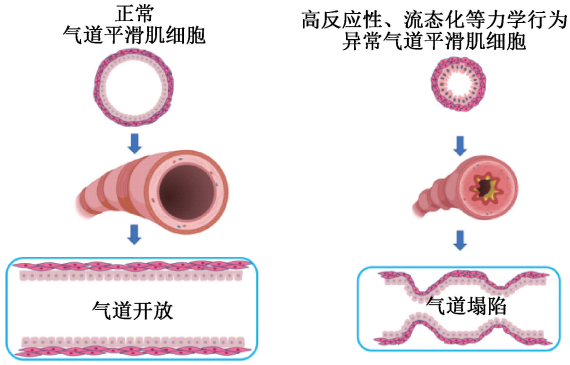

图 2 气道平滑肌细胞高反应性、流态化等力学行为异常导致气道塌陷

Fig. 2 Airway collapse caused by abnormal mechanical behaviors such as high reactivity and fluidity of airway smooth muscle cells

2 机械通气施加的高拉伸对 ASMC 力学行为的调控

2.1 机械通气施加的高拉伸应变是引起肺损伤的核心力学因素

健康人群气道长期受潮式呼吸引起的低拉伸应变作用(<5%),从形态到功能都发生了适应。而 ARDS 患者在机械通气时因为通气肺体积下降导致气道受到的拉伸应变大幅增加(>10%),引发气道上皮细胞脱落、气道炎症,甚至肺纤维化;国际多中心大样本随机对照研究显示,低潮气量可降低机械通气患者肺泡灌洗液中炎症因子水平[41],揭示高拉伸应变是 VILI 的核心致病力学因素[42-43](见图 3)。

2.2 机械通气相关高拉伸调控 ASMC 力学行为

ASMC 是一种力学敏感细胞,对潮式呼吸低拉伸应变(<5%)以及深吸气高拉伸应变(>10%)具有不同响应。机械通气时 ASMC 受到的高拉伸应变类似于深吸气的拉伸应变幅度(>10%)。因此,深吸气高拉伸对 ASMC 的相关研究,可能有助于理解在机械通气时 ASMC 的力学行为。研究发现,健康

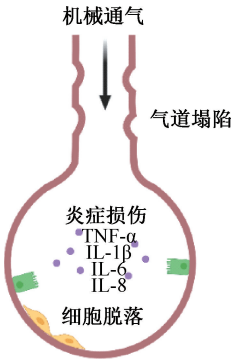

图 3　高拉伸应变是机械通气引发肺损伤的核心力学因素

Fig. 3　High stretch is the core mechanical factor causing lung injury during mechanical ventilation

人 ASMC 受激动剂刺激后的收缩可以通过深吸气舒张,但哮喘患者 ASMC 在深吸气后则进一步痉挛。该现象提示,哮喘 ASMC 对高拉伸应变的响应发生变化,导致高反应性引起气道缩窄甚至塌陷[44]。在机械通气条件下,ASMC 周围存在哮喘类似的炎症环境,但目前尚不清楚这种机械通气导致的炎症环境是否诱发 ASMC 哮喘类样的高反应性。

通过文献检索发现,关于机械通气如何影响 ASMC 的报道大多聚焦在炎症因子和 miRNA 表达方面(见表 1),还缺乏结合细胞力学技术研究机械通气时 ASMC 高反应性、流态化、张力变化等力学行为的报道,尤其是机械通气时 ASMC 力学行为变化规律与气道塌陷和肺损伤的关系还有待进一步阐明。

表 1　机械通气及相关高拉伸(>10% 应变)影响 ASMC 相关研究情况

Tab. 1　Related researches on impact of mechanical ventilation and related high stretching (>10% strain) on ASMC

实验模型	拉伸条件	拉伸时间/h	研究结果	文献
C57BL/6	V_T:18 mL/kg	3	Piezo1、integrin 表达下降促进细胞迁移	[45]
新生羊	1/6 Hz, 490~1 176 Pa	3	平滑肌长度降低	[46]
ASMC	1 Hz, 12%	1 /12	miR-26a 和 miR-140 上调	[47]
ASMC	1 Hz, 12%	12	通过 ERK1/p38 激活 AP-1 和 C-EBP 转录因子,促进 IL-8 合成	[48]
ASMC	0.5 Hz, 13%	72	激活内质网应激促进炎症响应	[49]
ASMC	0.5 Hz, 13%	72	通过 miR-370-5p 调节 ATP、cAMP 代谢	[50]
ASMC	0.5 Hz, 10%	3	细胞骨架流态化、软玻态	[51]

