· 综述 ·

抗凝治疗——急性肺损伤/急性呼吸窘迫综合征治疗的新思路

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【关键词】 急性肺损伤； 急性呼吸窘迫综合征； 抗凝

急性肺损伤/急性呼吸窘迫综合征(ALI/ARDS)是指由心源性以外的各种肺内外致病因素导致的急性、进行性呼吸衰竭，以呼吸窘迫和低氧血症为特点，常需要机械通气治疗[1]。到目前为止，大样本多中心的前瞻性研究提示 ALI/ARDS 的发病率和院内病死率仍然较高。ALI/ARDS 的发病机制目前比较公认的观点是炎症反应学说，机体应激后产生广泛而过度的炎症反应，炎性细胞及其释放的炎症介质和细胞因子最终引起肺泡毛细血管损伤，通透性增加和微血栓形成，肺泡上皮损伤，表面活性物质减少或消失，导致肺水肿，肺泡内透明膜形成和肺不张，从而引起肺的氧合功能障碍，导致顽固性低氧血症[2]。然而，无论是传统抗炎药物糖皮质激素，还是针对某种细胞因子的单克隆抗体，针对 ARDS 的抗炎治疗并未取得良好的效果[3-5]。几十年来对治疗 ARDS 真正有意义的仍然是支持治疗，肺保护通气策略是目前惟一被证明能降低 ARDS 病死率的方法[6]。

1 脓毒症与凝血功能紊乱

抗炎治疗的失败促使人们重新审视 ARDS 发病机制，并将目光转向炎症与凝血的关系，2001 年人重组活化蛋白 C(APC)治疗脓毒症的研究(PROVESS 研究)证实，APC 可降低严重脓毒症患者 28 d 病死率，提示炎症与凝血间有直接联系[7]。早已发现严重脓毒症有凝血系统紊乱，但直到近年人们才更多关注其对脓毒症发生发展及预后的影响。

1.1 凝血系统的激活：可通过以下方式激活外源性凝血系统：①炎症反应早期即有大量炎症介质如肿瘤坏死因子-α(TNF-α)、白细胞介素(IL-1、IL-6)释放，上调组织因子(TF)表达与释放，启动外源性凝血系统；②细胞损伤使位于细胞内膜的氨基磷脂暴露而促进凝血；③炎症反应损伤血管内膜，使胶原组织暴露而激活内源性凝血系统[8]。

1.2 抗凝系统抑制：天然抗凝系统主要包括 APC、抗凝血酶(AT)和组织因子途径活化抑制物(TFPI)3 条途径，其各自在不同水平影响 TF-FⅦa 复合物的生成。APC 通过灭活因子 Va(FVa)和 FⅧa 发挥作用；AT 能抑制凝血级联反应中多种酶的活性；TFPI 可直接抑制 FXa 和 TF-FⅦa 复合物。脓毒症时凝血活性的增加并未得到上述途径的有效抑制。由于消耗增加、合成减少和降解加快，循环血中 APC 和 AT 明显不足。在 TNF 和 IL-1 等炎症介质的影响下，内皮细胞表面血栓调节蛋白(TM)表达下调，后者在蛋白 C(PC)激活过程中发挥重要作用，导致 PC 功能障碍。TFPI 在抗凝系统中同样发挥重要作用，脓毒症时 TF 表达增加，而 TFPI 活性相对下降，导致抗凝异常[9]。

1.3 纤溶抑制：脓毒症时纤溶酶原激活物释放，纤溶活性增加，这一反应可被持续增加的纤溶酶原激活物抑制剂-1(PAI-1)抑制。PAI-1 是组织途径和尿激酶途径纤溶活化的主要抑制因子，TNF 和 IL-1 均能刺激 PAI-1 的释放[10-11]。

1.4 炎症和凝血的交互放大作用：被激活的凝血系统反过来进一步加剧炎症反应，多种活化的凝血蛋白与炎性细胞相应的受体结合，从而改变这些炎性细胞的炎症介质表达[12-13]。

APC 治疗脓毒症的成功提示，全身炎症反应必然伴有凝血功能紊乱，改善凝血功能将有助于炎症反应的控制。

2 ALI/ARDS 与凝血功能紊乱

ALI/ARDS 作为全身性炎症反应的一部分同样存在凝血功能紊乱，既然系统性炎症导致系统性凝血功能紊乱，在肺部炎症时应该存在同样的、但可能局限于肺部的凝血功能障碍和纤维蛋白循环障碍[14-16]。事实上，在肺炎患者中已发现有肺泡的纤维蛋白产生增加和降解减少，改变的程度与炎症的严重程度相关。需要机械通气的重症肺炎凝血功能紊乱与 ALI/ARDS 几乎一致，而不需机械通气的肺炎患者病变则不明显[17-18]。

2.1 促凝系统激活：ALI/ARDS 和肺炎时凝血系统的活化与脓毒症一样也与 TF-FⅦa 途径有关，肺内 TF 水平在炎症状态下明显升高。不同的炎症细胞因子和促纤维生长因子都能刺激多种细胞表达 TF，从而在血管外激活外源性凝血系统。动物实验中发现，脂多糖(LPS)或博莱霉素刺激肺泡巨噬细胞和Ⅰ型肺泡上皮细胞是 TF 的主要来源[19]。在创伤和脓毒症导致的 ARDS 患者中，血浆 TF 水平与肺损伤评分、血小板计数和弥散性血管内凝血(DIC)评分明显相关。除了促凝作用外，TF 介导凝血途径中的蛋白酶能通过蛋白酶活化受体(PARs)发挥其致炎和致纤维化功能[20]。

除了 TF-FⅦa 复合物途径外，最近有研究发现 ARDS 患者肺泡内/外源性凝血途径的激活可能部分与 FⅦ活化蛋白酶(FSAP)有关[21]。血浆中 FSAP 以单链的酶原形式存在，在多聚阴离子如肝素、硫酸葡聚糖或细胞外 RNA 的作用下，通过自身激活转化为双链具有活性的酶[22-23]。FSAP 在不同生理和病理状态下的准确作用尚未完全阐明，然而，在凝血系统中它可能有双向作用。在体外，FSAP 是潜在的 FⅦ激活剂，但也能激活尿激酶原并促进纤溶酶形成[24]。最近的研究发现，ARDS 患者的支气管肺泡灌洗液(BALF)中 FSAP 水平明显增高，致使 BALF 中 FⅦ激活和促凝活性增加。因此，FSAP 产生的促凝活性增加在 ARDS 患者肺内可能代表一种新的导致肺泡凝血功能紊乱和血管外纤维蛋白沉积的病理机制。而且，FSAP 表达与细胞的迁移和增殖有关，这可能是通过与多种生长因子相互作用实现的[25-26]。FSAP水平增高可能通过其细胞活性来

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调节 ARDS 患者肺内炎症反应过程。在 ARDS 患者 BALF 中同样能检测到细胞外 RNA 水平增高，后者是 FSAP 重要的辅助因子，可由肺损伤过程中破坏的细胞释放，并导致 FSAP 自身激活，使肺泡内纤维蛋白形成和炎症过程中的放大[27]。

2.2 促凝活性的天然抑制剂不足：在 ALI/ARDS 患者以及相应的动物模型中均发现，肺泡内凝血系统激活不能受到天然抑制物如 AT、TFPI 和 APC 等有效抑制[28-30]。这些抑制物在凝血级联反应不同阶段影响 TF-FⅦa 所致的凝血激活：AT 能中和凝血酶和几种其他蛋白酶；TFPI 主要抑制 TF-FⅦa-FⅩa 复合物；APC 灭活 FⅤa 和 FⅧa，限制凝血酶形成和纤维蛋白产生。APC 由相应酶原在 TM-凝血酶复合物作用下产生，氧化过程增加和 TM 在细胞表面脱落与肺部炎性病变中 APC 减少有关。在 ALI/ARDS 患者肺水肿液中，可溶性 TM 水平增高，并与不良预后有关[14]。

