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以快速起效爲特徵的水溶性丙泊酚前體藥的改良設計

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：設計丙泊酚的磷酸酯前體藥物（磷丙泊酚，HX0969W）是爲了避開母體藥物水溶性較差的特點。但在先前的臨床試驗中發現前體藥物有感覺異常和瘙癢的副作用，其主要原因是磷酸酯堆積。爲了規避這一潛在風險，本研究設計了兩種含氨基酸的丙泊酚前體藥物(HX0969-Gly-F3, HX0969-Ala-HCl)，即在前體藥物的先導化合物 HX0969 結構中加入氨基酸族。本研究假設改進後丙泊酚前體藥物不僅能消除副作用，也能保留其快速起效和優良的水溶性的特點。

方法：先導化合物 HX0969 由硼氫化鈉碘族合成。HX0969W, HX0969-Gly-F3, HX0969-Ala-HCl 均由 HX0969 合成。磷丙泊酚，HX0969W, HX0969-Gly-F3 和 HX0969-Ala-HCl 在生理鹽水中的溶解度已得到測試。這些前體藥在不同生理介質中（大鼠血漿，恒河猴血漿以及大鼠肝細胞微粒體）的生物轉化在體外試驗中已經確認。在鼠的在體試驗中測定四種前體藥的 50%有效劑量（ED50）。同時測定給予等效劑量後的起效時間和持續時間。

結果：(1) 磷丙泊酚, HX0969W, HX0969-Gly-F3 和 HX0969-Ala-HCl 的水溶解度分別爲 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) 在大鼠血漿和恒河猴血漿水解實驗中，5h 內兩種含氨基酸的前體藥較另兩種磷酸酯前體

藥能以更快的速度大量釋放丙泊酚。所有四種前體藥在大鼠肝酶存在的情況下均能迅速釋放丙泊酚；(3) 與之前的前體藥（磷丙泊酚，HX096W）相比，兩種新化合物(HX0969-Gly-F3, HX0969-Ala-HCl)在給予較小劑量時起效時間更短。

結論：在丙泊酚前體藥物中加入氨基酸族可以使藥物具有更佳的水溶性和更快的起效速度。在大鼠血漿中，兩種含氨基酸的前體藥(HX0969-Ala-HCl, HX0969-Gly-F3)釋放丙泊酚的速度較兩組磷酸酯前體藥(磷丙泊酚, HX0969W)更快。在體實驗顯示靜脈給予 HX0969-Ala-HCl 和 HX0969-Gly-F3，劑量較磷丙泊酚和 HX0969W 更小，但起效卻更快。新設計提高了前體藥轉化爲丙泊酚的效能。

（陸秉瑋 譯 陳傑 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.

減輕手術室火災：一種二氧化碳防火裝置的開發

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

Culp, William C. Jr MD; Kimbrough, Bradly A.; Luna, Sarah AA; Maguddayao, Aris J. AA

Anesthesia & Analgesia 2014 118 772–775

手術室火災是對外科病人有實質性危險的警訊事件，發生的頻率至少與手術部位錯誤的發生率相當。發生火災的三個要素是：氧化劑、火源、可燃物質。手術的電灼器是大多數手術室火災的觸發因素。CO2 是一種可以通過替換氧氣來預防和抑制火災的氣體。本研究設想可以製作一種通過在電灼筆尖周圍產生 CO2 錐形氣柱的方法來減少手術室火災的裝置。通過安裝與 CO2 源相連的分散噴嘴使此種裝置成爲現實。將其安裝在手術電灼筆尖上，可以使筆尖包裹在 CO2 的錐形氣柱內。在 21%、50%、100%的氧環境中檢測這種裝置。以 50 W 的電切模式打開手術電灼筆，放在置於鋁板上的剖腹手術綿上 30 秒或直至手術綿被點燃。用高速攝像裝置來識別點燃的時間。CO2 流量爲 8 L/分，與沒有 CO2 裝置的對照組相比較，在每一種氧環境中檢測 5 次。另外，用一項 CO2 採樣裝置來製作 CO2 濃度的三維空間圖。對照組在 21%、50%和 100%氧環境下的點燃時間均數±標準差（範圍）分別爲 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]。對照組均被點燃（15/15）；而應用裝置組均未被點燃(0/15, P < 0.0001)。手術電灼筆尖末端的 CO2 濃度爲 95%，在距筆尖 1 到 1.4 釐米水準的平均 CO2 濃度爲 64%。總之，可以通過使用 CO2 發射噴嘴，產生錐形的滅火氣場來製作手術室火災的預防裝置。以上演示證明這種裝置在可燃情況下可有效地降低火災風險。 CO2 的三維空間圖表明當 CO2 流量爲 8 L/min 時至少在離手術電灼筆筆尖 1 釐米的範圍內可以有效降低火災。下一步測驗應該探索最佳的 CO2 流量和理想的噴嘴形狀。利用這種裝置可以顯著減少手術室火災對病人損傷的風險。

