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以快速起效为特征的水溶性丙泊酚前体药的改良设计

An Improved Design of Water-Soluble Propofol Prodrugs Characterized by Rapid Onset of Action

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Anesthesia & Analgesia 2014 118 745–754

背景：设计丙泊酚的磷酸酯前体药物（磷丙泊酚，HX0969W）是为了避开母体药物水溶性较差的特点。但在先前的临床试验中发现前体药物有感觉异常和瘙痒的副作用，其主要原因是磷酸酯堆积。为了规避这一潜在风险，本研究设计了两种含氨基酸的丙泊酚前体药物(HX0969-Gly-F3, HX0969-Ala-HCl)，即在前体药物的先导化合物 HX0969 结构中加入氨基酸族。本研究假设改进后丙泊酚前体药物不仅能消除副作用，也能保留其快速起效和优良的水溶性的特点。

方法：先导化合物 HX0969 由硼氢化钠碘族合成。HX0969W, HX0969-Gly-F3, HX0969-Ala-HCl 均由 HX0969 合成。磷丙泊酚，HX0969W, HX0969-Gly-F3 和 HX0969-Ala-HCl 在生理盐水中的溶解度已得到测试。这些前体药在不同生理介质中（大鼠血浆，恒河猴血浆以及大鼠肝细胞微粒体）的生物转化在体外试验中已经确认。在鼠的在体试验中测定四种前体药的 50%有效剂量（ED50）。同时测定给予等效剂量后的起效时间和持续时间。

结果：(1) 磷丙泊酚，HX0969W, HX0969-Gly-F3 和 HX0969-Ala-HCl 的水溶解度分别为 461.46 ± 26.40 mg/ml, 189.45 ± 5.02 mg/ml, 49.88 ± 0.58 mg/ml 和 245.99 ± 4.83 mg/ml; (2) 在大鼠血浆和恒河猴血浆水解实验中，5h 内两种含氨基酸的前体药较另两种磷酸酯前体

药能以更快的速度大量释放丙泊酚。所有四种前体药在大鼠肝酶存在的情况下均能迅速释放丙泊酚；(3) 与之前的前体药（磷丙泊酚，HX096W）相比，两种新化合物(HX0969-Gly-F3, HX0969-Ala-HCl)在给予较小剂量时起效时间更短。

结论：在丙泊酚前体药物中加入氨基酸族可以使药物具有更佳的水溶性和更快的起效速度。在大鼠血浆中，两种含氨基酸的前体药(HX0969-Ala-HCl, HX0969-Gly-F3)释放丙泊酚的速度较两组磷酸酯前体药(磷丙泊酚, HX0969W)更快。在体实验显示静脉给予HX0969-Ala-HCl 和 HX0969-Gly-F3，剂量较磷丙泊酚和 HX0969W 更小，但起效却更快。新设计提高了前体药转化为丙泊酚的效能。

（陆秉玮 译 陈杰 校）

BACKGROUND: Phosphate ester prodrugs of propofol (fospropofol, HX0969W) were designed to avoid the unsatisfactory water solubility of the parent drug. However, in previous clinical trials, there were reported prodrug side effects such as paresthesia and pruritus. The accumulation of a phosphate ester component was found to be the main culprit. To exclude this potential risk, we designed 2 amino acid propofol prodrugs (HX0969-Gly-F3, HX0969-Ala-HCl) based on the lead compound (HX0969) by introducing the amino acid group into the structures of the propofol prodrugs. We hypothesized that the improved propofol prodrugs could not only eliminate those adverse effects but also retain their rapid action and good water solubility.

METHODS: The lead compound HX0969 was synthesized by the sodium borohydride-iodine system. HX0969W, HX0969-Gly-F3, and HX0969-Ala-HCl were synthesized from HX0969. The solubility of fospropofol, HX0969W, HX0969-Gly-F3, and HX0969-Ala-HCl in normal saline was tested. The bioconversions from those prodrugs to propofol in different physiological media (rat plasma, rhesus monkey plasma, and rat hepatic microsomes) were determined in vitro. An in vivo test in the rats was performed to measure the 50% effective dose (ED50) of the 4 propofol prodrugs. Their action onset time and duration time were also measured after their equipotent doses were given.

RESULTS: (1) The water solubility of fospropofol, HX0969W, HX0969-Gly-F3, and HX0969-Ala-HCl was 461.46 ± 26.40 mg/mL, 189.45 ± 5.02 mg/mL, 49.88 ± 0.58 mg/mL, and 245.99 ± 4.83 mg/mL, respectively; (2) The hydrolysis tests in both the rat plasma and the rhesus monkey plasma revealed that the 2 amino acid prodrugs released propofol to a greater extent at a more rapid rate than the 2 phosphate prodrugs during the testing period of 5 hours. All 4 prodrugs released propofol rapidly in the presence of rat hepatic enzymes; (3) Compared with the previous prodrugs (fospropofol, HX0969W), the 2 novel compounds (HX0969-Gly-F3, HX0969-Ala-HCl) had a much shorter onset time when a much lower dose was given.

CONCLUSIONS: Application of the amino acid group to the propofol prodrug can make the prodrug have good water solubility and a more rapid onset of action. In rat plasma, the 2 improved amino acid prodrugs (HX0969-Ala-HCl, HX0969-Gly-F3) had a more rapid rate of propofol release than the 2 phosphate ester prodrugs (fospropofol, HX0969W). The in vivo tests showed that HX0969-Ala-HCl and HX0969-Gly-F3 given IV could have a more rapid onset of action in a smaller dose than fospropofol and HX0969W. This novel design can enhance the efficiency of prodrugs converting to propofol.

减轻手术室火灾：一种二氧化碳防火装置的开发

Mitigating Operating Room Fires: Development of a Carbon Dioxide Fire Prevention Device

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Anesthesia & Analgesia 2014 118 772-775

手术室火灾是对外科病人有实质性危险的警讯事件，发生的频率至少与手术部位错误的发生率相当。发生火灾的三个要素是：氧化剂、火源、可燃物质。手术的电灼器是大多数手术室火灾的触发因素。CO₂ 是一种可以通过替换氧气来预防和抑制火灾的气体。本研究设想可以制作一种通过在电灼笔尖周围产生 CO₂ 锥形气柱的方法来减少手术室火灾的装置。通过安装与 CO₂ 源相连的分散喷嘴使此种装置成为现实。将其安装在手术电灼笔尖上，可以使笔尖包裹在 CO₂ 的锥形气柱内。在 21%、50%、100% 的氧环境中检测这种装置。以 50 W 的电切模式打开手术电灼笔，放在置于铝板上的剖腹手术绵上 30 秒或直至手术绵被点燃。用高速摄像装置来识别点燃的时间。CO₂ 流量为 8 L/分，与没有 CO₂ 装置的对照组相比较，在每一种氧环境中检测 5 次。另外，用一项 CO₂ 采样装置来制作 CO₂ 浓度的三维空间图。对照组在 21%、50% 和 100% 氧环境下的点燃时间均数±标准差（范围）分别为 2.9 s ± 0.44 [2.3–3.0]、0.58s± 0.12 [0.47–0.73] 和 0.48 s ± 0.50 [0.03–1.27]。对照组均被点燃（15/15）；而应用装置组均未被点燃（0/15, P < 0.0001）。手术电灼笔尖末端的 CO₂ 浓度为 95%，在距笔尖 1 到 1.4 厘米水平的平均 CO₂ 浓度为 64%。总之，可以通过使用 CO₂ 发射喷嘴，产生锥形的灭火气场来制作手术室火灾的预防装置。以上演示证明这种装置在可燃情况下可有效地降低火灾风险。CO₂ 的三维空间图表明当 CO₂ 流量为 8 L/min 时至少在离手术电灼笔笔尖 1 厘米的范围内可以有效降低火灾。下一步测验应该探索最佳的 CO₂ 流量和理想的喷嘴形状。利用这种装置可以显著减少手术室火灾对病人损伤的风险。

