doi: 10.13241/j.cnki.pmb.2019.15.035

枸橼酸咖啡因联合肺泡表面活性物质治疗新生儿呼吸窘迫综合征的疗效及对血清 BMP-7、CC16、SF 水平的影响 *

李兴朝 李 涛△ 谢集建 席世兵 刘 慧 杨 敏

（十堰市太和医院(湖北医药学院附属医院)儿科 湖北 十堰 442000）

摘要 目的：探讨枸橼酸咖啡因联合肺泡表面活性物质治疗新生儿呼吸窘迫综合征患儿的疗效及对血清骨形态发生蛋白 -7(BMP-7)、Clara 细胞分泌蛋白(CC16)、铁蛋白(SF)水平的影响。**方法：**选择 2016 年 3 月到 2018 年 3 月我院接诊的新生儿呼吸窘迫综合征患儿 90 例作为研究对象，以随机数表法分为观察组(n=48)和对照组(n=42)。对照组使用肺泡表面活性物质进行治疗，观察组在对照组的基础上加用枸橼酸咖啡因进行治疗。比较两组治疗后的疗效，治疗前后血清 BMP-7、CC16、SF 水平、血气指标[氢离子浓度指数(pH)、二氧化碳分压(PCO_2)、氧合指数(PaO_2/FiO_2)]的变化，通气时间及支气管肺发育不良(BPD)的发生率。**结果：**治疗后，观察组总有效率为 95.83%，明显高于对照组(71.43%，$P<0.05$)；两组患儿血清 BMP-7、CC16、SF 水平较治疗前均显著降低($P<0.05$)，且观察组以上指标均明显低于对照组($P<0.05$)；两组患儿 pH、PaO_2/FiO_2 均较治疗前明显升高，而 PCO_2 较治疗前显著降低($P<0.05$)，且观察组患儿 pH、PaO_2/FiO_2 显著高于对照组，而 PCO_2 明显低于对照组($P<0.05$)。观察组患儿通气时间明显短于对照组，BPD 发生率显著低于对照组($P<0.05$)。**结论：**枸橼酸咖啡因联合肺泡表面活性物质治疗新生儿呼吸窘迫综合征的临床效果显著优于单用肺泡表面活性物质治疗，其可有效改善患儿血清 BMP-7、CC16、SF 水平、缩短机械通气时间，降低支气管肺发育不良发生率。

关键词：枸橼酸咖啡因；肺泡表面活性物质；新生儿呼吸窘迫综合征；骨形态发生蛋白 -7；Clara 细胞分泌蛋白；铁蛋白

中图分类号：R725.6；R722.12 **文献标识码：**A **文章编号：**1673-6273(2019)15-2953-04

Curative Efficacy of Caffeine Citrate is Combined with Alveolar Surface Active Material in Treatment of Neonatal Respiratory Distress Syndrome and Its Effects on Serum BMP-7, CC16 and SF*

LI Xing-chao, LI Tao△, XIE Ji-jian, XI Shi-bing, LIU Hui, YANG Min

(Pediatrics, Shiyan Taihe Hospital (Affiliated Hospital of Hubei Medical College), Shiyan, Hubei, 442000, China)