（朱浩 譯 陳傑 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.

苯腎上腺素導致的由空間分辨近紅外光譜原理測定的前額腦氧飽和度的下降可以反映皮膚血流的下降

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

Ogoh, Shigehiko PhD*; Sato, Kohei PhD†; Okazaki, Kazunobu PhD‡; Miyamoto, Tadayoshi PhD§; Secher, Frederik ‖ ; Sørensen, Henrik PhD ‖ ; Rasmussen, Peter PhD¶; Secher, Niels H. MD, DMSc ‖

Anesthesia & Analgesia 2014 118 823–829

背景：給予苯腎上腺素後，用空間分辨近紅外光譜學測定的前額氧飽和度(ScO2)是下降的，但腦血流未受影響。本研究假設苯腎上腺素對 ScO2 的影響是由顱外血管收縮導致的。

方法：選取 7 名志願者（平均年齡±標準差爲 25±4 歲），靜脈輸注苯腎上腺素，期間通過二維超聲監測頸內動脈和頸外動脈 ScO2 及椎動脈的血流，同時監測大腦中動脈平均血流速率、前額皮膚血流及平均動脈壓。

結果：在苯腎上腺素輸注期間，平均動脈壓增加，同時 ScO2 下降-19%±3%（均數±標準差；P = 0.0005）。頸外動脈及皮膚血流也分別因此下降-27.5%±3.0%、-25.4%±7.8%。並發現 ScO2 依次與前額皮膚血流量（Pearson 相關係數 0.55, P = 0.042, 95% 可信區間 0.025–0.84; Spearman 相關係數 0.81, P < 0.001, 95%可信區間 0.49–0.94）及頸外動脈電導(Pearson 相關係數 0.62, P = 0.019, 95% 可信區間 0.13–0.86; Spearman 相關係數 0.64, P =0.012, 95% 可信區間 0.17–0.88)有關。

結論：此項研究發現經 INVOS-4100 近紅外光譜測定，苯腎上腺素可導致 ScO2 的下降，是由於顱外血管收縮而非腦氧飽和度下降的結果。

（梁玉丹 譯 陳傑 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.

爪部切割和脊神經結紮後大鼠顱內自我刺激、食物維持自發反應和開放域活動的差異性抑制

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

Ewan, Eric E. PhD*; Martin, Thomas J. PhD†

Anesthesia & Analgesia 2014 118 854–862

背景：監測實驗室動物持續自發疼痛行爲一直是個挑戰。大多數臨床前期疼痛研究監測機體對特定體外在害性刺激所引發的行爲反應。然而，人類和動物的持續自發性疼痛也許和高敏性無關，並且可能會減少很多行爲，尤其是動機性行爲，本研究假設急性和慢性疼痛出現後這種行爲會減少。

方法：在本研究中，201 只雄性大鼠接受爪部切割（INC）、L5/L6 脊神經結紮（SNL）或同時接受 INC 和 SNL，並評估這些處理對大鼠縮爪閾值（PWT）的影響。爲了進行對比，也對相同大鼠進行非誘發方法下的行爲學減退效應的評估，包括大腦腹側被蓋區的顱內自我刺激（VTA ICSS）或食物強化（FR）以及開放域活動（OFA）的獎勵性電刺激的按壓杠杆反應。

結果：INC 使得 PWT 降低持續 4 天，VTA ICSS 降低持續 2 天，FR 降低持續 1 天但並未改變 OFA。SNL 導致的 PWT 降低類似於 INC 但並未使 VTA ICSS 或 FR 產生變化；SNL 降低 OFA。同時接受 INC 和 SNL 大鼠，其 PWT、VTA ICSS 和 FR 的變化類似於 INC 組，與 SNL 組相比，，並未降低 OFA。