（朱浩 译 陈杰 校）

Operating room fires are sentinel events that present a real danger to surgical patients and occur at least as frequently as wrong-sided surgery. For fire to occur, the 3 points of the fire triad must be present: an oxidizer, an ignition source, and fuel source. The electrosurgical unit (ESU) pencil triggers most operating room fires. Carbon dioxide (CO₂) is a gas that prevents ignition and suppresses fire by displacing oxygen. We hypothesize that a device can be created to reduce operating room fires by generating a cone of CO₂ around the ESU pencil tip. One such device was created by fabricating a divergent nozzle and connecting it to a CO₂ source. This device was then placed over the ESU pencil, allowing the tip to be encased in a cone of CO₂ gas. The device was then tested in 21%, 50%, and 100% oxygen environments. The ESU was activated at 50 W cut mode while placing the ESU pencil tip on a laparotomy sponge resting on an aluminum test plate for up to 30 seconds or until the sponge ignited. High-speed videography was used to identify time of ignition. Each test was performed in each oxygen environment 5 times with the device activated (CO₂ flow 8 L/min) and with the device deactivated (no CO₂ flow-control). In addition, 3-dimensional spatial mapping of CO₂ concentrations was performed with a CO₂ sampling device. The median ± SD [range] ignition time of the control group in 21% oxygen was 2.9 s ± 0.44 [2.3–3.0], in 50% oxygen 0.58 s ± 0.12 [0.47–0.73], and in 100% oxygen 0.48 s ± 0.50 [0.03–1.27]. Fires were ignited with each control trial (15/15); no fires ignited when the device was used (0/15, P < 0.0001). The CO₂ concentration at the end of the ESU pencil tip was 95%, while the average CO₂ concentration 1 to 1.4 cm away from the pencil tip on the bottom plane was 64%. In conclusion, an operating room fire prevention device can be created by using a divergent nozzle design through which CO₂ passes, creating a cone of fire suppressant. This device as demonstrated in a flammability model effectively reduced the risk of fire. CO₂ 3-dimensional spatial mapping suggests effective fire reduction at least 1 cm away from the tip of the ESU pencil at 8 L/min CO₂ flow. Future testing should determine optimum CO₂ flow rates and ideal nozzle shapes. Use of this device may substantially reduce the risk of patient injury due to operating room fires.

苯肾上腺素导致的由空间分辨近红外光谱原理测定的前额脑氧饱和度的下降可以反映皮肤血流的下降

A Decrease in Spatially Resolved Near-Infrared Spectroscopy-Determined Frontal Lobe Tissue Oxygenation by Phenylephrine Reflects Reduced Skin Blood Flow

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背景：给予苯肾上腺素后，用空间分辨近红外光谱学测定的前额氧饱和度(ScO₂)是下降的，但脑血流未受影响。本研究假设苯肾上腺素对 ScO₂ 的影响是由颅外血管收缩导致的。

方法：选取 7 名志愿者（平均年龄±标准差为 25±4 岁），静脉输注苯肾上腺素，期间通过二维超声监测颈内动脉和颈外动脉 ScO₂ 及椎动脉的血流，同时监测大脑中动脉平均血流速率、前额皮肤血流及平均动脉压。

结果：在苯肾上腺素输注期间，平均动脉压增加，同时 ScO₂ 下降-19%±3%（均数±标准差；P = 0.0005）。颈外动脉及皮肤血流也分别因此下降-27.5%±3.0%、-25.4%±7.8%。并发现 ScO₂ 依次与前额皮肤血流量（Pearson 相关系数 0.55, P = 0.042, 95% 可信区间 0.025–0.84; Spearman 相关系数 0.81, P < 0.001, 95% 可信区间 0.49–0.94）及颈外动脉电导(Pearson 相关系数 0.62, P = 0.019, 95% 可信区间 0.13–0.86; Spearman 相关系数 0.64, P = 0.012, 95% 可信区间 0.17–0.88)有关。

结论：此项研究发现经 INVOS-4100 近红外光谱测定，苯肾上腺素可导致 ScO₂ 的下降，是由于颅外血管收缩而非脑氧饱和度下降的结果。

（梁玉丹 译 陈杰 校）

BACKGROUND: Spatially resolved near-infrared spectroscopy-determined frontal lobe tissue oxygenation (ScO₂) is reduced with administration of phenylephrine, while cerebral blood flow may remain unaffected. We hypothesized that extracranial vasoconstriction explains the effect of phenylephrine on ScO₂.

METHODS: We measured ScO₂ and internal and external carotid as well as vertebral artery blood flow in 7 volunteers (25 [SD 4] years) by duplex ultrasonography during IV infusion of phenylephrine, together with middle cerebral artery mean blood velocity, forehead skin blood flow, and mean arterial blood pressure.

RESULTS: During phenylephrine infusion, mean arterial blood pressure increased, while ScO₂ decreased by -19% ± 3% (mean ± SE; P = 0.0005). External carotid artery (-27.5% ± 3.0%) and skin blood flow (-25.4% ± 7.8%) decreased in response to phenylephrine administration, and there was a relationship between ScO₂ and forehead skin blood flow (Pearson r = 0.55, P = 0.042, 95% confidence interval [CI], = 0.025–0.84; Spearman r = 0.81, P < 0.001, 95% CI, 0.49–0.94) and external carotid artery conductance (Pearson r = 0.62, P = 0.019, 95% CI, 0.13 to 0.86; Spearman r = 0.64, P = 0.012, 95% CI, 0.17–0.88).

CONCLUSIONS: These findings suggest that a phenylephrine-induced decrease in ScO₂, as determined by INVOS-4100 near-infrared spectroscopy, reflects vasoconstriction in the extracranial vasculature rather than a decrease in cerebral oxygenation.

爪部切割和脊神经结扎后大鼠颅内自我刺激、食物维持自发反应和开放域活动的差异性抑制

Differential Suppression of Intracranial Self-Stimulation, Food-Maintained Operant Responding, and Open Field Activity by Paw Incision and Spinal Nerve Ligation in Rats

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背景：监测实验室动物持续自发疼痛行为一直是个挑战。大多数临床前期疼痛研究监测机体对特定体外有害性刺激所引发的行为反应。然而，人类和动物的持续自发性疼痛也许和高敏性无关，并且可能会减少很多行为，尤其是动机性行为，本研究假设急性和慢性疼痛出现后这种行为会减少。

方法：在本研究中，201 只雄性大鼠接受爪部切割（INC）、L5/L6 脊神经结扎（SNL）或同时接受 INC 和 SNL，并评估这些处理对大鼠缩爪阈值（PWT）的影响。为了进行对比，也对相同大鼠进行非诱发方法下的行为学减退效应的评估，包括大脑腹侧被盖区的颅内自我刺激（VTA ICSS）或食物强化（FR）以及开放域活动（OFA）的奖励性电刺激的按压杠杆反应。

结果：INC 使得 PWT 降低持续 4 天，VTA ICSS 降低持续 2 天，FR 降低持续 1 天但并未改变 OFA。SNL 导致的 PWT 降低类似于 INC 但并未使 VTA ICSS 或 FR 产生变化；SNL 降低 OFA。同时接受 INC 和 SNL 大鼠，其 PWT、VTA ICSS 和 FR 的变化类似于 INC 组，与 SNL 组相比，并未降低 OFA。