3　机械通气导致的高拉伸启动 ASMC 力-化学信号耦合

内质网是细胞中蛋白质合成、折叠的场所,在细胞应激响应中发挥重要作用。力学刺激等多种因素可导致内质网内合成的蛋白质错误折叠,这些错误折叠蛋白质会被感受蛋白(如 HSPA5 等)识别,进而激活下游分子如蛋白激酶 R 样内质网激酶(protein kinase R-like ER kinase,PERK)、肌醇需求酶 1α(inositol requiring enzyme lα, IRE1α)、激活转录因子 6(activating transcription factor 6,ATF6)等,从而活化 3 个主要信号通路(IRE1α-XBP1、ATF6 和 PERK-eIF2-ATF4)引发内质网应激并调节蛋白质合成。其中,PERK 信号降低通用蛋白质合成,ATF6 和 IREl 信号则增加伴侣蛋白合成,从而促进错误折叠蛋白质正确折叠或者降解(见图 4)。因此,适度内质网应激可以保护细胞,但持续内质网应激则损伤细胞。Dolinay 等[52]研究表明,机械通气可以激活内质网应激,即在高拉伸时,上皮细胞内质网钙离子释放激活 PERK 活化内质网应激,而 PERK 抑制剂改善肺泡炎性反应和通透性。罗明志等[49]基于全基因组测序和大数据分析的研究则发现,ASMC 对机械通气相关高拉伸的最主要响应是内质网应激。

此外,机械通气也可以通过活化力学敏感离子通道调控细胞行为[53-54]。特别是在 ASMC 等哺乳动物细胞中,广泛表达的 Piezo 离子通道对力学刺激较为敏感,Wang 等[55]的深入研究基本阐明了其

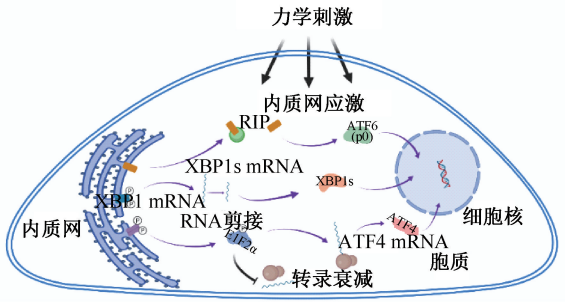

图 4　力学刺激导致 ASMC 内质网应激

Fig. 4　Mechanical stretch induces endoplasmic reticulum stress of ASMCs

结构和活化机制。罗明志等[45]则研究显示,机械通气及相关高拉伸调节 ASMC 的 Piezo1-整合素信号促进 ASMC 表型转换。而 ASMC 中 Piezo1 的表达量显著高于 Piezo2,且化学活化 Piezo1 可以激活内质网应激调控 ASMC 力学行为[56]。

4 总结与展望

本文从细胞力学角度探究机械通气导致气道塌陷中 ASMC 力学行为异常及其力-化学信号耦合机制,包括机械通气如何通过激活 Piezo1-内质网应激信号轴调节 ASMC 高反应性、流态化、细胞刚度变化等力学行为异常并导致气道塌陷,具有十分重要的理论意义和临床应用价值。但目前这方面的研究报道还比较少,故需要开展相关研究,尤其需要结合多组学分析、细胞力学与流变学等多学科的知识与手段,从分子、细胞到个体多尺寸地深入研究机械通气对气道和 ASMC 生物力学行为的影响及其作用机制,如 ASMC 在机械通气时的具体力学行为变化(如高反应性、流态化等)、细胞力学感知和响应机制(如内质网应激响应及其时间和幅度依赖特性等)及其与气道塌陷和肺损伤的关系。通过这些研究,有望进一步揭示机械通气导致气道塌陷的作用靶点和调控机制,从而有针对性地提出可能的药物干预途径和通气优化方案,为开拓新型机械通气策略提供科学依据和研究思路,助力解决 VILI 这一呼吸和危重症医学面临的重大难题[9]。

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