ABSTRACT Objective: To study the curative efficacy of caffeine citrate combined with alveolar surface active material in the treatment of neonatal respiratory distress syndrome and its effect on the serum Bone morphogenetic protein-7 (bmp-7), Protein excreted by Clara cells (CC16) and Ferritin (SF) levels. **Methods:** 90 cases of patients with neonatal respiratory distress syndrome treated in our hospital from March 2016 to March 2018 were selected and randomized into the observation group (n=48) and the control group (n=42). The control group was treated with pulmonary surfactant, while the observation group was treated with caffeine citrate on the basis of the control group. After treatment, the changes of serum BMP-7, CC16, SF, blood gas index (pH, PCO_2, PaO_2), ventilation time and incidence of bronchopulmonary dysplasia (BPD) were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was 95.83%, which was significantly higher than that of the control group (71.43%, P<0.05); the serum BMP-7, CC16, SF levels of both groups were significantly lower than those before treatment ($P<0.05$), and the above indicators of observation group were significantly lower than those of the control group ($P<0.05$); the pH, PaO_2/FiO_2 of both groups were significantly higher than those before treatment, while the PCO_2 was significantly lower than before treatment ($P<0.05$), which was significantly lower than those before treatment ($P<0.05$), the pH, PaO_2/FiO_2 were significantly higher than those in the control group, while PCO_2 was significantly lower than those in the control group ($P<0.05$). The ventilation time of the observation group was significantly shorter than that of the control group, and the incidence of BPD was significantly lower than that of the control group ($P<0.05$). **Conclusion:** The clinical effect of caffeine citrate combined with alveolar surfactant is significantly better than alveolar surfactant alone in the treatment of neonatal respiratory distress syndrome. It can effectively improve the serum BMP-7, CC16, SF levels, shorten the mechanical ventilation time and reduce the incidence of bronchopulmonary dysplasia.

Key words: Caffeine citrate; Alveolar surface active material; Neonatal respiratory distress syndrome; Bone morphogenetic protein-7; Clara cells secrete proteins; ferritin

Chinese Library Classification(CLC): R725.6; R722.12 Document code: A

Article ID: 1673-6273(2019)15-2953-04

* 基金项目：湖北省自然科学基金项目(2012FB0310)

作者简介：李兴朝(1983-)，男，硕士研究生，主治医师，研究方向：儿科心血管、新生儿及肾病，电话：15926171263，E-mail：honorjoker@163.com

△ 通讯作者：李涛(1963-)，男，主任医师、教授，博士，研究方向：儿科心血管、新生儿及肾病

(收稿日期：2018-11-30 接受日期：2018-12-23)

前言

新生儿呼吸窘迫综合征 (neonatal respiratory distress syndrome,NRDS) 是指新生儿在出生后不久出现的进行性呼吸困难和呼吸衰竭,通常是由于缺乏肺泡表面活性物质引起肺泡进行性萎陷所致,临床常表现为进行性呼吸困难、呼气性呻吟、紫绀、心率加快等症状,严重时会发生呼吸衰竭,甚至死亡,严重威胁患儿的生命[1-3]。新生儿呼吸窘迫综合征的治疗过程中,需要恰当的呼吸支持以减少呼吸做功、缓解呼吸困难并维持适当的氧饱和度[4,5]。近年来,有研究显示血清中的炎症因子、蛋白和酶的变化是评估新生儿呼吸窘迫综合征的重要指标[6,7]。肺泡表面活性物质是由肺泡Ⅱ型上皮细胞分泌的一种脂蛋白,可以保持大小肺泡容积的稳定性,防止肺泡萎限,有利于肺扩张,通常经气管给药用于治疗新生儿呼吸窘迫综合征。但是经气管滴入肺泡表面活性物质易致使其在肺泡中分布不均匀,造成肺损伤[8,9]。国外应用枸橼酸咖啡因治疗新生儿呼吸暂停及新生儿呼吸窘迫综合征已有 30 多年的历史,其能够提高患儿的疗效,改善临床症状[10,11]。近年来,国内也开始逐渐将枸橼酸咖啡因应用于临床。本研究旨在探讨枸橼酸咖啡因联合肺泡表面活性物质治疗新生儿呼吸窘迫综合征的疗效,并观察其对血清骨形态发生蛋白 -7(BMP-7)、Clara 细胞分泌蛋白(CC16)、铁蛋白(SF)水平的影响,旨在为临床治疗提供理论依据,现将结果报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 3 月到 2018 年 3 月我院新生儿重症监护室 (NICU) 接诊的新生儿呼吸窘迫综合征患儿 90 例进行研究,研究已获得我院伦理委员会批准实施。通过随机数表法将患者分为观察组和对照组。观察组:男 29 例,女 19 例;胎龄 29~34 周,平均(32.87± 2.39)周;出生体重(1.61± 0.35)Kg。对照组:男 24 例,女 18 例;胎龄 28~34 周,平均(33.19± 2.15)周;出生体重(1.59± 0.34)Kg。两组患儿性别(x^2=0.099,P=0.753)、胎龄(t=0.664,P=0.509)、体重(t=0.2741,P=0.785)等一般资料比较无明显差异(P>0.05),组间具有可比性。