结论：INC 减少 VTA ICSS 和 FR 按压杠杆反应（爪部切割后的 1~2 天）的急性效应与 INC 导致的持续自发性疼痛预期产生的时间段相符，因此，这些指标的下降可能是由持续自发疼后预期发生的持续性自发疼痛的时间窗一致。因此这些降低效应可能是持续性自发疼痛所介导的，而这种疼痛与 INC 导致的持续达 4 天的机械性高敏感性无关。INC 大鼠 PWT 的下降与 SNL 大鼠类似，然而自发性行为（VTA ICSS 和 FR 的按压杠杆反应）在 SNL 大鼠中并没有下降。SNL，而不是 INC，降低了饲养行为而非持续 OFA 全程。这进一步说明了高敏感性的出现和程度并不能预测大鼠许多行为的改变，后者原来被认为是持续疼痛介导后出现的。令人惊讶的是，INC 产生的行为学效应并没有加重 SNL 组的结果。这些数据支持了一种新近的观点：急性疼痛模型会产生短期自发疼痛行为，这种行为在神经病理性疼痛模型中比较少见或者不会出现，评估诱发性而非诱发性疼痛行为在未来研发急性和慢性疼痛治疗方案时的必要性。

（边文玉 译 陈杰 校）

BACKGROUND: Detection of ongoing spontaneous pain behaviors in laboratory animals remains a research challenge. Most preclinical pain studies measure elicited behavioral responses to an external noxious stimulus; however, ongoing spontaneous pain in humans and animals may be unrelated to hypersensitivity, and likely diminishes many behaviors, particularly motivated behaviors, that we hypothesize will decrease after induction of acute and chronic pain.

METHODS: In this study, 201 male rats were subjected to paw incision (INC), L5/L6 spinal nerve ligation (SNL), or INC in SNL rats, and the effects on paw withdrawal threshold (PWT) were assessed. For comparison, the behavioral-decreasing effects on nonevoked measures, including lever pressing for rewarding electrical stimulation of the ventral tegmental area intracranial self-stimulation (VTA ICSS) or food reinforcement (FR), and open field activity (OFA), were also assessed in these same rats.

RESULTS: INC decreased PWT for 4 days, decreased VTA ICSS for 2 days, and FR for 1 day but did not alter OFA. SNL decreased PWT similarly to INC but did not decrease VTA ICSS or FR; SNL did however decrease OFA. INC in SNL rats reduced PWT, VTA ICSS, and FR similarly to INC alone and did not decrease OFA compared with SNL alone.

CONCLUSIONS: The acute effects of INC on decreasing lever pressing for VTA ICSS and FR (1–2 days after incision) correspond to the timeframe in which ongoing spontaneous pain is expected to occur after INC. Therefore, these decreases are likely mediated by ongoing spontaneous pain, which may be unrelated to mechanical hypersensitivity that persists for up to 4 days after INC. PWT is decreased similarly by SNL, yet operant behavior (lever pressing for VTA ICSS and FR) was not decreased by SNL. SNL, but not INC, decreased rearing behavior but not total distance traveled during OFA. This further indicates that the presence and the extent of hypersensitivity are not predictive of many behavioral changes in rats thought to be mediated

by the presence of ongoing pain. Surprisingly, the behavioral effects of INC are not exacerbated in SNL rats. These data support the growing belief that acute pain models produce short-lived spontaneous pain behaviors that are often less pronounced or absent in neuropathic pain models, and highlight the need for assessment of both evoked and nonevoked pain behaviors in developing future therapies for acute and chronic pain.

在小猪中注射超声凝胶、内毒素、0.9% NaCl，或穿刺但不注射药物后的神经内和神经周围炎症性改变

Intraneural and Perineural Inflammatory Changes in Piglets After Injection of Ultrasound Gel, Endotoxin, 0.9% NaCl, or Needle Insertion without Injection

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背景：已有超声凝胶性神经炎症的报道。本研究在对猪进行周围神经阻滞，比较凝胶注射与内毒素注射（阳性对照），生理盐水注射，干针穿刺（阴性对照）后炎症的程度和性质的差异。

方法：用体表标记和神经刺激仪方法定位 12 只猪的选定神经。注射后 48 小时，通过定量聚合酶链反应对本标本进行免疫细胞分化/量化和细胞因子表达的检测。

结果：与干针穿刺和/或盐水注射相比，凝胶和内毒素注射导致更高密度炎症细胞的产生（淋巴细胞/粒细胞）（两者 $P < 0.001$ ）。无论在何种标本中均未检测到细胞因子。

结论：神经周围凝胶注射可引起严重的炎症。细胞因子的缺乏表明是注射相关的变化，而非机械性创伤。

（谈婧华 译 陈杰 校）

BACKGROUND: Ultrasound gel nerve inflammation has been reported. We evaluated the extent and nature of inflammation after gel injection with endotoxin (positive), saline, or dry needle puncture (negative) controls after peripheral blocks in piglets.

METHODS: Selected nerves of 12 piglets were localized by landmarks and nerve stimulator. Forty-eight hours after injection, specimens were examined for immunohistochemical cell differentiation/quantification and cytokine expression by using quantitative polymerase chain reaction.

RESULTS: Both gel and endotoxin injections resulted in a significantly higher density of inflammatory cells (lymphocytes/granulocytes) as compared with needle insertions and/or saline injections (both $P < 0.001$). Cytokines were not detected in any of the specimens.

CONCLUSIONS: Perineural gel injections cause significant inflammation. The lack of cytokines suggests injectate-related changes rather than mechanical trauma.

地塞米松呈剂量依赖性地抑制由 Sugammadex 逆转的体外神经支配的初级人类肌肉细胞

Dexamethasone produces dose-dependent inhibition of sugammadex reversal in in vitro innervated primary human muscle cells

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背景：糖皮质激素在麻醉过程中经常被用来作为肾上腺皮质功能不全患者的替代治疗。其作为威胁生命条件下的一线治疗药物，用于防止手术后的恶心和呕吐，以及作为多模式镇痛的组成部分。对于后两者，地塞米松是最经常使用的。由于甾类肌肉松弛药和地塞米松之间的结构相似。有关人士提出了关于可能的糖皮质激素抑制由 sugammadex 提供的神经肌肉阻滞的逆转效应。因此，我们研究了地塞米松对 sugammadex 逆转罗库溴铵引起的神经肌肉阻滞的影响，这可能在某些临床情况下是相关。

方法：首先在体外用鼠胚胎脊髓外植体培植特殊的人类肌肉细胞功能性神经肌肉接头培养模型，用于探究 4 和 10 μ M 罗库溴铵对肌肉收缩的影响，通过定量计算在收缩阳性的外植体共培养物的收缩单元。接下来，等摩尔和 3 倍等摩尔 sugammadex 用于 4 和 10 μ M 罗库溴铵的恢复。最后，用 1，100，和 10 μ M 地塞米松（正常，升高和高临床级）来评估其对由 sugammadex 逆转罗库溴铵诱导的神经肌肉阻滞的任何影响。

结果：实验包括了三段时间内培养的时间无关的七十八株外植体，其中收缩的数量增加至 10 天共培养。罗库溴铵表现出对神经肌肉阻滞深度的时间依赖性效应（4 μ M 罗库溴铵：基线，10，20 分钟给药， $P < 0.0001$ ），而剂量依赖性作用接近标称统计学意义（4,10 μ M， $P = 0.080$ ）。这是由等摩尔浓度 sugammadex 的逆转，进一步的，几乎完全恢复收缩需 3 倍等摩尔 sugammadex（ $P < 0.0001$ ）。地塞米松减少 sugammadex 逆转罗库溴铵诱导的神经肌肉阻滞程度并呈剂量依赖性（ $P = 0.026$ ），10 μ M sugammadex 上升至 30 μ M，即接近统计学显著改善恢复性（ $P = 0.065$ ）。地塞米松最高降低 sugammadex 恢复神经肌肉收缩的等摩尔浓度的 26%。；当 3 倍等摩尔（30 μ M）sugammadex 时，这种效果更为显著，为 48%。

结论：这是在高度可及的功能性人体神经肌肉细胞的体外实验模型中地塞米松罗库溴铵和 sugammadex 相互作用的影响的第一份报告。Sugammadex 逆转罗库溴铵引起的神经肌肉阻滞；然而，高浓度的地塞米松能减小 sugammadex 的效率。这需要进一步研究，以确定这些相互作用的临床意义。

（陈婉南译 薛张纲校）

BACKGROUND: Corticosteroids are frequently used during anesthesia to provide substitution therapy in patients with adrenal insufficiency, as a first-line treatment of several life-threatening conditions, to prevent postoperative nausea and vomiting, and as a component of multimodal analgesia. For these last 2 indications, dexamethasone is most frequently used. Due to the structural resemblance between aminosteroid muscle relaxants and dexamethasone, concerns have been raised about possible corticosteroid inhibition in the reversal of neuromuscular block by sugammadex. We thus investigated the influence of dexamethasone on sugammadex reversal of rocuronium-induced neuromuscular block, which could be relevant in certain clinical situations.