除了凝血级联反应抑制受到削弱外，肺内 APC 缺乏还与肺部炎性病变时肺内的纤维蛋白沉积有关。APC 能通过与 PAI-1 结合，并抑制其活性间接发挥促纤溶作用[31]。除了调节凝血和纤溶外，APC 的抗炎作用也不容忽视，APC 能抑制多种炎症介质的产生，抑制白细胞的活化和移位以及内皮细胞表面黏附分子的表达[32]。APC 能抑制血小板源性生长因子的表达，后者是纤维母细胞的潜在突变因子。因此可以想象，APC 缺乏在 ALI/ARDS 发病机制中不仅使抗凝和促纤溶功能削弱，还可导致直接的抗炎作用和抗纤维化作用丧失[33]。

2.3 抗纤维蛋白溶解活性增加导致肺泡内纤维蛋白沉积：在动物实验和临床研究中均发现，急、慢性肺炎性病变存在明显的肺泡内纤溶活性下降[34-35]。其原因可能在于 PAI-1/尿激酶型纤溶酶原激活物(u-PA)/组织型纤溶酶原激活物(t-PA)失衡和 α2-纤溶酶原抑制物表达增加[36]。肺泡巨噬细胞、Ⅱ型肺泡上皮细胞和纤维母细胞是局部 PAI-1 的主要来源。目前已有学者通过基因改变小鼠对 PAI-1/u-PA 系统改变在急、慢性肺病发病机制中的重要意义进行深入研究，发现注射博莱霉素后，PAI-1 缺乏小鼠表现出明显增强的纤溶活性和纤维增殖反应抑制，而 PAI-1 过表达小鼠的纤维增殖反应明显增强[37]。同样，在肺泡内诱导 u-PA 表达可减轻博莱霉素引起的小鼠肺损伤[38]；表达 u-PA 表面蛋白 B 的转基因小鼠能避免发生 LPS 吸入导致的 ALI，并表现出明显抑制的纤维化反应，且存活率提高[39]。

最近有研究发现凝血酶激活纤溶抑制物(TAFI)同样与肺炎性病变情况下的纤溶活性抑制有关，这可能与其能使纤溶酶和纤溶酶原结合部位的缺失有关[40]。目前还没有关于 ARDS 患者肺泡内 TAFI 水平的报道。

3 ALI/ARDS 的抗凝干预

大量的研究表明，ALI/ARDS 时存在明确的凝血/纤溶功能紊乱，基于上述考虑，对 ALI/ARDS 患者进行抗凝或促纤溶的治疗应该是合理的。事实上，目前已有许多研究证明在脓毒症动物模型和脓毒症患者中应用抗凝或改善凝血方面的治疗是有效的[19,41]，而脓毒症作为外源性 ARDS 的主要原因之一，其凝血功能的改变与 ALI/ARDS 时发生的凝血功能紊乱并无不同。总的来讲，在动物模型中应用抗凝和促纤溶治疗 ALI/ARDS 的结果还是令人满意的。与此形成对比的是，到目前为止在临床研究中应用抗凝剂和促纤溶剂治疗 ARDS 似乎并没有得到满意结果。

3.1 肝素：肝素在临床上被广泛用于 DIC 和血栓性疾病的防治[42-43]。除了增强 AT-Ⅲ的作用外，肝素还能够通过许多非依赖 AT 途径增强其抗凝和抗炎作用，如诱导 TFPI 释放、拮抗 TF、调理黏附分子、抑制血细胞附壁和聚集、促进纤溶等[44]。事实上，脓毒症、ALI/ARDS 时的凝血功能紊乱与 DIC 是一致的。因此有学者尝试用肝素来治疗脓毒症和肺损伤。有的研究证实肝素可以改善脓毒症动物的凝血系统激活，从而提高其存活率[45-46]；另一些研究并未证实肝素对脓毒症有益[47-48]。尽管在动物实验中所得到的结论并不一致，但对近年来几个大样本Ⅲ期临床研究的数据重新分析发现，与安慰剂组比较，应用肝素确实对改善患者生存率有益[49-50]。2008 年的一项回顾性研究观察了 2 356 例感染性休克患者，其中 722 例应用肝素，结果发现与对照组比较，肝素组 28 d 病死率下降了 5%，而在急性生理学与慢性健康状况评分系统Ⅱ(APACHEⅡ)评分大于 29 分的高危患者中，应用肝素能使其病死率下降 13%[51]。2009 年的一项单中心、前瞻性研究也证实，应用小剂量肝素能明显降低脓毒症患者 28 d 病死率[52]。在 ALI/ARDS 动物模型中也得出了类似的结论，静脉注射肝素能减轻烟雾吸入和气压伤所致的羊 ALI 模型中肺内纤维蛋白沉积并改善氧合[53]；而在烟雾吸入和气道内滴入铜绿假单胞菌造成的羊 ALI 模型中，通过雾化方式在局部应用肝素能减轻肺内的细胞浸润[54]。在 LPS 静脉注射导致的大鼠 ALI 模型中，应用低分子肝素能减少中性粒细胞及血小板黏附，从而减轻肺损伤程度[55]。2008 年的一项Ⅰ期临床研究对 16 例行机械通气的 ALI 患者进行不同剂量的肝素吸入治疗，结果显示，各组间氧合指数(PaO_2/FiO_2)、肺顺应性并无差异，也均无严重并发症出现，提示对 ALI/ARDS 患者肝素吸入治疗是可行的[56]。遗憾的是，目前为止尚无肝素治疗 ALI/ARDS 的大样本临床研究，原因可能是多方面的，如具体应用剂量、给药途径的不确定以及对出血等并发症的担心等等。但已有的动物实验和一些单中心研究结果均提示肝素对 ALI/ARDS 可能有益，也意味着进行大样本多中心、临床研究的可行性。

3.2 APC：Murakami 等[57-58]研究显示，APC 能减轻 LPS 致大鼠 ALI/ARDS 模型的肺内纤维蛋白沉积，减轻肺内白细胞集聚，降低细胞因子水平。Choi 等[59]发现，APC 能改善 LPS 模型和铜绿假单胞菌模型的凝血功能紊乱，但并不能减轻炎症反应。可能原因为：Murakami 等是在实验前 4 h 检测炎症介质；而 Choi 等则是在实验 6～16 h 检测。在采用烟雾吸入联合铜绿假单胞菌滴入制备羊 ALI/ARDS 模型中注射 APC，能改善氧合，但并不能减轻肺水肿[60]。还有其他的实验研究表明，APC 不仅能改善凝血功能紊乱，而且具有抗炎效应[61-62]。

Yasui 等[63]在博莱霉素造成的鼠肺损伤模型中发现，局部应用 APC 能降低 BALF 中凝血酶、TNF-α 和 IL-1 浓度，且能抑制肺纤维化的发展。在经鼻腔滴入 LPS 致 ALI/ARDS 动物模型中，吸入 APC 可明显减轻肺内炎症反应[64-65]。