纳入标准:(1) 符合新生儿呼吸窘迫综合征的诊断标准[12],并通过影像学检查等得以确诊;(2) 出生后 12 小时内发生呼吸窘迫需要机械通气者。排除标准:(1)其它疾病引起的呼吸困难;(2)合并:① 染色体疾病;② 严重复杂先天性畸形如先天性心脏病、先天性呼吸系统畸形等;③ 遗传代谢性疾病。

1.2 治疗方法

两组患儿均给予婴儿培养箱保暖、防治感染、改善微循环及营养支持治疗,对照组在此基础上给予猪肺磷脂(规格 3 mL:240 mg, 厂家: 意大利凯西制药公司, 进口药品注册证号:H20140848)100 mg/Kg,药剂加热至 37℃,清理呼吸道、气管插管后,经气管导管快速注入药物。观察组在对照组的基础上加用枸橼酸咖啡因(规格 1 mL:20 mg,厂家:意大利凯西制药公司,进口药品注册证号:H20171324),负荷量 20 mg/kg,使用输液泵缓慢静脉输注(30 分钟),间隔 24 小时后,每 24 小时给予 5 mg/kg 维持量,使用输液泵缓慢静脉输注(10 分钟),7 d 一个疗程。

1.3 观察指标

患儿治疗前后 pH、PCO_2、PaO_2/FiO_2 水平的变化; 治疗前后,分别采集患者空腹静脉血 1 mL,以 3000 r·min^{-1} 离心 15 min 后,提取上层血清,采用双抗体夹心酶联免疫吸附法(ELISA)测定血清 BMP-7、CC16、SF 水平,试剂盒购于上海研晶生物科技有限公司,所有操作均严格按照仪器操作流程及试剂盒说明书进行;患儿机械通气时间及 BPD 的发生情况。

1.4 疗效评价标准[13]

显效:患儿呼吸困难、缺氧等临床症状完全消失;有效:治疗后患儿呼吸困难、缺氧等临床症状有所好转;无效:临床症状无明显缓解甚至加重。以显效 + 有效为总有效率。

1.5 统计学分析

采用 SPSS 22.0 软件包处理研究数据, 计量资料均为正态分布,以均数± 标准差($\bar{x}$± s)表示,组间比较使用独立样本 t 检验,计数资料以率表示,组间比较使用 x^2 检验,以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组患儿临床疗效的比较

治疗后, 观察组总有效率为 95.83%, 明显高于对照组(71.43%),差异有统计学意义(P<0.05),见表 1。

表 1 两组患儿临床疗效比较[例(%)]

Table 1 Comparison of the efficacy between the two groups [n(%)]

Groups	n	Effective	Valid	Invalid	Total effective rate
Observation group	48	27(56.25)	19(39.58)	2(4.17)	46(95.83)
The control group	42	22(52.38)	8(19.05)	12(28.57)	30(71.43)
x^2 value					10.156
P value					0.001

2.2 两组患儿治疗前后血清 BMP-7、CC16、SF 水平的比较

治疗前,两组患儿血清 BMP-7、CC16、SF 水平比较差异无统计学意义(P>0.05);治疗后,两组患儿血清 BMP-7、CC16、SF 水平较治疗前均显著降低(观察组 P=0.004、0.000、0.000;对照组 P=0.000、0.000、0.015),且观察组患儿血清 BMP-7、CC16、SF 水平均明显低于对照组(P<0.05),见表 2。