METHODS: The unique co-culture model of human muscle cells innervated in vitro with rat embryonic spinal cord explants to form functional neuromuscular junctions was first used to explore the effects of 4 and 10 μ M rocuronium on muscle contractions, as quantitatively evaluated by counting contraction units in contraction-positive explant co-cultures. Next, equimolar and 3-fold equimolar sugammadex was used to investigate the recovery of contractions from 4 and 10 μ M rocuronium block. Finally, 1, 100, and 10 μ M dexamethasone (normal, elevated, and high clinical levels) were used to evaluate any effects on the reversal of rocuronium-induced neuromuscular block by sugammadex.

RESULTS: Seventy-eight explant co-cultures from 3 time-independent experiments were included, where the number of contractions increased to 10 days of co-culturing. Rocuronium

showed a time-dependent effect on depth of neuromuscular block (4 μ M rocuronium: baseline, 10, 20 minutes administration; $P < 0.0001$), while the dose-dependent effect was close to nominal statistical significance (4, 10 μ M; $P = 0.080$). This was reversed by equimolar concentrations of sugammadex, with further and virtually complete recovery of contractions with 3-fold equimolar sugammadex ($P < 0.0001$). Dexamethasone diminished 10 μ M sugammadex-induced recovery of contractions from rocuronium-induced neuromuscular block in a dose-dependent manner ($P = 0.026$) with a higher sugammadex concentration (30 μ M) being close to statistically significantly improving recovery ($P = 0.065$). The highest concentration of dexamethasone decreased the recovery of contractions by equimolar sugammadex by 26%; this effect was more pronounced when 3-fold equimolar (30 μ M) sugammadex was used for reversal (48%).

CONCLUSIONS: This is the first report in which the effects of rocuronium and sugammadex interactions with dexamethasone have been studied in a highly accessible in vitro experimental model of functionally innervated human muscle cells. Sugammadex reverses rocuronium-induced neuromuscular block; however, concomitant addition of high dexamethasone concentrations diminishes the efficiency of sugammadex. Further studies are required to determine the clinical relevance of these interactions.

低脑电双频指数值的累积时间与未知恶性肿瘤病人的癌症发生率和已知恶性肿瘤病人的五年死亡率无关。

Cumulated time with low bispectral index values is not related to the risk of new cancer or death within 5 years after surgery in patients with previous or prevailing malignancy.

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背景：有一些既往的临床数据表明麻醉和外科手术可能促进癌症的生长。我们已发现，在术前或术后一月以内没有恶性肿瘤诊断或病史的患者，在进行全麻，同时 BIS 值低于 45 时，并无增加五年内患癌症的风险。由于已知恶性肿瘤患者的免疫能力不同，我们研究了外科手术中早期或已知恶性肿瘤的病人所对应的风险。

方法：在预期的进行七氟醚麻醉的 766 例进行 BIS 监测的患者，随访术后恶性肿瘤的诊断和五年死亡率。在麻醉过程中跟踪记录 BIS 值小于 45，应用环氧合酶分析评估癌症的新发生率以及各种原因导致的死亡发生率。

结果：51 位患者（6.7%）术后五年内确诊了 54 个恶性肿瘤的诊断。有 387 例癌症病人安排了癌症治疗的外科手术，293 位病人（38%）死亡。麻醉与 BIS 值小于 45，以及癌症新发生率（风险比例相对为 0.64-1.11 和 0.76-1.30），以及死亡率（风险比例相对为 0.85-1.05 和 0.94-1.16 之间）无关。同时，在 BIS 值为其他值时（小于 30，40，50），也未发现明显关联。

结论：未知或已知恶性肿瘤的患者，持续的全身麻醉，或累积的七氟醚复合麻醉与外科术后癌症的新发生率和恶性肿瘤的五年生存率无关。监测下的深度麻醉对于改善恶性肿瘤患者外科术后的肿瘤预后无明显关系。

（蒋鑫梅译 薛张纲校）

BACKGROUND:Preclinical data indicate that anesthesia and surgery may promote cancer growth. We previously found no increased risk of malignant disease within 5 years regarding duration of general anesthesia (TANESTH) and time with Bispectral Index (BIS) under 45 (TBIS < 45) in patients without any diagnosis or history of malignancy before or within 1 month after surgery. Because immunocompetence may be different in patients with previous malignant disease, we investigated the corresponding risk in patients with earlier or existing malignant disease at the time of surgery.

METHODS:In a prospective cohort of 766 BIS-monitored patients anesthetized with sevoflurane, new malignant diagnoses and death within 5 years after surgery were retrieved. Cox regression was used to assess the risk of new cancer and all-cause death during follow-up in relation to (TANESTH) and (TBIS <45).

RESULT:Fifty-one patients (6.7%) were assigned 54 new malignant diagnoses within 5 years after surgery. Cancer surgery comprised 387 (51%) of the index operations. Two hundred ninety-three (38 %) of the patients died during follow-up. No relation between TANESTH or TBIS <45 and new malignant disease (hazard ratio [HR] 0.64-1.11 and 0.76-1.30, respectively) or death was found (HR 0.85-1.05 and 0.94-1.16, respectively). Nor were any corresponding significant relations obtained when other thresholds for BIS (i.e., < 30, 40, and 50, respectively) were investigated.

CONCLUSION : In patients with previous or existing malignant disease, neither duration of anesthesia nor increased cumulative time with profound sevoflurane anesthesia was associated with an increased risk for new cancer or death within 5 years after surgery. Monitoring "depth of anesthesia" is not expected to alter the risk of cancer proliferation after surgery.

心胸手术亚组病人术后谵妄的回顾性临床研究

Postoperative Delirium in a Substudy of Cardiothoracic Surgical Patients in the BAG-RECALL Clinical Trial

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背景：重症监护病房（ICU）发生术后谵妄是心胸外科手术后常见并发症，常伴随致死率和患病率的增加。

方法：在这种单中心研究的 bag-recall 试验（nct00682825），我们筛选病人的心脏或胸部手术后在重症监护病房每日两次使用混乱的评估方法对 ICU 谵妄。主要终点是患者谵妄的发生率被随机分为术中的脑电双频指数（BIS）引导和呼气末麻醉药浓度指导麻醉深度的协议。作为一个次要的分析，贝叶斯随机搜索变量选择策略被用来排名的一场谵妄的候选危险因素，其次是二元 Logistic 回归。

结果：评估的 310 例患者中，28，149（18.8%）在二组和 45 的 161（28%）在呼气末麻醉药浓度组术后谵妄在重症监护病房（比值比 0.60，95%置信区间，0.35-1.02，P = 0.058）。低挥发性麻醉剂的剂量，术中输血，ASA，和欧洲心脏手术风险评估系统被确定为谵妄的独立预测因素。

结论：一个更大规模的随机研究应确定是否与心脏或胸部手术后 BIS 或替代的方法减少谵妄脑监测。较低的药物浓度和谵妄之间的关联是一个惊人的发现，可能反映了患者的身体差是更敏感的挥发性麻醉药物的影响，也更容易发生术后谵妄。为了防止谵妄的候选方法的调查应在既定的联合术后谵妄和不良预后之间的观点优先。

(李春译 薛张纲校)

BACKGROUND: Postoperative delirium in the intensive care unit (ICU) is a frequent complication after cardiac or thoracic surgery and is associated with increased morbidity and mortality.