PROVESS 研究已经证实注射 APC 能降低严重脓毒症患者病死率，而该研究中很多患者同时伴有 ALI/ARDS，并且许多患者是以重症肺炎为脓毒症的病

因。应用 APC 能抑制肺内凝血系统激活和 PAI-1 表达。虽然目前尚未见到公开发表关于 APC 单独治疗 ALI/ARDS 的报道，但由于在凝血系统和炎症反应存在广泛的交叉对话，应用 APC 针对肺内凝血功能紊乱治疗可能同样影响肺内炎症反应，提示 APC 在 ALI/ARDS 的治疗中可能会发挥重要作用。

3.3 AT：在多种 ALI 模型中均已证明 AT 能减轻肺部凝血功能紊乱和炎症反应，改善氧合[66-67]。AT 的抗炎效应可能是通过促进内皮细胞释放前列环素来介导的，后者被认为是一种白细胞激活抑制剂。在其他几种 ALI/ARDS 模型中同样也发现 AT 有抗炎和抗凝作用[68]，但 Kipnis 等[69]在气道内滴入铜绿假单胞菌致鼠 ALI/ARDS 模型中发现，静脉注射重组人抗凝血酶(rh-AT)能增加组织和肺泡毛细血管屏障损伤。

3.4 AT 联合肝素：由于肝素是通过增加 AT 活性来发挥对 F X 和凝血酶抑制作用的，Enkhbaatar 等[70]在皮肤烧伤联合棉花烟雾吸入造成的羊 ALI/ARDS 模型中，应用静脉注射 AT 联合肝素吸入能减轻肺内各种病理生理改变。

3.5 TF-F Ⅶa 途径抑制剂：有多种 TF-F Ⅶa 途径抑制剂(如 TFPI、TF 单克隆抗体等)能显示抗凝和抗炎作用，在狒狒和鼠的 ALI/ARDS 模型中应用此类化合物能减轻肺损伤和抑制循环中炎症细胞因子的表达[71-72]。Choi 等[73]进行的一项研究未能在 LPS 致大鼠 ALI/ARDS 模型中证实 TFPI 的抗炎效应，可能是源于内毒素的样品、给药方式、调查时间点以及应用动物模型不同。

3.6 PA：目前已在两种 ALI/ARDS 模型中对 t-PA 和 u-PA 进行了研究，尽管二者具有同样的蛋白水解作用，结果却显示二者在肺内炎症反应方面有不同作用[74-75]。t-PA 具有抗炎和抗凋亡作用，而 u-PA 则具有促炎作用。不产生 u-PA 的转基因小鼠不能引起 ALI/ARDS。在创伤导致的猪 ALI/ARDS 模型中，静脉注射 t-PA 或 u-PA 能防止低氧血症，并提高存活率[76]。在气道内滴入 IL-1 致大鼠 ALI/ARDS 模型中，腹腔注射 t-PA 能减轻肺的炎性渗出和白细胞活化[77]。静脉应用 t-PA 能减轻铜绿假单胞菌和 LPS 致 ALI/ARDS 大鼠的凝血功能紊乱，并且不影响宿主的防御反应。由于大剂量的 PA 能增加出血风险，有学者研究发现，局部应用 t-PA 和 u-PA 能防止肺内促凝状态的形成，改善氧合，减轻肺水肿，并且无全身副作用，但在这些研究中并未评价肺内的炎症反应情况[78-79]。

3.7 TM：TM 是在内皮细胞表面表达的一种蛋白质，其作为辅助因子与凝血酶形成复合物后可激活 PC。在 LPS 致大鼠 ALI/ARDS 模型中，注射 TM 能减轻肺内凝血功能紊乱，表现为纤维蛋白沉积和微血栓形成减少，血管通透性增加，肺水肿和白细胞集聚减轻[80-81]。然而在不能产生 APC 的 TM 突变体小鼠中，应用肺炎链球菌、肺炎克雷伯杆菌和 LPS 后仍有上述宿主防御反应。

4 总 结

ALI/ARDS 及其随后的组织修复过程中存在凝血/纤溶系统紊乱，纤维蛋白沉积是 ALI 的重要特征，抗凝治疗可能是 ALI/ARDS 治疗的一个新靶点或是一个新的保护性措施。在动物实验中已证明，应用抗凝剂如肝素、TFPI、AT、TM、APC 等能减轻肺损伤，改善氧合。但临床研究尚无准确结论，今后的研究方向可考虑通过雾化方式局部给药，以减少全身并发症；另外还需要大样本的临床研究来验证这个假设。

参考文献

[1] Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med, 2000, 342: 1334-1349.

[2] Guimbaud R, Bertrand V, Chauvelot-Moachon L, et al. Network of inflammatory cytokines and correlation with disease activity in ulcerative colitis. Am J Gastroenterol, 1998, 93: 2397-2404.

[3] Fernandes AB, Zin WA, Rocco PR. Corticosteroids in acute respiratory distress syndrome. Braz J Med Biol Res, 2005, 38: 147-159.

[4] 宋志芳，谢伟，单慧敏，等. 糖皮质激素治疗大肠杆菌致急性呼吸窘迫综合征的实验研究. 中国危重病急救医学, 2006, 18: 716-720.

[5] Raghavendran K, Pryhuber GS, Chess PR, et al. Pharmacotherapy of acute lung injury and acute respiratory distress syndrome. Curr Med Chem, 2008, 15: 1911-1924.

[6] The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med, 2000, 342: 1301-1308.

[7] Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med, 2001, 344: 699-709.

[8] Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. Circulation, 2004, 109: 2698-2704.

[9] Hardaway RM, Williams CH, Vasquez Y. Disseminated intravascular coagulation in sepsis. Semin Thromb Hemost, 2001, 27: 577-583.

[10] Opal SM, Esmon CT. Bench-to-bedside review: functional relationships between coagulation and the innate immune response and their respective roles in the pathogenesis of sepsis. Crit Care, 2003, 7: 23-38.

[11] Gando S, Tedo I, Kubota M. Posttrauma coagulation and fibrinolysis. Crit Care Med, 1992, 20: 594-600.

[12] Mavrommatis AC, Theodoridis T, Orfanidou A, et al. Coagulation system and platelets are fully activated in uncomplicated sepsis. Crit Care Med, 2000, 28: 451-457.

[13] McGee MP, Foster S, Wang X. Simultaneous expression of tissue factor and tissue factor pathway inhibitor by human monocytes, a potential mechanism for localized control of blood coagulation. J Exp Med, 1994, 179: 1847-1854.

[14] Ware LB, Fang X, Matthay MA. Protein C and thrombomodulin in human acute lung injury. Am J Physiol Lung Cell Mol Physiol, 2003, 285: L514-521.

[15] Günther A, Mosavi P, Heinemann S, et al. Alveolar fibrin formation caused by enhanced procoagulant and depressed fibrinolytic capacities in severe pneumonia, comparison with the acute respiratory distress syndrome. Am J Respir Crit Care Med, 2000, 161: 454-462.

[16] Schultz MJ, Millo J, Levi M, et al. Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator associated pneumonia. Thorax, 2004, 59: 130-135.

[17] Abraham E. Coagulation abnormalities in acute lung injury and sepsis. Am J Respir Cell Mol Biol, 2000, 22: 401-404.

[18] Schultz MJ, Haitsma JJ, Zhang H, et al. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia—— a review. Crit Care Med, 2006, 34: 871-877.

[19] Miller DL, Welty-Wolf K, Carraway MS, et al. Extrinsic coagulation blockade attenuates lung injury and proinflammatory cytokine release after intratracheal lipopolysaccharide. Am J Respir Cell Mol Biol, 2002, 26: 650-658.

[20] Wygrecka M, Jablonska E, Guenther A, et al. Current view on alveolar coagulation and fibrinolysis in acute inflammatory and chronic interstitial lung diseases. Thromb Haemost, 2008, 99: 494-501.