結論：INC 減少 VTA ICSS 和 FR 按壓杠杆反應（爪部切割後的 1~2 天）的急性效應與 INC 導致的持續自發性疼痛預期產生的時間段相符，因此，這些指標的下降可能是由持續自發疼後預期發生的持續性自發疼痛的時間窗一致。因此這些降低效應可能是持續性自發疼痛所介導的，而這種疼痛與 INC 導致的持續達 4 天的機械性高敏感性無關。INC 大鼠 PWT 的下降與 SNL 大鼠類似，然而自發性行爲（VTA ICSS 和 FR 的按壓杠杆反應）在 SNL 大鼠中並沒有下降。SNL，而不是 INC，降低了飼養行爲而並非持續 OFA 全程。這進一步說明了高敏感性的出現和程度並不能預測大鼠許多行爲的改變，後者原來被認爲是持續疼痛介導後出現的。令人驚訝的是，INC 產生的行爲學效應並沒有加重 SNL 組的結果。這些資料支援了一種新近的觀點：急性疼痛模型會產生短期自發疼痛行爲，這種行爲在神經病理性疼痛模型中比較少見或者不會出現，評估誘發性和非誘發性疼痛行爲在未來研發急性和慢性疼痛治療方案時的必要性。

（邊文玉 譯 陳傑 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.

在小豬中注射超聲凝膠、內毒素、0.9% NaCl，或穿刺但不注射藥物後的神經內和神經周圍炎症性改變

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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Anesthesia & Analgesia 2014 118 4 869–873

背景：已有超聲凝膠性神經炎症的報導。本研究在對豬進行周圍神經阻滯後，比較凝膠注射與內毒素注射（陽性對照），生理鹽水注射，幹針穿刺（陰性對照）後炎症的程度和性質的差異。

方法：用體表標記和神經刺激儀方法定位 12 只豬的選定神經。注射後 48 小時，通過定量聚合酶鏈反應對標本進行免疫細胞分化/量化和細胞因數表達的檢測。

結果：與幹針穿刺和/或鹽水注射相比，凝膠和內毒素注射導致更高密度炎症細胞的產生（淋巴細胞/粒細胞）（兩者 $P < 0.001$）。無論在何種標本中均未檢測到細胞因數。

結論：神經周圍凝膠注射可引起嚴重的炎症。細胞因數的缺乏表明是注射相關的變化，而非機械性創傷。

（談婧華 譯 陳傑 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.

地塞米松呈劑量依賴性地抑制由 Sugammadex 逆轉的體外神經支配的初級人類肌肉細胞

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

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Anesthesia & Analgesia 2014 118 755–763

背景：糖皮質激素在麻醉過程中經常被用來作爲腎上腺皮質功能不全患者的替代治療。其作爲威脅生命條件下的一線治療藥物，用於防止手術後的噁心和嘔吐，以及作爲多模式鎮痛的組成部分。對於後兩者，地塞米松是最經常使用的。由於甾類肌肉鬆弛藥和地塞米松之間的結構相似。有關人士提出了關於可能的糖皮質激素抑制由 sugammadex 提供的神經肌肉阻滯的逆轉效應。因此，我們研究了地塞米松對 sugammadex 逆轉羅庫溴銨引起的神經肌肉阻滯的影響，這可能在某些臨床情況下是相關。

方法：首先在體外用鼠胚胎脊髓外植體培植特殊的人類肌肉細胞功能性神經肌肉接頭培養模型，用於探究 4 和 10μM 羅庫溴銨對肌肉收縮的影響，通過定量計算在收縮陽性的外植體共培養物的收縮單元。接下來，等摩爾和 3 倍等摩爾 sugammadex 用於 4 和 10μM 羅庫溴銨的恢復。最後，用 1，100，和 10μM 地塞米松（正常，升高和高臨床級）來評估其對由 sugammadex 逆轉羅庫溴銨誘導的神經肌肉阻滯的任何影響。