METHODS: In this single-center substudy of the BAG-RECALL trial (NCT00682825), we screened patients after cardiac or thoracic surgery in the ICU twice daily for delirium using the Confusion Assessment Method for the ICU. The primary outcome was the incidence of delirium in patients who had been randomized to intraoperative Bispectral Index (BIS)-guided and end-tidal anesthetic concentration-guided depth of anesthesia protocols. As a secondary analysis, a Bayesian stochastic search variable selection strategy was used to rank a field of candidate risk factors for delirium, followed by binary logistic regression.

RESULTS: Of 310 patients assessed, 28 of 149 (18.8%) in the BIS group and 45 of 161 (28.0%) in the end-tidal anesthetic concentration group developed postoperative delirium in the ICU (odds ratio 0.60, 95% confidence interval, 0.35-1.02, $P=0.058$). Low average volatile anesthetic dose, intraoperative transfusion, ASA physical status, and European System for Cardiac Operative Risk Evaluation were identified as independent predictors of delirium.

CONCLUSIONS: A larger randomized study should determine whether brain monitoring with BIS or an alternative method decreases delirium after cardiac or thoracic surgery. The association between low anesthetic concentration and delirium is a surprising finding and could reflect that patients with poor health are both more sensitive to the effects of volatile anesthetic drugs and are also more likely to develop postoperative delirium. Investigation of candidate methods to prevent delirium should be prioritized in view of the established association between postoperative delirium and adverse patient outcomes.

局部组合法治疗微血管功能障碍引起慢性缺血后疼痛

Topical Combinations to Treat Microvascular Dysfunction of Chronic Postischemia Pain.

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背景：越来越多的证据表明：复杂区域疼痛综合征(CRPS)患者的皮肤，肌肉血管和神经组织存在微血管功能障碍并因此组织学有异常表现。我们测试了旨在改善微血管功能的局部组合法是否可以缓解 CRPS 动物模型的异常疼痛。我们假设局部给予 $\alpha 2$ -肾上腺素受体激动剂($\alpha 2A$)或一氧化氮(NO)以增加动脉血流，结合磷脂酸(PA)或磷酸二酯酶(PDE)抑制剂以增加毛细血管血流量，可以有效地缓解 CRPS 动物模型的异常疼痛以及微血管功能障碍。

方法：使用慢性缺血后疼痛(CPIP)的方法诱导大鼠的后爪产生机械性异常疼痛。在使用单药或者多药联合的前后分别评估异常疼痛的情况，药物包括 $\alpha 2A$ (阿普可乐定)或者可以产生 NO 的林西多明，PA 或者 PDE 抑制剂(利索茶碱，可可碱)。局部联合使用阿普可乐定+利索茶碱的组合也进行了评价，观察了其对 CPIP 大鼠微血管功能(闭塞后反应性充血)和组织的氧化能力的影响。

结果：对于 CPIP 大鼠，每个局部使用的药物都可以产生明显的剂量依赖性镇痛作用 (N=30)。联合使用了低于镇痛剂量的 $\alpha 2A$ 受体激动剂或者 NO 前体药物后，PA 和 PDE 抑制剂的剂量反应曲线左移了 5 到 10 倍(N=28)。 $\alpha 2A$ 受体激动剂或者 NO 前体药物联合 PA 或者 PE 抑制剂对于同侧肢体可以产生强效的抗异常疼痛作用但是对侧肢体却影响甚微(N=28)。局部组合法的疗效可以持续长达 6 小时(N=15)，并且全身使用低剂量普瑞巴林早期可以显著增强局部组合法的作用但是并不持久(N=18)。同时还发现阿普可乐定+利索茶碱的组合可以有效地减轻 CPIP 大鼠闭塞后反应性充血(N=61)，并增加缺血后组织(皮肤和肌肉)生成甲贍(N=56)。

结论：本研究结果支持我们提出的假设： $\alpha 2A$ 受体激动剂或者 NO 前体 联合 PA 或者 PDE 抑制剂的局部组合疗法可以明显缓解 CRPS 动物模型的异常疼痛。这表明，局部治疗通过增加动脉和毛细血管血流从而改善微血管功能，对于 CRPS 可以发挥有效的治疗作用。

(凌晓敏译 薛张纲校)

BACKGROUND:Growing evidence indicates that patients with complex regional pain syndrome(CRPS) exhibit tissue abnormalities caused by microvascular dysfunction in the blood vessels of skin, muscle, and nerve. We tested whether topical combinations aimed at improving microvascular function would relieve allodynia in an animal model of CRPS. We hypothesized that topical administration of either $\alpha 2$ -adrenergic ($\alpha 2A$) receptor agonists or nitric oxide (NO) donors given to increase arterial blood flow, combined with either phosphatidic acid (PA) or phosphodiesterase (PDE) inhibitors to increase capillary blood flow, would effectively reduce allodynia and signs of microvascular dysfunction in the animal model of chronic pain.

METHODS:Mechanical allodynia was induced in the hindpaws of rats with chronic postschemiapain (CPIP). Allodynia was assessed before and after topical application of vehicle, single drugs or combinations of an $\alpha 2A$ receptor agonist (apraclonidine) or an NO donor (linsidomine), with PA or PDE inhibitors (lisofylline, pentoxifylline). A topical combination of apraclonidine + lisofylline was also evaluated for its effects on a measure of microvascular function (postocclusive reactive hyperemia) and tissue oxidative capacity (formazan production by tetrazolium reduction) in CPIP rats.

RESULTS:Each of the single topical drugs produced significant dose-dependent antiallodynic effects compared with vehicle in CPIP rats (N = 30), and the antiallodynic dose-response curves of either PA or PDE inhibitors were shifted 5- to 10-fold to the left when combined with nonanalgesic doses of $\alpha 2A$ receptor agonists or NO donors (N = 28). The potent antiallodynic effects of ipsilateral treatment with combinations of $\alpha 2A$ receptor agonists or NO donors with PA or PDE inhibitors were not reproduced by the same treatment of the contralateral hindpaw (N = 28). Topical combinations produced antiallodynic effects lasting up to 6 hours (N = 15) and were significantly enhanced by low-dose systemic pregabalin in early, but not late, CPIP rats (N = 18). An antiallodynic topical combination of apraclonidine + lisofylline was also found to effectively relieve depressed postocclusive reactive hyperemia in CPIP rats (N = 61) and to increase formazan production in postschemic tissues (skin and muscle) (N = 56).

CONCLUSIONS:The present results support the hypothesis that allodynia in an animal model of CRPS is effectively relieved by topical combinations of $\alpha 2A$ receptor agonists or NO donors with PA or PDE inhibitors. This suggests that topical treatments aimed at improving microvascular function by increasing both arterial and capillary blood flow produce effective analgesia for CRPS.