2.3 两组患儿治疗前后血气指标的比较

治疗前,两组患儿血气指标水平比较无显著差异(P>0.05);治疗后,两组患儿 pH、PaO_2/FiO_2 均较治疗前明显升高,而 PCO_2 较治疗前显著降低,(观察组 P<0.000、0.000、0.000; 对照组

P=0.000、0.007、0.000)，且观察组患儿 pH、PaO_2/FiO_2 显著高于对照组，而 PCO_2 明显低于对照组($P<0.05$)，见表 3。

表 2 两组患儿治疗前后血清 BMP-7、CC16、SF 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum BMP-7, CC16 and SF levels between the two groups before and after treatment($\bar{x}\pm s$)

Groups	n	BMP-7(ng/mL)		CC16(mg/L)		SF(μg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	46.20± 4.35	43.65± 4.05	55.29± 0.83	17.63± 1.12	176.15± 77.42	83.47± 31.02
Control group	42	46.19± 4.13	49.98± 4.12	55.42± 0.86	34.18± 1.08	179.28± 69.76	211.45± 46.58
t value		0.011	7.338	0.729	71.108	0.200	15.512
P value		0.991	0.000	0.468	0.000	0.842	0.000

表 3 两组患儿治疗前后血气指标比较($\bar{x}\pm s$)

Table 3 Comparison of the blood and gas index before and after treatment between two groups($\bar{x}\pm s$)

Groups	n	pH		PCO_2(mmHg)		PaO_2/FiO_2	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	7.12± 0.08	7.41± 0.11	41.75± 4.37	38.51± 3.32	112.94± 16.35	235.64± 31.67
The control group	42	7.13± 0.09	7.29± 0.09	41.76± 4.56	43.57± 4.76	115.74± 15.63	185.65± 26.79
t value		0.558	5.614	0.011	5.906	0.827	8.021
P value		0.578	0.000	0.992	0.000	0.410	0.000

2.4 两组患儿辅助通气时间及 BPD 发生情况的比较

观察组患儿辅助通气时间明显短于对照组，BPD 的发生率显著低于对照组($P<0.05$)，见表 4。

表 4 两组患儿辅助通气时间及 BPD 发生情况的比较

Table 4 Comparison of the auxiliary ventilation time and incidence of BPD between two groups

Groups	n	Aeration time(d)	BPD occur
Observation group	48	4.31± 1.32	2(4.17)
The control group	42	9.75± 3.34	9(21.43)
t value		t=10.401	x^2=6.221
P value		0.000	0.013

3 讨论

新生儿呼吸窘迫综合征是新生儿期危重症之一，常发生于早产儿，其发病率与胎龄呈负相关[14,15]。新生儿尤其是早产儿肺发育相对不成熟，因肺表面活性物质先天缺乏、合成不足或消耗过度，容易发生新生儿呼吸窘迫综合征，临床治疗过程中应维持新生儿呼吸窘迫综合征患儿适当的血氧分压和血氧饱和度，减少并发症，提高生存率[16,17]。