結果：實驗包括了三段時間內培養的時間無關的七十八株外植體，其中收縮的數量增加至 10 天共培養。羅庫溴銨表現出對神經肌肉阻滯深度的時間依賴性效應（4μM 羅庫溴銨：基線，10，20 分鐘給藥，P <0.0001），而劑量依賴性作用接近標稱統計學意義（4,10μM，P =0.080）。這是由等摩爾濃度 sugammadex 的逆轉，進一步的，幾乎完全恢復收縮需 3 倍等摩爾 sugammadex（P <0.0001）。地塞米松減少 sugammadex 逆轉羅庫溴銨誘導的神經肌肉阻滯程度並呈劑量依賴性（P=0.026），10μMsugammadex 上升至 30μM，即接近統計學顯著改善恢復性（P =0.065）。地塞米松最高降低 sugammadex 恢復神經肌肉收縮的等摩爾濃度的 26％。;當 3 倍等摩爾（30μM）sugammadex 時，這種效果更爲顯著，爲 48％。

結論：這是在高度可及的功能性人體神經肌肉細胞的體外實驗模型中地塞米松羅庫溴銨和 sugammadex 相互作用的影響的第一份報告。Sugammadex 逆轉羅庫溴銨引起的神經肌肉阻滯;然而，高濃度的地塞米松能減小 sugammadex 的效率。這需要進一步研究，以確定這些相互作用的臨床意義。

（陳婉南譯 薛張綱校）

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 μM 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 μM rocuronium block. Finally, 1, 100, and 10 μM 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 μM rocuronium: baseline, 10, 20 minutes administration; P < 0.0001), while the dose-dependent effect was close to nominal statistical significance (4, 10 μM; 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 μM sugammadex-induced recovery of contractions from rocuronium-induced neuromuscular block in a dose-dependent manner (P = 0.026) with a higher sugammadex concentration (30 μM) 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 μM) 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.

低腦電雙頻指數值的累積時間與未知惡性腫瘤病人的癌症發生率和已知惡性腫瘤病人的五年死亡率無關。

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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Anesthesia & Analgesia 2014 118 782–787

背景：有一些既往的臨床資料表明麻醉和外科手術可能促進癌症的生長。我們已發現，在術前或術後一月以內沒有惡性腫瘤診斷或病史的患者，在進行全麻，同時 BIS 值低於 45 時，並無增加五年內患癌症的風險。由於已知惡性腫瘤患者的免疫能力不同，我們研究了外科手術中早期或已知惡性腫瘤的病人所對應的風險。

方法：在預期的進行七氟醚麻醉的 766 例進行 BIS 監測的患者，隨訪術後惡性腫瘤的診斷和五年死亡率。在麻醉過程中跟蹤記錄 BIS 值小於 45，應用環氧合酶分析評估癌症的新發生率以及各種原因導致的死亡發生率。

結果：51 位患者（6.7%）術後五年內確診了 54 個惡性腫瘤的診斷。有 387 例癌症病人安排了癌症治療的外科手術，293 位病人（38%）死亡。麻醉與 BIS 值小於 45，以及癌症新發率（風險比例相對爲 0.64-1.11 和 0.76-1.30），以及死亡率（風險比例相對爲 0.85-1.05 和 0.94-1.16 之間）無關。同時，在 BIS 值爲其他值時（小於 30，40，50），也未發現明顯關聯。

結論：未知或已知惡性腫瘤的患者，持續的全身麻醉，或累積的七氟醚複合麻醉與外科術後癌症的新發率和惡性腫瘤的的五年生存率無關。監測下的深度麻醉對於改善惡性腫瘤患者外科術後的腫瘤預後無明顯關係。

（蔣鑫梅譯 薛張綱校）

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.

心胸手術亞組病人術後譫妄的回顧性臨床研究

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

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Anesthesia & Analgesia 2014 118 809–817

背景：重症監護病房（ICU）發生術後譫妄是心胸外科手術後常見併發症，常伴隨致死率和患病率的增加。

方法：在這種單中心研究的 bag-recall 試驗（nct00682825），我們篩選病人的心臟或胸部手術後在重症監護病房每日兩次使用混亂的評估方法對 ICU 譫妄。主要終點是患者譫妄的發生率被隨機分爲術中的腦電雙頻指數（BIS）引導和呼氣末麻醉藥濃度指導麻醉深度的協議。作爲一個次要的分析，貝葉斯隨機搜索變數選擇策略被用來排名的一場譫妄的候選危險因素，其次是二元 Logistic 回歸。

