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以快速起效為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

Lang, Bing-Chen MS*†; Yang, Jun PhD†; Wang, Yu MS†; Luo, Yun MS†‡; Kang, Yi BS†; Liu, Jin MD†; Zhang, Wen-Sheng MD†

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）是為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。為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。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 的水溶解度分別為 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物較另兩種磷酸酯前體
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.
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 ± 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.

A Decrease in Spatially Resolved Near-Infrared Spectroscopy-Determined Frontal Lobe Tissue Oxygenation by Phenylephrine Reflects Reduced Skin Blood Flow
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 ± 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, 0.13–0.86; Spearman r = 0.64, P = 0.012, 95% CI, 0.17–0.88) had.

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.

爪部切割和脊神経結紮後大鼠顱內自刺激、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
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 nenevoked 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.

**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

**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.

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

Rezonja K1, Sostaric M, Vidmar G, Mars T.
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.

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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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。

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。由於已知惡性腫瘤病人的免疫能力不同，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，以及癌症新發生率（風險比例相對為 0.64-1.11 和 0.76-1.30），以及死亡率（風險比例相對為 0.85-1.05 和 0.94-1.16）之間無關。同時，在 BIS 值為其他值時（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生率和惡性腫瘤的五年生存率無關。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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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為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%）在三組和 45 的 161（28%）在呼氣末麻醉濃度組術後譫妄在重症監護病房（比例比 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為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係是一個驚人的發現，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。
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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背景：越来越多的证据表明：复杂区域疼痛综合征(CRPS)患者的皮质，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疗法是否可以缓解CRPS动物模型的异常疼痛。我们假设局部给予α2-肾上腺素受体激动剂(α2A)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α2A(阿普可乐定)或者可以产生NO的西多明，PA或者PDE抑制剂(利索茶碱，可哥碱)。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。
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 postischemia pain (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.
A Comparison of Posterior and Medial Cord Stimulation for Neurostimulation-Guided Vertical Infraclavicular Block: A Randomized Noninferiority Clinical Trial

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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.

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

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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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背後：我們研究的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 例側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）從最初的結果點到阻滯過程的特點到有不良事件的第二結果點。

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 薛張鎮校）
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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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 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熒光測定法測試 MMP-8，ELISA 法測試 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。
**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.
**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-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 ± 1.7 pg/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.

**Intrathecal Injection of JWH015 Attenuates Remifentanil-Induced Postoperative Hyperalgesia by Inhibiting Activation of Spinal Glia in a Rat Model.**
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.
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為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為5min 時為 L1-L2，10min 時為 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 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 31- to 40-, 8.37 mg (95% CI, 7.56-9.26 mg) in 31- to 40-, 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.
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.