在早产儿呼吸窘迫综合征的临床治疗中，根据患儿的病情和各种高危因素给予针对性的合理诊断、治疗和护理对改善新生儿的预后至关重要。既往通常使用肺泡表面活性物质治疗该病，肺泡表面活性物质是分布在肺泡液体分子层的表面，即在液 - 气界面之间的一种脂蛋白，具有降低肺泡表面张力的作用，能维持大小肺泡容积的相对稳定，增强肺的顺应性。使用外源性肺泡表面活性物质替代治疗可以降低其发病率，减轻 NRDS 的严重程度，但是早产婴儿可能因发育不全而有其他合并症，因此肺泡表面活性物质的使用不可能完全消除与早产有关的病死率而且有时效果并不特别显著，还可能使新生儿呼吸窘迫综合征患儿发生肺出血、支气管肺发育不良，这在发育越不成熟的早产儿中发生率越高[18,19]。分析原因可能与使用肺泡表面活性物质过程中需要同步人工辅助通气导致肺内压急剧改变产生肺气压伤等因素相关。枸橼酸咖啡因是甲基黄嘌呤类药物，主要通过提高机体对血 CO_2 升高的敏感性，刺激延髓的呼吸中枢，增加每分钟通气量，同时具有扩张支气管作用，可有效预防新生儿呼吸暂停。有研究显示枸橼酸咖啡因用于治疗新生儿呼吸窘迫综合征安全有效，能减少呼吸支持强度与时间并缩短用氧时间[20,21]。

本研究结果显示联合用药的患儿的临床总有效率为 95.83%，明显高于单独使用肺泡表面活性物质的患儿，说明联合用药能明显提高患儿的临床疗效，与上述观点一致。联合用药治疗后患儿的血气指标明显改善，辅助通气时间明显缩短，且其 pH、PaO_2/FiO_2 水平均明显高于，PCO_2 水平、辅助通气时间、BPD 的发生率明显低于单独使用肺泡表面活性物质的患儿，提示联合用药安全性高，能明显改善患儿的血气指标，缩短

辅助通气时间,降低 BPD 发生率。分析原因是因为枸橼酸咖啡因中的咖啡因主要是作为中枢神经系统刺激剂而发挥作用,能提高机体对血 CO_2 升高的反应性,增强骨骼肌张力,减轻膈肌疲劳,有效预防了新生儿呼吸窘迫综合征患儿呼吸暂停的发生,利于及早拔管并脱离呼吸机,减少了气管插管、呼吸机及氧暴露机会及时间,由此减轻了机械通气、氧气、感染等因素对早产儿不成熟肺所产生的气压伤、生物伤。

BMP-7 能够调控细胞的增殖分化,在肺的炎症反应中起着积极的作用[22,23]。CC16 为细支气管、终末细支气管的特异性分泌蛋白,能够抑制细胞膜磷脂酶 A2 活性,减少细胞膜磷脂释放花生四烯酸,抑制脂类介质如前列腺素、白三烯等物质的产生,抑制中性粒细胞趋化性,从而表现出较好的抗炎作用[24,25]。国外有研究证实新生儿呼吸窘迫综合征患儿血清 CC16 水平升高,提示肺泡上皮及血管内皮完整性受损,且早于临床肺功能的改变,可作为预测肺泡上皮及血管内皮完整性早期改变的敏感指标[26,27]。SF 是一种急性期蛋白,由肝细胞和网状内皮细胞合成的,是人体普遍存在的储铁蛋白复合物,具有免疫抑制和组织修复的功能,在铁代谢方面起重要作用[28,29]。有研究显示 SF 水平高低能反映病情变化严重程度,构成了发展肺损伤的基础,其水平升高则代表发生肺损伤。有研究显示血清 BMP-7、CC16、SF 水平升高在新生儿呼吸窘迫综合征的发生发展中起着重要的作用 [30]。本研究结果显示联合治疗的患儿的血清 BMP-7、CC16、SF 水平明显低于单独使用肺泡表面活性物质治疗的患儿。分析是由于患儿一旦发生新生儿呼吸窘迫综合征,其血清 BMP-7、CC16、SF 水平则会明显发生改变,肺泡表面活性物质是以单层分子垂直排列于肺泡液一气界面,能够降低患儿肺表面张力作用;而枸橼酸咖啡因作为甲基黄嘌呤类药物,能够刺激呼吸中枢,达到兴奋呼吸,以解除呼吸抑制,刺激膈肌收缩,减轻膈肌疲劳,增加每分通气量,提高机体对血 CO_2 升高的反应及敏感性,改善其呼吸肌收缩力,增加心脏排出,从而改善氧合作用,最终改善患儿的血清 BMP-7、CC16、SF 水平。