結果：評估的 310 例患者中，28，149（18.8%）在二組和 45 的 161（28%）在呼氣末麻醉藥濃度組術後譫妄在重症監護病房（比值比 0.60，95%置信區間，0.35-1.02，P = 0.058）。低揮發性麻醉劑的劑量，術中輸血，ASA，和歐洲心臟手術風險評估系統被確定爲譫妄的獨立預測因素。

結論：一個更大規模的隨機研究應確定是否與心臟或胸部手術後 BIS 或替代的方法減少譫妄腦監測。較低的藥物濃度和譫妄之間的關聯是一個驚人的發現，可能反映了患者的身體差是更敏感的揮發性麻醉藥物的影響，也更容易發生術後譫妄。爲了防止譫妄的候選方法的調查應在既定的聯合術後譫妄和不良預後之間的觀點優先。

（李春譯 薛張綱校）

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.

局部組合法治療微血管功能障礙引起慢性缺血後疼痛

Topical Combinations to Treat Microvascular Dysfunction of Chronic Postischemia Pain.

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Anesthesia & Analgesia 2014 118 830–840

背景：越來越多的證據表明：複雜區域疼痛綜合征(CRPS)患者的皮膚，肌肉血管和神經組織存在微血管功能障礙並因此組織學有異常表現。我們測試了旨在改善微血管功能的局部組合療法是否可以緩解 CRPS 動物模型的異常疼痛。我們假設局部給予 α 2-腎上腺素受體激動劑(α2A)或一氧化氮(NO)以增加動脈血流，結合磷脂酸(PA)或磷酸二酯酶(PDE)抑制劑以增加毛細血管血流量，可以有效地緩解 CRPS 動物模型的異常疼痛以及微血管功能障礙。

方法：使用慢性缺血後疼痛(CPIP)的方法誘導大鼠的後爪產生機械性異常疼痛。在使用單藥或者多藥聯合的前後分別評估異常疼痛的情況，藥物包括 α 2A(阿普可樂定)或者可以產生 NO 的林西多明，PA 或者 PDE 抑制劑(利索茶鹼，可哥城)。局部聯合使用阿普可樂定+利索茶鹼的組合也進行了評價，觀察了其對 CPIP 大鼠微血管功能(閉塞後反應性充血)和組織的氧化能力的影響。

結果：對於 CPIP 大鼠，每個局部使用的藥物都可以產生明顯的劑量依賴性鎮痛作用(N=30)。聯合使用了低於鎮痛劑量的α2A 受體激動劑或者 NO 前體藥物後，PA 和 PDE 抑制劑的劑量反應曲線左移了 5 到 10 倍(N=28)。α2A 受體激動劑或者 NO 前體藥物聯合 PA 或者 PE 抑制劑對於同側肢體可以產生強效的抗異常疼痛作用但是對側肢體卻影響甚微(N=28)。局部組合法的療效可以持續長達 6 小時(N=15)，並且全身使用低劑量普瑞巴林早期可以顯著增強局部組合法的作用但是並不持久(N=18)。同時還發現阿普可樂定+利索茶鹼的組合可以有效地減輕 CPIP 大鼠閉塞後反應性充血(N=61)，並增加缺血後組織(皮膚和肌肉)生成甲臢(N=56)。

結論：本研究結果支持我們提出的假設：α2A 受體激動劑或者 NO 前體 聯合 PA 或者 PDE 抑制劑的局部組合療法可以明顯緩解 CRPS 動物模型的異常疼痛。這表明，局部治療通過增加動脈和毛細血管血流從而改善微血管功能，對於 CRPS 可以發揮有效的治療作用。

（淩曉敏譯 薛張綱校）

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 α2-adrenergic (α2A) 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 postischemiapain (CPIP). Allodynia was assessed before and after topical application of vehicle, single drugs or combinations of an α2A 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 α2A receptor agonists or NO donors (N = 28). The potent antiallodynic effects of ipsilateral treatment with combinations of α2A 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 postischemic 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 α2A 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.