在神经刺激器引导下的垂直锁骨下阻滞对脊髓后索和内侧的比较：一项随机性的临床试验

A Comparison of Posterior and Medial Cord Stimulation for Neurostimulation-Guided Vertical Infraclavicular Block: A Randomized Noninferiority Clinical Trial

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背景：我们研究的是是否在垂直锁骨下阻滞，脊髓内侧刺激不如脊髓后索刺激成功。

方法：96 例择期上肢手术患者被随机抽选出进行脊髓背索或脊髓内侧阻滞，用 40 毫升 0.5% 罗哌卡因进行锁骨下阻滞。我们评估了阻滞成功（在前臂的 5 条神经有完整的感觉阻滞达到 50 分钟）从最初的结束点到阻滞过程的特点到有不良事件的第二结束点。

结果：阻滞成功率在脊髓内侧和后索的电刺激之间没有显著的不同（95.7% [44/46] vs 91.7% [44/48], 95% CI of difference, -7.4% to 15.6%），即使把两组次要终点都考虑在内。

结论：在神经刺激仪指导下的垂直进针的锁骨下阻滞，引起的脊髓内侧的反应劣于脊髓背索的反应。

（徐峥译 薛张纲校）

BACKGROUND: We investigated whether medial cord stimulation is inferior to posterior cord stimulation for vertical infraclavicular block with respect to block success.

METHODS: Ninety-six patients scheduled for upper limb surgery were randomly elicited a medial or posterior cord response for infraclavicular block using 40 mL of 0.5% ropivacaine. We assessed block success (complete sensory block of the 5 nerves in the forearm at 50 minutes) as the primary end point and block procedure characteristics and adverse events as secondary end points.

RESULTS: The block success rates did not differ significantly between medial and posterior cord stimulation (95.7% [44/46] vs 91.7% [44/48], 95% CI of difference, -7.4% to 15.6%), while the secondary end points were comparable in both groups.

CONCLUSIONS: Needle manipulation to elicit medial cord response is noninferior to posterior cord response of block success during neurostimulation-guided vertical infraclavicular block

成人体外膜肺氧合：抗凝监测及输血的回顾

Extracorporeal membrane oxygenation in the adult: a review of anticoagulation monitoring and transfusion.

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体外膜肺氧合（ECMO）是一种控制心肺功能的生命支持的方法。自从将 ECMO 用于治疗复杂的病情，如急性呼吸衰竭综合征，心肌缺血、心肌病及脓毒症性休克，其作为一种医疗手段的用途大大增加了。在接受 ECMO 的患者中最常见的并发症是出凝血病，同时

还有神经系统及肾脏损害。ECMO 与促使机体进入高凝状态的炎症反应有关，常需要使用抗凝药来防止非血管内皮表面网罗的血小板的产生。然而过度的抗凝可能会导致包括颅内出血等出血性并发症。对 ECMO 的抗凝监测最初起源于心脏外科手术的心肺流转术。然而目前仍缺乏抗凝的理想水平及标准化方法来监测抗凝，对抗凝治疗的药物同样缺乏标准化规范。在近期手术开始时，在抗凝治疗的同时使用多种血制品来减少出血，通常会导致接受 ECMO 的患者费用的增加及引发输血相关的并发症。在本综述中，我们讨论了 ECMO 治疗的方式的进展，适应症，禁忌症及并发症等。此外，我们回顾了在接受 ECMO 时不同的抗凝治疗策略及凝血的治疗。最后，我们讨论了 ECMO 的费用及相关的血液制品输送问题。

（王赞译，李士通校）

Extracorporeal membrane oxygenation (ECMO) is a method of life support to maintain cardiopulmonary function. Its use as a medical application has increased since its inception to treat multiple conditions including acute respiratory distress syndrome, myocardial ischemia, cardiomyopathy, and septic shock. While complications including neurological and renal injury occur in patients on ECMO, bleeding and coagulopathy are most common. ECMO is associated with an inflammatory response promoting a hypercoagulable state, requiring anticoagulation to avoid thromboembolism originating in the nonendothelial surfaced circuit. However, excessive anticoagulation may result in bleeding complications including intracerebral hemorrhage. Monitoring anticoagulation for ECMO has its origins in cardiopulmonary bypass for cardiac surgery; however, there is no ideal level of anticoagulation, no standardized method to monitor anticoagulation, nor are all centers standardized on what is used for anticoagulation. Multiple blood products are used in an effort to decrease bleeding in the setting of anticoagulation, often in the setting of recent surgery, and this leads to significant increases in cost for patients on ECMO and transfusion-related complications. In this review article, we discuss the evolution of the various modalities of ECMO, indications, contraindications, and complications. Furthermore, we review the different strategies for anticoagulation and treatment of coagulopathy while on ECMO. Finally, we discuss the cost of ECMO and associated blood product transfusion.

血清 MMP-8 和 TIMP-1 在急性呼吸衰竭危重患者中的作用：TIMP-1 与 90 天病死率增加有关

Serum MMP-8 and TIMP-1 in Critically Ill Patients with Acute Respiratory Failure: TIMP-1 Is Associated with Increased 90-Day Mortality.

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背景：基质金属蛋白酶（MMPS）可能在急性肺损伤的病理生理中起到重要作用。近期的研究中，急性呼吸衰竭（ARDS）儿科患者的气道灌洗液 MMP-8 水平越高预后越差。脓毒症患者中，MMPS 及基质金属蛋白酶抑制因子（TIMPs）比例失调常与低生存率有关。我们假设全身性 MMP-8 和 TIMP-1 升高与急性呼吸衰竭预后有关。

方法：该研究是在 25 个芬兰的重症监护室内进行的逾期超过 8 周的 FINNALI 观察试验的亚组研究。所有入组患者均大于 16 周岁并使用机械通气超过 6 小时。分别采集了入组时及 48 小时后的血液样本，并分析其 MMP-8 和 TIMP-1 水平。实验室检查方法采用了免疫荧光测量法检测 MMP-8，ELISA 法检测 TIMP-1。对比了 90 天存活组和死亡组的 MMP-8 和 TIMP-1 水平。存活组组间比较了 TIMP-1 水平的四分位离差，采用 ROC 分析计算了曲线下面积，并且分析了 MMP-8 和 TIMP-1 水平和低氧血症程度的关系。

结果：最后入组的 563 名患者中死亡组入组时 TIMP-1 水平较高，中位数为 367 ng/mL（四分位区间=199-562），存活组中位数为 240 ng/mL（四分位区间=142-412），WMW 比为 1.68（95%可信区间=1.43-2.08）。存活组和死亡组 MMP-8 水平有可能有差异，WMW 比为 1.20（95%可信区间=1.01-1.43），但是 MMP-8/TIMP-1 的摩尔比没有发现明显差异，WMW 比为 0.83（95%可信区间= 0.67-1.04）。存活组组间 TIMP-1 的四分位离差有明显差异（log-rank 检验， $P < 0.001$ ）。ROC 分析计算了 TIMP-1 的曲线下面积为 0.63（95%可信区间=0.58-0.69）。TIMP-1 与低氧血症严重程度有关，在整个队列中 ARDS 亚组的 TIMP-1 较高，WMW 比为 1.65（95%可信区间=1.15-2.44）。

结论： MMP-8 水平在 90 天死亡组中更高，但不能够预测预后。在大部分机械通气的危重患者中和 ARDS 亚组患者中升高的全身性 TIMP-1 与低氧血症程度和预后差有关。

（盛嘉君 译，李士通 审校）

BACKGROUND: Matrix metalloproteinases (MMPs) likely have an important role in the pathophysiology of acute lung injury. In a recent study, high matrix metalloproteinases (MMP-8) levels in tracheal aspirates of pediatric acute respiratory distress syndrome (ARDS) patients were associated with worse outcome. In patients with sepsis, an imbalance between MMPs and their tissue inhibitors (TIMPs) has been associated with impaired survival. We hypothesized that the elevated systemic MMP-8 and TIMP-1 are associated with worse outcome in acute respiratory failure.

METHODS: This was a substudy of the observational FINNALI study conducted in 25 Finnish intensive care units over an 8-week period. All patients older than 16 years requiring mechanical ventilation for >6 hours were included. MMP-8 and TIMP-1 levels were analyzed from blood samples taken on enrollment in the study and 48 hours later. Laboratory analyses were performed by using immunofluorometric assay for MMP-8 and ELISA for TIMP-1. MMP-8 and TIMP-1 levels were compared between 90-day survivors and nonsurvivors. Survival was compared in quartiles based on TIMP-1 levels, and ROC analysis was performed to calculate areas under the curves. The relationship between MMP-8 and TIMP-1 levels and degree of hypoxemia was examined.