[21] Wygrecka M, Markart P, Fink L, et al. Raised protein levels and altered cellular expression of factor Ⅶ activating protease (FSAP) in the lungs of patients with acute respiratory distress syndrome (ARDS). Thorax, 2007, 62: 880-888.

[22] Choi-Miura NH, Tobe T, Sumiya J, et al. Purification and characterization of a novel hyaluronan-binding protein (PHBP) from human plasma: it has three EGF, a kringle and a serine protease domain, similar to hepatocyte growth factor activator. J Biochem, 1996, 119: 1157-1165.

[23] Röemisch J, Feussner A, Vermöhlen S, et al. A protease isolated from human plasma activating factor Ⅶ independent of tissue factor. Blood Coagul Fibrinolysis, 1999, 10: 471-479.

[24] Römisch J, Vermöhlen S, Feussner A, et al. The F Ⅶ activating protease cleaves single-chain plasminogen activators. Haemostasis, 1999, 29: 292-299.

[25] Kannemeier C, Al-Fakhri N, Preissner KT, et al. Factor Ⅶ-activating protease (FSAP) inhibits growth factor-mediated cell proliferation and migration of vascular smooth muscle cells. FASEB J, 2004, 18: 728-730.

[26] Roderfeld M, Weiskirchen R, Atanasova S, et al. Altered factor Ⅶ activating protease expression in murine hepatic fibrosis and its influence on hepatic stellate cells. Liver Int, 2009, 29: 686-691.

[27] Wygrecka M, Morty RE, Markart P, et al. Plasminogen activator inhibitor-1 is an inhibitor of factor Ⅶ-activating protease in patients with acute respiratory distress syndrome. J Biol Chem, 2007, 282: 21671-21682.

[28] Wygrecka M, Markart P, Ruppert C, et al. Compartment-and cell-specific expression of coagulation and fibrinolysis factors in the murine lung undergoing inhalational versus intravenous endotoxin application. Thromb Haemost, 2004, 92: 529-540.

[29] Gando S, Kameue T, Matsuda N, et al. Imbalances between the levels of tissue factor and tissue factor pathway inhibitor in ARDS patients. Thromb Res, 2003, 109: 119-124.

[30] Ambrus JL, Ambrus CM. Changes in the fibrinolysin system in infantile and adult respiratory distress syndrome (ARDS), caused by trauma and/or septic shock in patients and in experimental animals. J Med, 1990, 21: 67-84.

[31] D'Angelo A, Lockhart MS, D'Angelo SV, et al. Protein S is a cofactor for activated protein C neutralization of an inhibitor of plasminogen activation released from platelets. Blood, 1987, 69: 231-237.

[32] Esmon CT. Inflammation and activated protein C anticoagulant pathway. Semin Thromb Hemost, 2006, 32 Suppl 1: 49-60.

[33] Shimizu S, Gabazza EC, Taguchi O, et al. Activated protein C inhibits the expression of platelet-derived growth factor in the lung. Am J Respir Crit Care Med, 2003, 167: 1416-1426.

[34] Idell S, James KK, Levin EG, et al. Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome. J Clin Invest, 1989, 84: 695-705.

[35] Bertozzi P, Astedt B, Zenzius L, et al. Depressed bronchoalveolar urokinase activity in patients with adult respiratory distress syndrome. N Engl J Med, 1990, 322: 890-897.

[36] Günther A, Mosavi P, Ruppert C, et al. Enhanced tissue factor pathway activity and fibrin turnover in the alveolar compartment of patients with interstitial lung disease. Thromb Haemost, 2000, 83: 853-860.

[37] Wygrecka M, Markart P, Ruppert C, et al. Cellular origin of pro-coagulant and (anti)-fibrinolytic factors in bleomycin-injured lungs. Eur Respir J, 2007, 29: 1105-1114.

[38] Sisson TH, Hanson KE, Subbotina N, et al. Inducible lung-specific urokinase expression reduces fibrosis mortality after lung injury in mice. Am J Physiol Lung Cell Mol Physiol, 2002, 283: L1023-1032.

[39] Markart P, Ruppert C, Petri K, et al. Transgenic Mice expressing a surfactant protein B urokinase fusion protein in the distal respiratory epitehelium show improved survival after bleomycin-induced lung injury. Am J Respir Crit Care Med, 2005: A346.

[40] Fujimoto H, Gabazza EC, Hataji O, et al. Thrombin-activatable fibrinolysis inhibitor and protein C inhibitor in interstitial lung disease. Am J Respir Crit Care Med, 2003, 167: 1687-1694.

[41] 吴允孚，陈刚，席与斌. 血必净注射液对内毒素性肺损伤治疗作用的实验研究. 中国中西医结合急救杂志，2008，15：181-182.

[42] Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med, 1999, 341: 586-592.

[43] Pernerstorfer T, Hollenstein U, Hansen J, et al. Heparin blunts endotoxin-induced coagulation activation. Circulation, 1999, 100: 2485-2490.

[44] Fareed J, Hoppensteadt DA, Bick RL. An update on heparins at the beginning of the new millennium. Semin Thromb Hemost, 2000, 26 Suppl 1: 5-21.

[45] Griffin MP, Gore DC, Zwischenberger JB, et al. Does heparin improve survival in experimental porcine gram-negative septic shock? Circ Shock, 1990, 31: 343-349.

[46] Yang S, Hauptman JG. The efficacy of heparin and antithrombin Ⅲ in fluid-resuscitated cecal ligation and puncture. Shock, 1994, 2: 433-437.

[47] Gaskins RA Jr, Dalldorf FG. Experimental meningococcal septicemia, effect of heparin therapy. Arch Pathol Lab Med, 1976, 100: 318-324.

[48] Corrigan JJ Jr, Kiernat JF. Effect of heparin in experimental gram-negative septicemia. J Infect Dis, 1975, 131: 138-143.

[49] Davidson BL, Geerts WH, Lensing AW. Low-dose heparin for severe sepsis. N Engl J Med, 2002, 347: 1036-1037.

[50] Polderman KH, Girbes AR. Drug

intervention trials in sepsis: divergent results. Lancet, 2004, 363: 1721-1723.

[51] Zarychanski R, Doucette S, Fergusson D, et al. Early intravenous unfractionated heparin and mortality in septic shock. Crit Care Med, 2008, 36: 2973-2979.

[52] 赵聪，章志丹，张晓娟，等. 小剂量肝素治疗脓毒症的临床分析. 中华内科杂志，2009，48：566-569.

[53] Murakami K, McGuire R, Cox RA, et al. Heparin nebulization attenuates acute lung injury in sepsis following smoke inhalation in sheep. Shock, 2002, 18: 236-241.

[54] Tasaki O, Mozingo DW, Dubick MA, et al. Effects of heparin and lisofylline on pulmonary function after smoke inhalation injury in an ovine model. Crit Care Med, 2002, 30: 637-643.

[55] 栾正刚，娜拉·普鲁，章志丹，等. 低分子肝素和阿司匹林对急性肺损伤的治疗作用. 中国危重病急救医学，2006，18：456-458.

[56] Dixon B, Santamaria JD, Campbell DJ. A phase 1 trial of nebulised heparin in acute lung injury. Crit Care, 2008, 12: R64.

[57] Murakami K, Okajima K, Uchiba M, et al. Activated protein C attenuates endotoxin-induced pulmonary vascular injury by inhibiting activated leukocytes in rats. Blood, 1996, 87: 642-647.

[58] Murakami K, Okajima K, Uchiba M, et al. Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production. Am J Physiol, 1997, 272: L197-202.