在神經刺激器引導下的垂直鎖骨下阻滯對脊髓後索和內側的比較：一項隨機性的臨床試驗

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

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Anesthesia & Analgesia 2014 118 874–878

背景：我們研究的是是否在垂直鎖骨下阻滯，脊髓內側刺激不如脊髓後索刺激成功。

方法：96 例擇期上肢手術患者被隨機抽選出進行脊髓背索或脊髓內側阻滯，用 40 毫升 0.5%羅呱卡因進行鎖骨下阻滯。我們評估了阻滯成功（在前臂的 5 條神經有完整的感覺阻滯達到 50 分鐘）從最初的結束點到阻滯過程的特點到有不良事件的第二結束點。

結果：阻滯成功率在脊髓內側和後索的電刺激之間沒有顯著的不同（95.7% [44/46] vs 91.7% [44/48], 95% CI of difference, -7.4% to 15.6%），即使把兩組次要終點都考慮在內。

結論：在神經刺激儀指導下的垂直進針的鎖骨下阻滯，引起的脊髓內側的反應劣于脊髓背索的反應。

（徐崢譯 薛張綱校）

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

成人體外膜肺氧合：抗凝監測及輸血的回顧

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

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Anesthesia& Analgesia 2014 118 731–743

體外膜肺氧合（ECMO）是一種控制心肺功能的生命支援的方法。自從將 ECMO 用於治療複雜的病情，如急性呼吸衰竭綜合征，心肌缺血、心肌病及膿毒症性休克，其作爲一種醫療手段的用途大大增加了。在接受 ECMO 的患者中最常見的併發症是出凝血病，同時

還有神經系統及腎臟損害。ECMO 與促使機體進入高凝狀態的炎症反應有關，常需要使用抗凝藥來防止非血管內皮表面網羅的血小板的產生。然而過度的抗凝可能會導致包括顱內出血等出血性併發症。對 ECMO 的抗凝監測最初起源於心臟外科手術的心肺流轉術。然而目前仍缺乏抗凝的理想水準及標準化方法來監測抗凝，對抗凝治療的藥物同樣缺乏標準化規範。在近期手術開始時，在抗凝治療的同時使用多種血製品來減少出血，通常會導致接受 ECMO 的患者費用的增加及引發輸血相關的併發症。在本綜述中，我們討論了 ECMO 治療的方式的進展，適應症，禁忌症及併發症等。此外，我們回顧了在接受 ECMO 時不同的抗凝治療策略及凝血的治療。最後，我們討論了 ECMO 的費用及相關的血液製品輸送問題。

（王贇譯，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 與 90 天病死率增加有關

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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Anesthesia & Analgesia 2014 118 790–798

背景：基質金屬蛋白酶（MMPS）可能在急性肺損傷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）兒科患者的氣道灌洗液 MMP-8 水準越高預後越差。膿毒症患者中，MMPS 及基質金屬蛋白酶抑制因數（TIMPs）比例失調常與低生存率有關。我們假設全身性 MMP-8 和 TIMP-1 升高與急性呼吸衰竭預後有關。

方法：該研究是在 25 個芬蘭的重症監護室內進行的逾期超過 8 周的 FINNALI 觀察試驗的亞組研究。所有入組患者均大於 16 周歲並使用機械通氣超過 6 小時。分別採集了入組時及 48 小時後的血液樣本，並分析其 MMP-8 和 TIMP-1 水準。實驗室檢查方法採用了免疫螢光測量法檢測 MMP-8，ELISA 法檢測 TIMP-1。對比了 90 天存活組和死亡組的 MMP-8 和 TIMP-1 水準。存活組組間比較了 TIMP-1 水準的四分位離差，採用 ROC 分析計算了曲線下面積，並且分析了 MMP-8 和 TIMP-1 水準和低氧血症程度的關係。

結果：最後入組的 563 名患者中死亡組入組時 TIMP-1 水準較高，中位數爲 367 ng/mL（四分位區間=199-562），存活組中位數爲 240 ng/mL（四分位區間=142-412），WMW 比爲 1.68（95%可信區間=1.43-2.08）。存活組和死亡組 MMP-8 水準有可能有差異，WMW 比爲 1.20（95%可信區間=1.01-1.43），但是 MMP-8/TIMP-1 的摩爾比沒有發現明顯差異，WMW 比爲 0.83（95%可信區間= 0.67-1.04）。存活組組間 TIMP-1 的四分位離差有明顯差異（log-rank 檢驗，P < 0.001）。ROC 分析計算了 TIMP-1 的曲線下面積爲 0.63（95%可信區間=0.58-0.69）。TIMP-1 與低氧血症嚴重程度有關，在整個佇列中 ARDS 亞組的 TIMP-1 較高，WMW 比爲 1.65（95%可信區間=1.15-2.44）。

結論： MMP-8 水準在 90 天死亡組中更高，但不能夠預測預後。在大部分機械通氣的危重患者中和 ARDS 亞組患者中升高的全身性 TIMP-1 與低氧血症程度和預後差有關。

（盛嘉君 譯，李士通 審校）

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.