RESULTS: The final analyses included 563 patients. Admission TIMP-1 levels were higher in nonsurvivors, median 367 ng/mL (interquartile range 199-562), than survivors, median 240 ng/mL (interquartile range 142-412), WMW odds 1.68 (95% confidence interval [CI], 1.43-2.08). MMP-8 levels may have differed between survivors and nonsurvivors, WMW odds 1.20 (95% CI, 1.01-1.43), but no difference was found in the MMP-8/TIMP-1 molar ratio, WMW odds 0.83 (95% CI, 0.67-1.04). Difference in survival between quartiles based on TIMP-1 was significant (log-rank, $P < 0.001$). ROC analysis produced an area under the curve 0.63 (95% CI, 0.58-0.69) for TIMP-1. TIMP-1 was associated with severity of hypoxemia. TIMP-1 levels were higher in an ARDS subgroup than in the whole cohort, WMW odds 1.65 (95% CI, 1.15-2.44).

CONCLUSIONS: MMP-8 levels were possibly higher in 90-day nonsurvivors but performed poorly in predicting outcome. Increased systemic levels of TIMP-1 were associated with more severe hypoxemia and worse outcome in a large cohort of mechanically ventilated critically ill patients and in a subgroup of ARDS patients.

年轻和年老患者在七氟烷和瑞芬太尼麻醉下进行择期腰椎外科手术时的血浆食欲素水平的变化情况

Changes in plasma orexin-a levels in sevoflurane-remifentanyl anesthesia in young and elderly patients undergoing elective lumbar surgery.

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背景：年老患者在全身麻醉的情况下经常出现觉醒延迟，但具体原因不详。食欲素已被证明参与全身麻醉的觉醒。在此研究中，我们研究了在麻醉觉醒周期中老年和年轻患者血浆食欲素 A 的水平情况。

方法：我们招募了 41 例进行择期腰椎手术的患者，最终评估 34 例患者。患者被分配到年轻组（年龄 30-55，N=16）和老年组（年龄 65-77，N=18）。七氟醚复合瑞芬太尼麻醉滴定保持 45 和 65 之间的脑电双频指数。记录从停止麻醉到眼睛睁开和开始拔管的时间。采集动脉血，用放射免疫法测定以下四个时间点的血浆食欲素-A 的水平：麻醉前（T0），诱导麻醉后 1h(T1),出现（气管拔管后 5 分钟）（T2），和气管拔管后 30 分钟（T3）。

结果：老年组从停止麻醉到眼睛睁开和气管拔出的时间均长于年轻组（分别为 $P=0.004$ ， $P=0.01$ ）。基础（T0）食欲素-A 在老年组的水平高于年轻组（T0， 26.13 ± 1.25 vs 17.9 ± 1.30 pg/mL, $P < 0.0001$ ）。血浆食欲素-A 的水平在麻醉诱导时没有变化，而在 T2 时老年组（ 35.0 ± 1.7 pg/mL）和年轻组（ 29.2 ± 1.9 pg/mL）均出现显著性增加（vs T0, $P < 0.0001$ ）。在 T1, T2 和 T3，老年组血浆食欲素-A 的水平均明显高于年轻组。

结论：血浆食欲素-A 的水平并不能说明老年患者全身麻醉觉醒的延迟。

（董静译 李士通校）

BACKGROUND: Delayed emergence from general anesthesia frequently occurs in elderly patients, but the reason is not clear. Orexin has been shown to be involved in arousal from general anesthesia. In this study, we examined plasma orexin-A levels in both elderly and young patients during the anesthesia arousal cycle.

METHODS: We recruited 41 patients scheduled for elective lumbar surgery

and eventually evaluated 34 patients. Patients were divided into a young group (age 30-55, N = 16) and an elderly group (age 65-77, N = 18). Anesthesia with sevoflurane-remifentanyl was titrated to maintain the Bispectral Index between 45 and 65. The times from stopping anesthesia to eyes opening and extubation were recorded. Arterial blood was collected, and plasma orexin-A was determined by radioimmunoassay at the following 4 time points: preanesthesia (T0), 1 hour after anesthesia induction (T1), emergence (5 minutes after tracheal extubation) (T2), and 30 minutes after tracheal extubation (T3).

RESULTS: The times from stopping anesthesia to eyes opening and tracheal extubation were both significantly longer in the elderly group than in the young group ($P = 0.004$, $P = 0.01$, respectively). Basal (T0) orexin-A levels were higher in the elderly group than in the young group (T0, 26.13 ± 1.25 vs 17.9 ± 1.30 pg/mL,

$P < 0.0001$). Plasma orexin-A levels did not change during induction of anesthesia in either group but significantly increased at T2 (vs T0, $P < 0.0001$) in both elderly (35.0 ± 1.7 pg/mL) and young (29.2 ± 1.9 pg/mL) groups. Orexin-A levels were significantly higher in the elderly than in the young group at T1, T2, and T3.

CONCLUSION: Plasma orexin-A levels are not responsible for the delayed emergence from general anesthesia in elderly patients.

大鼠模型中鞘内注射 JWH015 可通过抑制脊髓胶质细胞的激活减轻瑞芬太尼导致的术后痛觉过敏

Intrathecal Injection of JWH015 Attenuates Remifentanyl-Induced Postoperative Hyperalgesia by Inhibiting Activation of Spinal Glia in a Rat Model.

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背景：痛觉过敏和神经炎症均与胶质细胞有关，胶质细胞由星形细胞和小胶质细胞组成。本研究中，我们使用了一种选择性大麻素 2 型受体（CB2）激动剂 JWH015 来研究瑞芬太尼导致的术后痛觉过敏。

方法：在术后痛觉过敏及鞘内注射 JWH015 后，我们使用机械刺激缩足反射阈值和热刺激缩足反射潜伏期试验来测定机械刺激痛和热痛觉过敏。在大鼠由瑞芬太尼导致的术后痛觉过敏处理后，我们使用免疫组化和免疫印迹来研究 JWH015 对 CB2 受体、NR2B 亚组、激活的神经胶质细胞以及促炎性细胞因子的表达。

结果：术中输注瑞芬太尼导致了术后痛觉过敏。神经胶质细胞被激活，并且某些基因的表达水平显著增高，其中包括白细胞介素 6、肿瘤坏死因子 α 、CB2 和 Tyr-1472 磷酸化 NR2B 亚组(p-NR2B)。鞘内注射 JWH015 显著抑制神经胶质细胞的激活，并抑制白细胞介素 6、肿瘤坏死因子 α 、p-NR2B 和 CB2 的表达，因此减轻了术后痛觉过敏。然而，在提前使用 AM630 的组中这些现象并不存在。

结论：在瑞芬太尼导致的术后痛觉过敏过程中，神经胶质细胞的激活、促炎性细胞因子产物和脊髓背角中 CB2 及 p-NR2B 的表达显著增加。这些改变可以通过使用 JWH015 预处理来控制，这或许是 JWH015 抗痛觉过敏的主要机制。

（张怡译，李士通审校）

BACKGROUND: Hyperalgesia and neuroinflammation are associated with glia, which consists of macroglia and microglia. In this study, we used a selective cannabinoid receptor type 2 (CB2) agonist JWH015 to investigate remifentanil-induced postoperative hyperalgesia.

METHODS: Mechanical allodynia and thermal hyperalgesia after postoperative hyperalgesia and intrathecal injection of JWH015 were assessed by the paw withdrawal mechanical threshold and paw withdrawal thermal latency tests. We used immunohistochemistry and immunoblotting to investigate the effect of JWH015 on CB2 receptor, NR2B subunits, activated glial cells, and proinflammatory cytokine expression in rats after remifentanil-induced postoperative hyperalgesia.