[59] Choi G, Hofstra JJ, Roelofs JJ, et al. Recombinant human activated protein C inhibits local and systemic activation of coagulation without influencing inflammation during *Pseudomonas aeruginosa* pneumonia in rats. Crit Care Med, 2007, 35: 1362-1368.

[60] Maybauer MO, Maybauer DM, Fraser JF, et al. Recombinant human activated protein C improves pulmonary function in ovine acute lung injury resulting from smoke inhalation and sepsis. Crit Care Med, 2006, 34: 2432-2438.

[61] Jian MY, Koizumi T, Tsushima K, et al. Activated protein C attenuates acid-aspiration lung injury in rats. Pulm Pharmacol Ther, 2005, 18: 291-296.

[62] Wong SS, Sun NN, Hyde JD, et al. Drotrecogin alfa (activated) prevents smoke-induced increases in pulmonary microvascular permeability and proinflammatory cytokine IL-1beta in rats. Lung, 2004, 182: 319-330.

[63] Yasui H, Gabazza EC, Tamaki S, et al. Intratracheal administration of activated protein C inhibits bleomycin-induced lung fibrosis in the mouse. Am J Respir Crit Care Med, 2001, 163: 1660-1668.

[64] Kotanidou A, Loutrari H, Papadomichelakis E, et al. Inhaled activated protein C attenuates lung injury induced by aerosolized endotoxin in mice. Vascul Pharmacol, 2006, 45: 134-140.

[65] Slofstra SH, Groot AP, Maris NA, et al. Inhalation of activated protein C inhibits endotoxin-induced pulmonary inflammation in mice independent of neutrophil recruitment. Br J Pharmacol, 2006, 149: 740-746.

[66] Giebler R, Schmidt U, Koch S, et al. Combined antithrombin Ⅲ and C1-esterase inhibitor treatment decreases intravascular fibrin deposition and attenuates cardiorespiratory impairment in rabbits exposed to *Escherichia coli* endotoxin. Crit Care Med, 1999, 27: 597-604.

[67] Uchiba M, Okajima K, Murakami K. Effects of various doses of antithrombin Ⅲ on endotoxin-induced endothelial cell injury and coagulation abnormalities in rats. Thromb Res, 1998, 89: 233-241.

[68] Murakami K, McGuire R, Cox RA, et al. Recombinant antithrombin attenuates pulmonary inflammation following smoke inhalation and pneumonia in sheep. Crit Care Med, 2003, 31: 577-583.

[69] Kipnis E, Guery BP, Tournoys A, et al. Massive alveolar thrombin activation in *Pseudomonas aeruginosa*-induced acute lung injury. Shock, 2004, 21: 444-451.

[70] Enkhbaatar P, Cox RA, Traber LD, et al. Aerosolized anticoagulants ameliorate acute lung injury in sheep after exposure to burn and smoke inhalation. Crit Care Med, 2007, 35: 2805-2810.

[71] Carraway MS, Welty-Wolf KE, Miller DL, et al. Blockade of tissue factor: treatment for organ injury in established sepsis. Am J Respir Crit Care Med, 2003, 167: 1200-1209.

[72] Enkhbaatar P, Okajima K, Murakami K, et al. Recombinant tissue factor pathway inhibitor reduces lipopolysaccharide-induced pulmonary vascular injury by inhibiting leukocyte activation. Am J Respir Crit Care Med, 2000, 162: 1752-1759.

[73] Choi G, Vlaar AP, Schouten M, et al. Natural anticoagulants limit lipopolysaccharide-induced pulmonary coagulation but not inflammation. Eur Respir J, 2007, 30: 423-428.

[74] Abraham E, Gyetko MR, Kuhn K, et al. Urokinase-type plasminogen activator potentiates lipopolysaccharide-induced neutrophil activation. J Immunol, 2003, 170: 5644-5651.

[75] Stringer KA, Lindenfeld J, Repine AJ, et al. Tissue plasminogen activator (tPA) inhibits human neutrophil superoxide anion production in vitro. Inflammation, 1997, 21: 27-34.

[76] Hardaway RM, Williams CH, Marvasti M, et al. Prevention of adult respiratory distress syndrome with plasminogen activator in pigs. Crit Care Med, 1990, 18: 1413-1418.

[77] Stringer KA, Hybertson BM, Cho OJ, et al. Tissue plasminogen activator (tPA) inhibits interleukin-1 induced acute lung leak. Free Radic Biol Med, 1998, 25: 184-188.

[78] Enkhbaatar P, Murakami K, Cox R, et al. Aerosolized tissue plasminogen inhibitor improves pulmonary function in sheep with burn and smoke inhalation. Shock, 2004, 22: 70-75.

[79] Münster AM, Rasmussen L, Sidelmann J, et al. Effects of inhaled plasminogen activator on the balance between coagulation and fibrinolysis in traumatized pigs. Blood Coagul Fibrinolysis, 2002, 13: 591-601.

[80] Uchiba M, Okajima K, Murakami K, et al. Recombinant human soluble thrombomodulin reduces endotoxin-induced pulmonary vascular injury via protein C activation in rats. Thromb Haemost, 1995, 74: 1265-1270.

[81] Uchiba M, Okajima K, Murakami K, et al. Recombinant thrombomodulin prevents endotoxin-induced lung injury in rats by inhibiting leukocyte activation. Am J Physiol, 1996, 271: L470-475.

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抗凝治疗——急性肺损伤/急性呼吸窘迫综合征治疗的新思路

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参考文献(162条)

1. Uchiba M;Okajima K;Murakami K Recombinant human soluble thrombomodulin reduces endotoxininduced pulmonary vascular injury via protein C activation in rats 1995

2. Ware LB.Matthay MA The acute respiratory distress syndrome 2000

3. Hardaway RM;Williams CH;Vasquez Y Disseminated intravascular coagulation in sepsis[外文期刊] 2001(6)

4. Guimbaud R.Bertrand V.Chauvelot-Moachon L Network of inflammatory cytokines and correlation with disease activity in ulcerative colitis 1998

5. Münster AM;Rasmussen L;Sidelmann J Effects of inhaled plasminogen activator on the balance between coagulation and fibrinolysis in traumatized pigs 2002

6. Fernandes AB.Zin WA.Rocco PR Corticosteroids in acute respiratory distress syndrome 2005

7. Enkhbaatar P;Murakami K;Cox R Aerosolized tissue plasminogen inhibitor improves pulmonary function in sheep with burn and smoke inhalation[外文期刊] 2004(1)

8. 宋志芳.谢伟.单慧敏.郭晓红.孙波 糖皮质激素治疗大肠杆菌致急性呼吸窘迫综合征的实验研究 2006(12)

9. Stringer KA;Hybertson BM;Cho OJ Tissue plasminogen activator (tPA) inhibits interleukin-1 induced acute lung leak 1998

10. Raghavendran K.Pryhuber GS.Chess PR Pharmacotherapy of acute lung injury and acute respiratory distress syndrome 2008

11. Hardaway RM;Williams CH;Marvasti M Prevention of adult respiratory distress syndrome with plasminogen activator in pigs[外文期刊] 1990

12. The Acute Respiratory Distress Syndrome Network Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome 2000

13. Stringer KA;Lindenfeld J;Repine AJ Tissue plasminogen activator (tPA) inhibits human neutrophil superoxide anion production in vitro 1997

14. Bernard GR.Vincent JL.Laterre PF Efficacy and safety of recombinant human activated protein C for severe sepsis 2001

15. Uchiba M;Okajima K;Murakami K Recombinant thrombomodulin prevents endotoxin-induced lung injury in rats by inhibiting leukocyte activation 1996