年輕和年老患者在七氟烷和瑞芬太尼麻醉下進行擇期腰椎外科手術時的血漿食欲素水準的變化情況

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

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Anesthesia & Analgesia 2014 118 818-822

背景：年老患者在全身麻醉的情況下經常出現覺醒延遲，但具體原因不詳。食欲素已被證明參與全身麻醉的覺醒。在此研究中，我們研究了在麻醉覺醒週期中老年和年輕患者血漿食欲素 A 的水準情況。

方法：我們招募了 41 例進行擇期腰椎手術的患者，最終評估 34 例患者。 患者被分配到年輕組（年齡 30-55，N=16）和老年組（年齡 65-77，N=18）。七氟醚複合瑞芬太尼麻醉滴定保持 45 和 65 之間的腦電雙頻指數。記錄從停止麻醉到眼睛睜開和開始拔管的時間。採集動脈血，用放射免疫法測定以下四個時間點的血漿食欲素-A 的水準：麻醉前（T0），誘導麻醉後 1h(T1),出現（氣管拔管後 5 分鐘）（T2），和氣管拔管後 30 分鐘（T3）。

結果：老年組從停止麻醉到眼睛睜開和氣管拔出的時間均長於年輕組（分別爲 P=0.004，P=0.01）。基礎（T0）食欲素-A 在老年組的水準高於年輕組（T0，26.13 ± 1.25 vs 17.9 ± 1.30 pg/mL, P < 0.0001）。血漿食欲素-A 的水準在麻醉誘導時沒有變化，而在 T2 時老年組（35.0 ± 1.7 pg/mL）和年輕組（29.2±1.9pg/mL）均出現顯著性增加（vs T0, P <0.0001）。在 T1,T2 和 T3，老年組的血漿食欲素-A 的水平均明顯高於年輕組。

結論：血漿食欲素-A 的水準並不能說明老年患者全身麻醉覺醒的延遲。

（董靜 譯 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 recruited41 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-remifentanil 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 ± 1.7pg/mL) and young (29.2±1.9pg/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.

大鼠模型中鞘內注射 JWH015 可通過抑制脊髓膠質細胞的啓動減輕瑞芬太尼導致的術後痛覺過敏

Intrathecal Injection of JWH015 Attenuates Remifentanil-Induced Postoperative Hyperalgesia by InhibitingActivation of Spinal Glia in a Rat Model.

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Anesthesia& Analgesia 2014 118 841–853

背景：痛覺過敏和神經炎症均與膠質細胞有關，膠質細胞由星形細胞和小膠質細胞組成。本研究中，我們使用了一種選擇性大麻素 2 型受體（CB2）激動劑 JWH015 來研究瑞芬太尼導致的術後痛覺過敏。

方法：在術後痛覺過敏及鞘內注射 JWH015 後，我們使用機械刺激縮足反射閾值和熱刺激縮足反射潛伏期試驗來測定機械刺激痛和熱痛覺過敏。在大鼠由瑞芬太尼導致的術後痛覺過敏處理後，我們使用免疫組化和免疫印跡來研究 JWH015 對 CB2 受體、NR2B 亞組、啓動的神經膠質細胞以及促炎性細胞因數的表達。

結果：術中輸注瑞芬太尼導致了術後痛覺過敏。神經膠質細胞被啓動，並且某些基因的表達水準顯著增高，其中包括白細胞介素 6、腫瘤壞死因數α、CB2 和 Tyr-1472 磷酸化 NR2B 亞組(p-NR2B)。鞘內注射 JWH015 顯著抑制神經膠質細胞的啓動，並抑制白細胞介素 6、腫瘤壞死因數α、p-NR2B 和 CB2 的表達，因此減輕了術後痛覺過敏。然而，在提前使用 AM630 的組中這些現象並不存在。

結論：在瑞芬太尼導致的術後痛覺過敏過程中，神經膠質細胞的啓動、促炎性細胞因數產物和脊髓背角中 CB2 及 p-NR2B 的表達顯著增加。這些改變可以通過使用 JWH015 預處理來控制，這或許是 JWH015 抗痛覺過敏的主要機制。

（張怡譯，李士通審校）

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 afterremifentanil-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.