综上所述,枸橼酸咖啡因联合肺泡表面活性物质治疗新生儿呼吸窘迫综合征的临床效果显著优于单用肺泡表面活性物质治疗,其可有效改善患儿血清 BMP-7、CC16、SF 水平、缩短机械通气时间,降低支气管肺发育不良发生率。

参 考 文 献(References)

[1] Hiles M, Culpan A M, Watts C, et al. Neonatal respiratory distress syndrome: Chest X-ray or lung ultrasound? A systematic review [J]. Ultrasound, 2017, 25(2): 80-91

[2] Abdelsadek A, Khair M D A, Naga O A. Lung ultrasound as early diagnostic tool in neonatal respiratory distress syndrome (RDS)[J]. Egyptian Journal of Chest Diseas es & Tuberculosis, 2016, 65 (1): 377-382

[3] Agarwal N, Bathwal S, Kriplani A, et al. Intra-amniotic instillation of surfactants for the prevention of neonatal respiratory distress syndrome following preterm delivery[J]. International Journal of Gynaecology & Obstetrics the Official Organ of the International Federation of Gynaecology & Obstetrics, 2016, 135(2): 196-199

[4] Thaller P, Blanchet C, Badr M, et al. Neonatal respiratory distress syndrome revealing a cervical bronchogenic cyst: a case report [J]. BMC Pediatrics, 2015, 15(1): 1-4

[5] Laban M, Mansour G M, Elsafty M S, et al. Prediction of neonatal respiratory distress syndrome in term pregnancies by assessment of fetal lung volume and pulmonary artery resistance index [J]. International Journal of Gynecology & Obstetrics, 2015, 128(3): 246-250

[6] Guan Y, Li S, Luo G, et al. The role of doppler waveforms in the fetal main pulmonary artery in the prediction of neonatal respiratory distress syndrome [J]. Journal of Clinical Ultrasound Jcu, 2015, 43(6): 375-383

[7] Naderi H M, Murray J C, Dagle J M. Single mutations in ABCA3 increase the risk for neonatal respiratory distress syndrome in late preterm infants (gestational age 34-36 weeks)[J]. American Journal of Medical Genetics Part A, 2015, 164(10): 2676-2678

[8] Smolarova S, Kocvarova L, Matasova K, et al. Impact of updated European Consensus Guidelines on the management of neonatal respiratory distress syndrome on clinical outcome of preterm infants[J].Oxygen Transport to Tissue XXXIII, 2015, 835(1): 61-66

[9]Dai Y, Wang Q W, He S, et al. Correlation of ECR1 A3650G polymorphism with neonatal respiratory distress syndrome [J]. Genetic Testing & Molecular Biomarkers, 2015, 19(1): 18-23

[10] El-Malah E D G M, Hany S, Mahmoud M K, et al. Lung ultrasonography in evaluation of neonatal respiratory distress syndrome [J]. Egyptian Journal of Radiology & Nuclear Medicine, 2015, 46 (2): 469-474

[11] Alkan S, Ozer E A, Ilhan O, et al. Surfactant treatment for neonatal respiratory disorders other than respiratory distress syndrome[J]. Journal of Maternal-Fetal Medicine, 2015, 28(2): 131-133

[12] Gao C J. Comparison on Treatment of Neonatal Respiratory Distress Syndrome by Nasal Bi-level Positive Airway Pressure Ventilation and Continuous Positive Pressure Ventilation [J]. Medical Innovation of China, 2015, 38(6): 677-695

[13] Li Y, Lin L, Wang Q. Correlation of expression levels of caspase-3 and Bcl-2 in alveolar lavage fluid in neonatal respiratory distress syndrome and prognosis [J]. Experimental & Therapeutic Medicine, 2018, 15(3): 2891-2895