16. Levi M.van der Poll T.Büller HR Bidirectional relation between inflammation and coagulation 2004

17. Abraham E;Gyetko MR;Kuhn K Urokinase-type plasminogen activator potentiates lipopolysaccharide-induced neutrophil activation 2003

18. Hardaway RM.Williams CH.Vasquez Y Disseminated intravascular coagulation in sepsis 2001

19. Choi G;Vlaar AP;Schouten M Natural anticoagulants limit lipopolysaccharide-induced pulmonary coagulation but not inflammation 2007

20. Opal SM. Esmon CT Bench-to-bedside review:functional relationships between coagulation and the innate immune response and their respective roles in the pathogenesis of sepsis 2003

21. Enkhbaatar P;Okajima K;Murakami K Recombinant tissue factor pathway inhibitor reduces lipopolysaccharide-induced pulmonary vascular injury by inhibiting leukocyte activation 2000

22. Gando S. Tedo I. Kubota M Posttrauma coagulation and fibrinolysis 1992

23. Carraway MS;Welty-Wolf KE;Miller DL Blockade of tissue factor:treatment for organ injury in established sepsis[外文期刊] 2003(9)

24. Mavrommatis AC. Theodoridis T. Orfanidou A Coagulation system and platelets are fully activated in uncomplicated sepsis 2000

25. Enkhbaatar P;Cox RA;Traber LD Aerosolized anticoagulants ameliorate acute lung injury in sheep after exposure to burn and smoke inhalation 2007

26. McGee MP. Foster S. Wang X Simultaneous expression of tissue factor and tissue factor pathway inhibitor by human monocytes,a potential mechanism for localized control of blood coagulation 1994

27. Wong SS;Sun NN;Hyde JD Drotrecogin alfa (activated) prevents smoke-induced increases in pulmonary microvascular permeability and proinflammatory cytokine IL-1beta in rats[外文期刊] 2004(6)

28. Ware LB. Fang X. Matthay MA Protein C and thrombomodulin in human acute lung injury 2003

29. Jian MY;Koizumi T;Tsushima K Activated protein C attenuates acid-aspiration lung injury in rats 2005

30. Günther A. Mosavi P. Heinemann S Alveolar fibrin formation caused by enhanced procoagulant and depressed fibrinolytic capacities in severe pneumonia,comparison with the acute respiratory distress syndrome 2000

31. Maybauer MO;Maybauer DM;Fraser JF Recombinant human activated protein C improves pulmonary function in ovine acute lung injury resulting from smoke inhalation and sepsis 2006

32. Schultz MJ. Millo J. Levi M Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator associated pneumonia 2004

33. The Acute Respiratory Distress Syndrome Network Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome 2000

34. Abraham E Coagulation abnormalities in acute lung injury and sepsis 2000

35. Kotanidou A;Loutrari H;Papadomichelakis E Inhaled activated protein C attenuates lung injury induced by aerosolized endotoxin in mice[外文期刊] 2006(2)

36. Schultz MJ. Haitsma JJ. Zhang H Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia--a review 2006

37. Levi M;van der Poll T;Büller HR Bidirectional relation between inflammation and coagulation[外文期刊] 2004

38. Miller DL. Welty-Wolf K. Carraway MS Extrinsic coagulation blockade attenuates lung injury and

proinflammatory cytokine release after intratracheal lipopolysaccharide 2002

39. Bernard GR;Vincent JL;Laterre PF Efficacy and safety of recombinant human activated protein C for severe sepsis[外文期刊] 2001(10)

40. Wygrecka M. Jablonska E. Guenther A Current view on alveolar coagulation and fibrinolysis in acute inflammatory and chronic interstitial lung diseases 2008

41. Yasui H;Gabazza EC;Tamaki S Intratracheal administration of activated protein C inhibits bleomycininduced lung fibrosis in the mouse 2001

42. Wygrecka M. Markart P. Fink L Raised protein levels and altered cellular expression of factor Ⅷ activating protease (FSAP) in the lungs of patients with acute respiratory distress syndrome (ARDS) 2007

43. Tasaki O;Mozingo DW;Dubick MA Effects of heparin and lisofylline on pulmonary function after smoke inhalation injury in an orine model[外文期刊] 2002

44. Choi-Miura NH. Tobe T. Sumiya J Purification and characterization of a novel hyaluronan-binding protein (PHBP) from human plasma:it has three EGF,a kringle and a serine protease domain,similar to hepatocyte growth factor activator 1996

45. Murakami K;McGuire R;Cox RA Heparin nebulization attenuates acute lung injury in sepsis following smoke inhalation in sheep[外文期刊] 2002(3)

46. R(o)emisch J. Feussner A. Verm(o)hlen S A protease isolated from human plasma activating factor Ⅷ independent of tissue factor 1999

47. Raghavendran K;Pryhuber GS;Chess PR Pharmacotherapy of acute lung injury and acute respiratory distress syndrome[外文期刊] 2008(19)

48. R(o)misch J. Verm(o)hlen S. Feusaner A The F Ⅷ activating protease cleaves single-chain plasminogen activators 1999

49. 赵聪;章志丹;张晓娟 小剂量肝素治疗脓毒症的临床分析[期刊论文]-中华内科杂志 2009(7)

50. Kannemeier C. Al-Fakhri N. Preissner KT Factor Ⅷ-activating protease (FSAP) inhibits growth factor-mediated cell proliferation and migration of vascular smooth muscle cells 2004

51. Zarychanski R;Doucette S;Fergusson D Early intravenous unfractionated heparin and mortality in septic shock[外文期刊] 2008

52. Roderfeld M. Weiskirchen R. Atanaso va S Altered factor Ⅷ activating protease expression in murine hepatic fibrosis and its influence on hepatic stellate cells 2009

53. Polderman KH;Girbes AR Drugintervention trials in sepsis:divergent results[外文期刊] 2004(9422)

54. Wygrecka M. Morty RE. Markart P Plasminogen activator inhibitor-1is an inhibitor of factor Ⅷ-activating protease in patients with acute respiratory distress syndrome 2007

55. Davidson BL;Geerts WH;Lensing AW Low-dose heparin for severe sepsis[外文期刊] 2002

56. Wygrecka M. Markart P. Ruppert C Compartment-and cell-specific expression of coagulation and fibrinolysis factors in the murine lung undergoing inhalational versus intravenous endotoxin application 2004

57. Choi G;Hofstra JJ;Roelofs JJ Recombinant human activated protein C inhibits local and systemic

activation of coagulation without influencing inflammation during Pseudomonas aeruginosa pneumonia in rats[外文期刊] 2007(5)

58. Gando S. Kameue T. Matsuda N Imbalances between the levels of tissue factor and tissue factor pathway inhibitor in ARDS patients 2003

59. Murakami K;Okajima K;Uchiba M Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production 1997

60. Ambrus JL. Ambrus CM Changes in the fibrinolysin system in infantile and adult respiratory distress syndrome (ARDS),caused by trauma and/or septic shock in patients and in experimental animals 1990

61. Kipnis E;Guery BP;Tournoys A Massive alveolar thrombin activation in Pseudomonas aeruginosa-induced acute lung injury[外文期刊] 2004(5)

62. D'Angelo A. Lockhart MS. D'Angelo SV Protein S is a cofactor for activated protein C neutralization of an inhibitor of plasminogen activation released from platelets 1987

63. Murakami K;McGuire R;Cox RA Recombinant antithrombin attenuates pulmonary inflammation following smoke inhalation and pneumonia insheep[外文期刊] 2003(2)