年齡對鞘內阻滯運動神經所需布比卡因 ED50 的影響

The Effect of Age on the Median Effective Dose (ED50) of Intrathecally Administerd Plain Bupivacaine for MotorBlock

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Anesthesia & Analgesia 2014 118 863–868

背景：在這項研究中，我們探討給予 20-80 歲患者通過鞘內注射布比卡因進行運動神經阻滯的 ED50，評估年齡對運動神經阻滯所需 ED50 的影響。

方法：研究選擇了 129 例在腰硬聯合下進行前列腺，泌尿外科，下肢手術的患者。根據年齡將患者分層如下： 20-30 歲, 31-40 歲, 41-50 歲, 51-60 歲, 61-70 歲, 71-80 歲。腰麻的藥量是根據 Dixon 法給予 0.75%布比卡因。經鞘內給予每一劑量的運動神經阻滯的程度通過修改過的 Bromage 和髖關節運動功能得分來評估。ED50 值通過 Dixon，Massey 和邏輯回歸來評估。其他終點指標包括感覺阻滯程度的偏倚，神經阻滯的耐受，低血壓，血管加壓藥的需要量。

結果：鞘內阻滯運動神經所需布比卡因的 ED50 爲 20-30 歲 10.22mg（95%CI9.96-10.49mg），31-40 歲 9.52mg（95%CI9.02-10.07mg），41-50 歲 8.37mg（95%CI7.56-9.26 mg），51-60 歲 7.30 mg (95% CI, 6.84-7.79 mg)，61-70 歲 6.55 mg (95% CI, 6.01-7.13 mg)，71-80 歲 5.78 mg (95% CI, 5.01-6.67 mg)。經鞘內給予布比卡因的六個年齡組中，最高的頭側鎮痛水準爲 5min 時爲 L1-L2，10min 時爲 T10-L1 水準。運動神經阻滯的持續上在組間有明顯差異。

結論：鞘內進行運動神經阻滯所需布比卡因的 ED50 隨年齡增長而急劇減少。

（王曉莉譯 李士通校）

BACKGROUND: In this study, we sought to determine the median effective dose (ED50) for motor block of intrathecally administered plainbupivacaine 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.

臨終診斷

Diagnosing Dying

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Anesthesia & Analgesia 2014 118 879–882

作爲麻醉與危重症醫師，我們有責任識別出垂死的患者並關注涉及生命末期的諸多問題。僅有 45%的患者認識到他們的生命即將結束，而大部分的患者並沒有意識到自身病情的嚴峻性，如果他們瞭解實際，則可能會做出其他的選擇。基於此，我們的這項工作至關重要。例如，即使大多數人並不希望在醫院中過世，醫院卻仍是超過半數人的臨終地。在英國有 58%的患者死于醫院，美國也有超過 20%的人在重症監護病房（ICU）去世。不僅是患者的“渾然不覺”（或抗拒現實），同時可能病情很難去評估或定位，而且他們的助陣醫生也拒絕接受現實。醫生們更傾向于對患者的存活抱過高期望，特別是對熟悉的患者更是如此。如果我們意識到一名患者正走向死亡，什麼時候將治療轉變爲臨終關懷，這個轉變的確是一項對理智的挑戰。醫生短期內（數天到數周）預測結果的能力不見得很好，但是較長期的（數周到數月）預測會更准一點，而預測精准的能力對於患者及其家人關於臨終治療的決定有著深遠影響，當面對毫無惡意的患者這一點顯得特別重要。識別出死亡進程顧及到一項計畫的發展，涉及減輕症狀，涉及減壓患者及其家人討論希望和偏好，涉及事前承諾的兌現以及向姑息性治療和臨終關懷的轉變。我們相信麻醉和危重症醫學對生命末期的諸多問題需要更多的關注，在患者臨終前高科技的使用，目標評估和垂危計畫的制定，還有那些將承受高風險的外科手術的決定。

（趙曉 譯 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 endof-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 highrisk surgical procedures.