RESULTS: Postoperative hyperalgesia was induced by intraoperative infusion of remifentanil. Glial cells were activated, and expression levels of several genes were significantly increased, including interleukin 6, tumor necrosis factor α , CB2, and the NR2B subunit phosphorylated at Tyr-1472 (p-NR2B). Intrathecal injection of JWH015 significantly inhibited glial cell activation, suppressed expression of interleukin 6, tumor necrosis factor α , and p-NR2B, and stimulated CB2 expression, thus attenuating postoperative hyperalgesia. However, these phenomena were abolished in the group that was preadministered with AM630.

CONCLUSIONS: The activation of glia, the production of proinflammatory cytokines, and the expression of CB2 and p-NR2B in the spinal dorsal horn increase significantly during the process of remifentanil-induced hyperalgesia. These changes can be regulated by pretreatment with JWH015, which may be the main mechanism underlying the antihyperalgesia effects of JWH015.

年龄对鞘内阻滞运动神经所需布比卡因 ED50 的影响

The Effect of Age on the Median Effective Dose (ED50) of Intrathecally Administered Plain Bupivacaine for Motor Block

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背景：在这项研究中，我们探讨给予 20-80 岁患者通过鞘内注射布比卡因进行运动神经阻滞的 ED50，评估年龄对运动神经阻滞所需 ED50 的影响。

方法：研究选择了 129 例在腰硬联合下进行前列腺，泌尿外科，下肢手术的患者。根据年龄将患者分层如下：20-30 岁，31-40 岁，41-50 岁，51-60 岁，61-70 岁，71-80 岁。腰麻的药量是根据 Dixon 法给予 0.75% 布比卡因。经鞘内给予每一剂量的运动神经阻滞的程度通过修改过的 Bromage 和髋关节运动功能得分来评估。ED50 值通过 Dixon，Massey 和逻辑回归来评估。其他终点指标包括感觉阻滞程度的偏倚，神经阻滞的耐受，低血压，血管加压药的需要量。

结果：鞘内阻滞运动神经所需布比卡因的 ED50 为 20-30 岁 10.22mg (95% CI 9.96-10.49mg)，31-40 岁 9.52mg (95% CI 9.02-10.07mg)，41-50 岁 8.37mg (95% CI 7.56-9.26 mg)，51-60 岁 7.30 mg (95% CI, 6.84-7.79 mg)，61-70 岁 6.55 mg (95% CI, 6.01-7.13 mg)，71-80 岁 5.78 mg (95% CI, 5.01-6.67 mg)。经鞘内给予布比卡因的六个年龄组中，最高的头侧镇痛水平为 5min 时为 L1-L2，10min 时为 T10-L1 水平。运动神经阻滞的持续上在组间有明显差异。

结论：鞘内进行运动神经阻滞所需布比卡因的 ED50 随年龄增长而急剧减少。

(王晓莉译 李士通校)

BACKGROUND: In this study, we sought to determine the median effective dose (ED50) for motor block of intrathecally administered plain bupivacaine in adults (20-80 years) and to assess the effect of age on ED50 required for motor block.

METHODS: This study was performed in 129 adult patients undergoing transurethral, urological, or lower limb surgery under combined spinal and epidural anesthesia. Patients were stratified according to age as follows: 20 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, and 71 to 80 years. The spinal component of the anesthetic was established by bolus administration of up-and-down doses of 0.75% plain bupivacaine, determined by Dixon's method. The degree of motor block after intrathecal administration of each dose was evaluated by the modified Bromage and hip motor function score. The ED50 values were estimated from the up-and-down sequences using the method of Dixon and Massey and logistic regression. Other end points were included on the basis of sensory block level, duration of motor blockade, hypotension, and vasopressor requirements.

RESULTS: ED50 for motor block using intrathecal bupivacaine was 10.22 mg (95% confidence interval [CI], 9.96-10.49 mg) in 20- to 30-, 9.52 mg (95% CI, 9.02-10.07 mg) in 31- to 40-, 8.37 mg (95% CI, 7.56-9.26 mg) in 41- to 50-, 7.30 mg (95% CI, 6.84-7.79 mg) in 51 to 60, 6.55 mg (95% CI, 6.01-7.13 mg) in 61- to 70-, and 5.78 mg (95% CI, 5.01-6.67 mg) in 71- to 80-year-old patients.

The maximum cephalic analgesic level was L1-L2 level at 5 minutes and T10-L1 at 10 minutes after administration of intrathecal plain bupivacaine in the 6 age groups. There was a significant difference in the duration of motor blockade among groups.

CONCLUSION: The ED50 for motor block of intrathecally administered plain bupivacaine decreased steeply with advancing age.

临终诊断

Diagnosing Dying

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作为麻醉与危重症医师，我们有责任识别出垂死的患者并关注涉及生命末期的诸多问题。仅有 45% 的患者认识到他们的生命即将结束，而大部分的患者并没有意识到自身病情的严峻性，如果他们了解实际，则可能会做出其他的选择。基于此，我们的这项工作至关重要。例如，即使大多数人并不希望在医院中过世，医院却仍是超过半数人的临终地。在英国有 58% 的患者死于医院，美国也有超过 20% 的人在重症监护病房（ICU）去世。不仅是患者的“浑然不觉”（或抗拒现实），同时可能病情很难去评估或定位，而且他们的助阵医生也拒绝接受现实。医生们更倾向于对患者的存活抱过高期望，特别是对熟悉的患者更是如此。如果我们意识到一名患者正走向死亡，什么时候将治疗转变为临终关怀，这个转变的确是一项对理智的挑战。医生短期内（数天到数周）预测结果的能力不见得很好，但是较长期的（数周到数月）预测会更准一点，而预测精准的能力对于患者及其家人关于临终治疗的决定有着深远影响，当面对毫无恶意的患者这一点显得特别重要。识别出死亡进程顾及到一项计划的发展，涉及减轻症状，涉及减压患者及其家人讨论希望和偏好，涉及事前承诺的兑现以及向姑息性治疗和临终关怀的转变。我们相信麻醉和危重症医学对生命末期的诸多问题需要更多的关注，在患者临终前高科技的使用，目标评估和垂危计划的制定，还有那些将承受高风险的外科手术的决定。

（赵晓译 李士通校）

As anesthesiologists and intensivists, we have a responsibility to recognize the dying patient and to be more involved in end-of-life issues. This is essential because only about 45% of patients actually recognize that they are, indeed, dying, and more than half of patients then are not aware of the gravity of their situation. If they were, they might choose other options. For example, although a majority of the population does not wish to die in a hospital, more than half do so. Fifty-eight percent of patients in the United Kingdom die in a hospital, and over 20% of U.S. deaths occur in an intensive care unit (ICU). Not only are patients “unaware” (or in denial), either of which may be difficult to assess or address, but their primary physician may also be in denial. Physicians tend to overestimate patient survival, especially if they are familiar with the patient. If we recognize that a patient is dying, when does one transition from cure to palliative care, a transition that is truly an intellectual challenge? Physicians’ ability to predict outcome is not particularly good in the short term (days to weeks) but better in the long term (weeks to months) and the ability to prognosticate accurately has a profound influence on patients’ and families’ decisions regarding end-of-life care, which can be especially difficult when dealing with patients who do not have a malignancy. Recognition of the dying process allows for development of a plan to alleviate symptoms, facilitation of patient discussions with family regarding wishes and preferences, implementation of advanced directives, and transition to palliative and comfort care. We believe that anesthesiologists and intensivists need to become more involved in end-of-life issues, the use of advanced technology for patients at the end of their lives, goal assessment and planning for the critically ill, and decisions for those about to undergo high-risk surgical procedures.