[14] Büke B, Destegü l E, Akkaya H, et al. Prediction of neonatal respiratory distress syndrome via pulmonary artery Doppler examination[J]. J Matern Fetal Neonatal Med, 2017(6): 1-6

[15] Wang W X, Chen B, Zhang W, et al. Association between high-mobility group box 1 and neonatal respiratory distress syndrome[J]. Chinese Journal of Contemporary Pediatrics, 2017, 19(4): 398-401

[16] Saboute M, Kashaki M, Bordbar A, et al. The Incidence of Respiratory Distress Syndrome among Preterm Infants Admitted to Neonatal Intensive Care Unit: A Retrospective Study [J]. Open Journal of Pediatrics, 2015, 5(4): 285-289

[17] Mortier I, Blanc J, Tosello B, et al. Is gestational diabetes an independent risk factor of neonatal severe respiratory distress syndrome after 34 weeks of gestation? A prospective study[J]. Archives of Gynecology & Obstetrics, 2017, 296(6): 1071-1077

[18] Mei H, Zhang Y, Liu C, et al. Messenger RNA sequencing reveals similar mechanisms between neonatal and acute respiratory distress syndrome[J]. Molecular Medicine Reports, 2018, 17(1): 59-70

[19] Wong J J, Quek B H, Lee J H. Establishing the entity of neonatal acute respiratory distress syndrome [J]. Journal of Thoracic Disease, 2017, 9(11): 4244-4247

(下转第 2965 页)

[17] Gilev KV, Yastrebova ES, Strokotov DI, et al. Advanced consumable-free morphological analysis of intact red blood cells by a compact scanning flow cytometer[J]. Cytometry A, 2017, 91(9): 867-873

[18] Szablewski L. Glucose transporters in healthy heart and in cardiac disease[J]. Int J Cardiol, 2017, 230: 70-75

[19] Beg M, Abdullah N, Thowfeik FS, et al. Distinct Akt phosphorylation states are required for insulin regulated Glut4 and Glut1-mediated glucose uptake[J]. Elife, 2017, 6

[20] Tung CW, Hsu YC, Shih YH, et al. Glomerular mesangial cell and podocyte injuries in diabetic nephropathy [J]. Nephrology (Carlton), 2018, 23 Suppl 4: 32-37

[21] Barros LF, San Martin A, Ruminot I, et al. Near-critical GLUT1 and Neurodegeneration[J]. J Neurosci Res, 2017, 95(11): 2267-2274

[22] Carelli-Alinovi C, Misiti F. Erythrocytes as Potential Link between Diabetes and Alzheimer's Disease [J]. Front Aging Neurosci, 2017, 9: 276

[23] Ioja S, Singamsetty S, Corey C, et al. Nocturnal Hypoxia Improves Glucose Disposal, Decreases Mitochondrial Efficiency, and Increases Reactive Oxygen Species in the Muscle and Liver of C57BL/6J Mice Independent of Weight Change [J]. Oxid Med Cell Longev, 2018, 2018: 9649608

[24] Katsel P, Roussos P, Beeri MS, et al. Parahippocampal gyrus expression of endothelial and insulin receptor signaling pathway genes is modulated by Alzheimer's disease and normalized by treatment with anti-diabetic agents[J]. PLoS One, 2018, 13(11): e0206547

[25] Pomytkin I, Costa-Nunes JP, Kasatkin V, et al. Insulin receptor in the brain: Mechanisms of activation and the role in the CNS pathology and treatment[J]. CNS Neurosci Ther, 2018

[26] Serpente M, Fenoglio C, Cioffi SMG, et al. Profiling of Specific Gene Expression Pathways in Peripheral Cells from Prodromal Alzheimer's Disease Patients[J]. J Alzheimers Dis, 2018, 61(4): 1289-1294