64. Esmon CT Inflammation and activated protein C anticoagulant pathway 2006(Suppl 1)

65. Uchiba M;Okajima K;Murakami K Effects of various doses of antithrombin Ⅲ on endotoxin-induced endothelial cell injury and coagulation abnormaalities in rats[外文期刊] 1998

66. Shimizu S. Gabazza EC. Taguchi O Activated protein C inhibits the expression of platelet-derived growth factor in the lung 2003

67. Giebler R;Schmidt U;Koch S Combined antithrombin Ⅲ and Cleeterase inhibitor treatment decreases intravascular fibrin deposition and attenuates cardiorespiratory impairment in rabbits exposed to Escherichia coli endotoxin[外文期刊] 1999(3)

68. Idell S. James KK. Levin EG Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome 1989

69. Slofstra SH;Groot AP;Maris NA Inhalation of activated protein C inhibits endotoxin-induced pulmonary inflammation in mice independent of neutrophil recruitment[外文期刊] 2006(6)

70. Bertozzi P. Astedt B. Zenzius L Depressed bronchoalveolar urokinase activity in patients with adult respiratory distress syndrome 1990

71. Murakami K;Okajima K;Uchiba M Activated protein C attenuates endotoxin-induced pulmonary vascular injury by inhibiting activated leukocytes in rats 1996

72. Günther A. Mosavi P. Ruppert C Enhanced tissue factor pathway activity and fibrin turnover in the alveolar compartment of patients with interstitial lung disease 2000

73. Dixon B;Santamaria JD;Campbell DJ A phase 1 trial of nebulised heparin in acute lung injury[外文期刊] 2008(3)

74. Wygrecka M. Markart P. Ruppert C Cellular origin of pro-coagulant and (anti)-fibrinolytic factors in bleomycin-injured lungs 2007

75. 栾正刚;娜拉?普鲁;章志丹 低分子肝素和阿司匹林对急性肺损伤的治疗作用[期刊论文]-中国危重病急救医学

2006(8)

76. Sisson TH. Hanson KE. Subbotina N Inducible lung-specific urokinase expression reduces fibrosis mortality after lung injury in mice 2002

77. 吴允孚;陈刚;席与斌 血必净注射液对内毒素性肺损伤治疗作用的实验研究[期刊论文]-中国中西医结合急救杂志 2008(3)

78. Markart P. Ruppert C. Petri K Transgenic Mice expressing a surfactant protein B urokinase fusion protein in the distal respiratory epitehelium show improved survival after bleomycin-induced lung injury 2005

79. Fujimoto H;Gabazza EC;Hataji O Thrombin-activatable fibrinolysis inhibitor and protein C inhibitor in interstitial lung disease[外文期刊] 2003(12)

80. Fujimoto H. Gabazza EC. Hataji O Thrombin-activatable fibrinolysis inhibitor and protein C inhibitor in interstitial lung disease 2003

81. Markart P;Ruppert C;Petri K Transgenic Mice expressing a surfactant protein B urokinase fusion protein in the distal respiratory epitehelium show improved survival after bleomycin-induced lung injury 2005

82. 吴允孚. 陈刚. 席与斌 血必净注射液对内毒素性肺损伤治疗作用的实验研究 2008(3)

83. Sisson TH;Hanson KE;Subbotina N Inducible lung-specific urokinase expression reduces fibrosis mortality after lung injury in mice 2002

84. Levi M. Ten Cate H Disseminated intravascular coagulation 1999

85. Wygrecka M;Markart P;Ruppert C Cellular origin of pro-coagulant and (anti)-fibrinolytic factors in bleomycin-injured lungs[外文期刊] 2007

86. Pernerstorfer T. Hollenstein U. Hansen J Heparin blunts endotoxininduced coagulation activation 1999

87. 宋志芳;谢伟;单慧敏 糖皮质激素治疗大肠杆菌致急性呼吸窘迫综合征的实验研究[期刊论文]-中国危重病急救医学 2006(12)

88. Fareed J. Hoppensteadt DA. Bick RL An update on heparins at the beginning of the new millennium 2000(Suppl 1)

89. Griffin MP;Gore DC;Zwischenberger JB Does heparin improve survival in experimental porcine gram-negative septic shock 1990

90. Griffin MP. Gore DC. Zwischenberger JB Does heparin improve survival in experimental porcine gram-negative septic shock 1990

91. Fareed J;Hoppensteadt DA;Bick RL An update on heparins at the beginning of the new millennium 2000(Suppl 1)

92. Yang S. Hauptman JG The efficacy of heparin and antithrombin III in fluid-resuscitated cecal ligation and puncture 1994

93. Pernerstorfer T;Hollenstein U;Hansen J Heparin blunts endotoxininduced coagulation activation 1999

94. Gaskins RA Jr. Dalldorf FG Experimental meningococcal septicemia,effect of heparin therapy 1976

95. Levi M;Ten Cate H Disseminated intravascular coagulation 1999

96. Corrigan JJ Jr.Kiernat JF Effect of heparin in experimental gram-negative septicemia 1975

97. D'Angelo A;Lockhart MS;D'Angelo SV Protein S is a cofactor for activated protein C neutralization of an inhibitor of plasminogen activation released from platelets 1987

98. Davidson BL.Geerts WH.Lensing AW Low-dose heparin for severe sepsis 2002

99. Ambrus JL;Ambrus CM Changes in the fibrinolysin system in infantile and adult respiratory distress syndrome (ARDS),caused by trauma and/or septic shock in patients and in experimental animals 1990

100. Polderman KH.Girbes AR Drugintervention trials in sepsis:divergent results 2004

101. Gando S;Kameue T;Matsuda N Imbalances between the levels of tissue factor and tissue factor pathway inhibitor in ARDS patients[外文期刊] 2003(2/3)

102. Zarychanski R.Doucette S.Fergusson D Early intravenous unfractionated heparin and mortality in septic shock 2008

103. Wygrecka M;Markart P;Ruppert C Compartment-and cell-specific expression of coagulation and fibrinolysis factors in the murine lung undergoing inhalational versus intravenous endotoxin application 2004

104. 赵聪.章志丹.张晓娟.李旭.朱然.马晓春 小剂量肝素治疗脓毒症的临床分析 2009(7)

105. Wygrecka M;Morty RE;Markart P Plasminogen activator inhibitor-1is an inhibitor of factor Ⅷ-activating protease in patients with acute respiratory distress syndrome[外文期刊] 2007

106. Murakami K.McGuire R.Cox RA Heparin nebulization attenuates acute lung injury in sepsis following smoke inhalation in sheep 2002

107. Corrigan JJ Jr;Kiernat JF Effect of heparin in experimental gram-negative septicemia[外文期刊] 1975

108. Tasaki O.Mozingo DW.Dubick MA Effects of heparin and lisofylline on pulmonary function after smoke inhalation injury in an orine model 2002

109. Gaskins RA Jr;Dalldorf FG Experimental meningococcal septicemia,effect of heparin therapy 1976

110. 栾正刚.娜拉·普鲁.章志丹.马晓春 低分子肝素和阿司匹林对急性肺损伤的治疗作用 2006(8)

111. Yang S;Hauptman JG The efficacy of heparin and antithrombin Ⅲ in fluid-resuscitated cecal ligation and puncture[外文期刊] 1994

112. Dixon B.Santamaria JD.Campbell DJ A phase 1 trial of nebulised heparin in acute lung injury 2008

113. Roderfeld M;Weiskirchen R;Atanaso va S Altered factor Ⅷ activating protease expression in murine hepatic fibrosis and its influence on hepatic stellate cells[外文期刊] 2009(5)

114. Murakami K.Okajima K.Uchiba M Activated protein C attenuates endotoxin-induced pulmonary vascular injury by inhibiting activated leukocytes in rats 1996

115. Bertozzi P;Astedt B;Zenzius L Depressed bronchoalveolar urokinase activity in patients with adult respiratory distress syndrome[外文期刊] 1990

116. Murakami K.Okajima K.Uchiba M Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production 1997

117. Idell S;James KK;Levin EG Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome 1989

118. Choi G.Hofstra JJ.Roelofs JJ Recombinant human activated protein C inhibits local and systemic activation of coagulation without influencing inflammation during Pseudomonas aeruginosa pneumonia in rats 2007

119. Shimizu S;Gabazza EC;Taguchi O Activated protein C inhibits the expression of platelet-derived growth factor in the lung[外文期刊] 2003(10)

120. Maybauer MO.Maybauer DM.Fraser JF Recombinant human activated protein C improves pulmonary function in ovine acute lung injury resulting from smoke inhalation and sepsis 2006

121. Esmon CT Inflammation and activated protein C anticoagulant pathway 2006(Suppl 1)

122. Jian MY.Koizumi T.Tsushima K Activated protein C attenuates acid-aspiration lung injury in rats 2005

123. Schultz MJ;Haitsma JJ;Zhang H Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia--a review 2006

124. Wong SS.Sun NN.Hyde JD Drotrecogin alfa (activated) prevents smoke-induced increases in pulmonary microvascular permeability and proinflammatory cytokine IL-1beta in rats 2004

125. Abraham E Coagulation abnormalities in acute lung injury and sepsis 2000

126. Yasui H.Gabazza EC.Tamaki S Intratracheal administration of activated protein C inhibits bleomycininduced lung fibrosis in the mouse 2001

127. Schultz MJ;Millo J;Levi M Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator associated pneumonia[外文期刊] 2004

128. Kotanidou A.Loutrari H.Papadomichelakis E Inhaled activated protein C attenuates lung injury induced by aerosolized endotoxin in mice 2006

129. Günther A;Mosavi P;Heinemann S Alveolar fibrin formation caused by enhanced procoagulant and depressed fibrinolytic capacities in severe pneumonia,comparison with the acute respiratory distress syndrome 2000

130. Slofstra SH.Groot AP.Maris NA Inhalation of activated protein C inhibits endotoxin-induced pulmonary inflammation in mice independent of neutrophil recruitment 2006

131. Guimbaud R;Bertrand V;Chauvelot-Moachon L Network of inflammatory cytokines and correlation with disease activity in ulcerative colitis 1998

132. Giebler R.Schmidt U.Koch S Combined antithrombin III and Cleeterase inhibitor treatment decreases intravascular fibrin deposition and attenuates cardiorespiratory impairment in rabbits exposed to Escherichia coli endotoxin 1999

133. Fernandes AB;Zin WA;Rocco PR Corticosteroids in acute respiratory distress syndrome 2005

134. Uchiba M.Okajima K.Murakami K Effects of various doses of antithrombin III on endotoxin-induced endothelial cell injury and coagulation abnormaalities in rats 1998

135. Günther A;Mosavi P;Ruppert C Enhanced tissue factor pathway activity and fibrin turnover in the alveolar compartment of patients with interstitial lung disease 2000

136. Murakami K. McGuire R. Cox RA Recombinant antithrombin attenuates pulmonary inflammation following smoke inhalation and pneumonia insheep 2003

137. R(o)emisch J;Feussner A;Verm(o)hlen S A protease isolated from human plasma activating factor Ⅷ independent of tissue factor 1999

138. Kipnis E. Guery BP. Tournoys A Massive alveolar thrombin activation in Pseudomonas aeruginosa-induced acute lung injury 2004

139. Choi-Miura NH;Tobe T;Sumiya J Purification and characterization of a novel hyaluronan-binding protein (PHBP) from human plasma:it has three EGF,a kringle and a serine protease domain,similar to hepatocyte growth factor activator 1996

140. Enkhbaatar P. Cox RA. Traber LD Aerosolized anticoagulants ameliorate acute lung injury in sheep after exposure to burn and smoke inhalation 2007

141. Wygrecka M;Markart P;Fink L Raised protein levels and altered cellular expression of factor Ⅷ activating protease (FSAP) in the lungs of patients with acute respiratory distress syndrome (ARDS) [外文期刊] 2007

142. Carraway MS. Welty-Wolf KE. Miller DL Blockade of tissue factor:treatment for organ injury in established sepsis 2003

143. Wygrecka M;Jablonska E;Guenther A Current view on alveolar coagulation and fibrinolysis in acute inflammatory and chronic interstitial lung diseases 2008

144. Enkhbaatar P. Okajima K. Murakami K Recombinant tissue factor pathway inhibitor reduces lipopolysaccharide-induced pulmonary vascular injury by inhibiting leukocyte activation 2000

145. Miller DL;Welty-Wolf K;Carraway MS Extrinsic coagulation blockade attenuates lung injury and proinflammatory cytokine release after intratracheal lipopolysaccharide 2002

146. Choi G. Vlaar AP. Schouten M Natural anticoagulants limit lipopolysaccharide-induced pulmonary coagulation but not inflammation 2007

147. Ware LB;Fang X;Matthay MA Protein C and thrombomodulin in human acute lung injury 2003

148. Abraham E. Gyetko MR. Kuhn K Urokinase-type plasminogen activator potentiates lipopolysaccharide-induced neutrophil activation 2003

149. Kannemeier C;Al-Fakhri N;Preissner KT Factor Ⅷ-activating protease (FSAP) inhibits growth factor-mediated cell proliferation and migration of vascular smooth muscle cells 2004

150. Stringer KA. Lindenfeld J. Repine AJ Tissue plasminogen activator (tPA) inhibits human neutrophil superoxide anion production in vitro 1997

151. R(o)misch J;Verm(o)hlen S;Feusaner A The F Ⅷ activating protease cleaves single-chain plasminogen activators 1999

152. Hardaway RM. Williams CH. Marvasti M Prevention of adult respiratory distress syndrome with plasminogen activator in pigs 1990

153. McGee MP;Foster S;Wang X Simultaneous expression of tissue factor and tissue factor pathway inhibitor by human monocytes,a potential mechanism for localized control of blood coagulation[外文期刊] 1994

154. Stringer KA. Hybertson BM. Cho OJ Tissue plasminogen activator (tPA) inhibits interleukin-1 induced acute lung leak 1998

155. Mavrommatis AC;Theodoridis T;Orfanidou A Coagulation system and platelets are fully activated in uncomplicated sepsis 2000

156. Enkhbaatar P. Murakami K. Cox R Aerosolized tissue plasminogen inhibitor improves pulmonary function in sheep with burn and smoke inhalation 2004

157. Gando S;Tedo I;Kubota M Posttrauma coagulation and fibrinolysis[外文期刊] 1992

158. Münster AM. Rasmussen L. Sidelmann J Effects of inhaled plasminogen activator on the balance between coagulation and fibrinolysis in traumatized pigs 2002

159. Opal SM;Esmon CT Bench-to-bedside review:functional relationships between coagulation and the innate immune response and their respective roles in the pathogenesis of sepsis 2003

160. Uchiba M. Okajima K. Murakami K Recombinant human soluble thrombomodulin reduces endotoxininduced pulmonary vascular injury via protein C activation in rats 1995

161. Ware LB;Matthay MA The acute respiratory distress syndrome[外文期刊] 2000

162. Uchiba M. Okajima K. Murakami K Recombinant thrombomodulin prevents endotoxin-induced lung injury in rats by inhibiting leukocyte activation 1996