[27] Islam RM, Pourmousa M, Sviridov D, et al. Structural properties of apolipoprotein A-I mimetic peptides that promote ABCA1-dependent cholesterol efflux[J]. Sci Rep, 2018, 8(1): 2956

[28] Nielsen DL, Palshof JA, Brunner N, et al. Implications of ABCG2 Expression on Irinotecan Treatment of Colorectal Cancer Patients: A Review[J]. Int J Mol Sci, 2017, 18(9)

[29] Heyes N, Kapoor P, Kerr ID. Polymorphisms of the multidrug pump ABCG2: a systematic review of their effect on protein expression, function and drug pharmacokinetics[J]. Drug Metab Dispos, 2018

[30] Zhang W, Sun S, Zhang W, et al. Polymorphisms of ABCG2 and its impact on clinical relevance [J]. Biochem Biophys Res Commun, 2018, 503(2): 408-413

[31] Pereira CD, Martins F, Wiltfang J, et al. ABC Transporters Are Key Players in Alzheimer's Disease [J]. J Alzheimers Dis, 2018, 61(2): 463-485

[32] Stevenson A, Lopez D, Khoo P, et al. Exploring Erythrocytes as Blood Biomarkers for Alzheimer's Disease [J]. J Alzheimers Dis, 2017, 60(3): 845-857

（上接第 2956 页）

[20] Rojas M A. Equipoise in Research and the Development of Neonatal Interventions for the Management of Respiratory Distress Syndrome: A Historical Perspective[J]. Am J Perinatol, 2015, 32(10): 910-915

[21] Kang D, Chugunova M, Nadim A, et al. Modeling coating flow and surfactant dynamics inside the alveolar compartment [J]. Journal of Engineering Mathematics, 2018, 113(1): 23-43

[22] Kononenko V, Erman A, Petan T, et al. Harmful at non-cytotoxic concentrations: SiO2-SPIONs affect surfactant metabolism and lamellar body biogenesis in A549 human alveolar epithelial cells [J]. Nanotoxicology, 2017, 11(3): 419-429

[23] Hasan D, Blankman P, Nieman G F. Purinergic signalling links mechanical breath profile and alveolar mechanics with the pro-inflammatory innate immune response causing ventilation-induced lung injury[J]. Purinergic Signalling, 2017, 13(3): 363-386

[24] Tq D A V, Lee E, Merriott D J, et al. ABCG1 regulates pulmonary surfactant metabolism in mice and men[J]. Journal of Lipid Research, 2017, 58(5): 941-954

[25] Gando S, Duré R, Violi D, et al. Bilateral lung disease, extensive and diffuse. Diagnosis of pulmonary alveolar proteinosis by bronchoscopic cryobiopsy [J]. Respir Med Case Rep, 2017, 22(C): 260-262

[26] Fiaturi N, Russo J W, Nielsen H C, et al. CCN5 in alveolar epithelial proliferation and differentiation during neonatal lung oxygen injury [J]. Journal of Cell Communication & Signaling, 2018, 12(1): 1-13

[27] Rab A, Arimura F E, Kairalla R A, et al. Characterization and outcomes of pulmonary alveolar proteinosis in Brazil: a case series [J]. J Bras Pneumol, 2018, 44(3): 231-236

[28] Stachowicz-Kuśnierz A, Cwiklik L, Korchowiec J, et al. The impact of lipid oxidation on the functioning of a lung surfactant model [J]. Physical Chemistry Chemical Physics, 2018, 20(38): 24968-24978

[29] Poon J, Liao Z, Suzuki T, et al. Design of biomimetic substrates for long-term maintenance of alveolar epithelial cells [J]. Biomater Sci, 2018, 6(2): 292-303

[30] Barbosa R F, Silva A C S E, Silva Y P. A randomized controlled trial of the laryngeal mask airway for surfactant administration in neonates [J]. J Pediatr, 2017, 93(4): 343-350