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聚焦：旨在促进心血管手术室质量和安全性的心血管麻醉医生协会倡议

FOCUS: The Society of Cardiovascular Anesthesiologists’ Initiative to Improve Quality and Safety in the Cardiovascular Operating Room

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Anesthesia & Analgesia 2014 119 777–783

为了寻找一种促进心血管外科手术室(CVOR)的质量和安全性的严格科学方法，心血管麻醉医师协会(SCA)首次于2005年提出倡议：心血管手术完美标准化系统。本项目由SCA基金赞助，主要目的在于区分危害以及发展基于证据的临床决策以提高心脏手术的安全性。危害是指任何可能导致潜在的可预防性不良事件。聚焦策略性计划具体包括以下三个目标：(1) 确认CVOR中存在的危害；(2) 危害分级并发展降低风险的手术；(3) 推广此类手术。总之，此项倡议，通过各学科人员的配合，包括临床医学、人因工程、心理学以及组织社会学等，已经区分和记录了每天发生在CVOR内显而易见的危害。一些比较常见的可以降低心脏手术安全性和质量的例子包括工作团队内人员不足、手术室设计缺陷，技术不足以及未能遵守最佳操作。目前有数项计划致力于更好地理解这些危害以及研究缓解措施。通过倡议，SCA开启了科学引导质量和安全性改进之旅。然而，这是一条漫长且充满艰辛的必然道路。

(俞芳 译 陈杰 校)

The Society of Cardiovascular Anesthesiologists (SCA) introduced the FOCUS initiative (Flawless Operative Cardiovascular Unified Systems) in 2005 in response to the need for a rigorous scientific approach to improve quality and safety in the cardiovascular operating room (CVOR). The goal of the project, which is supported by the SCA Foundation, is to identify hazards and develop evidence-based protocols to improve cardiac surgery safety. A hazard is anything that has the potential to cause a preventable adverse event. Specifically, the strategic plan of FOCUS includes 3 goals: (1) identifying hazards in the CVOR, (2) prioritizing hazards and developing risk-reduction interventions, and (3) disseminating these interventions. Collectively, the FOCUS initiative, through the work of several groups composed of members from different disciplines such as clinical medicine, human factors engineering, industrial psychology, and organizational sociology, has identified and documented significant hazards occurring daily in our CVORs. Some examples of frequent occurrences that contribute to reduce the safety and quality of care provided to cardiac surgery patients include deficiencies in teamwork, poor OR design, incompatible technologies, and failure to adhere to best practices. Several projects are currently under way that are aimed at better understanding these hazards and developing interventions to mitigate them. The SCA, through the FOCUS initiative, has begun this journey of science-driven improvement in quality and safety. There is a long and arduous road ahead, but one we need to continue to travel.
Intravenous Lidocaine Decreases Tumor Necrosis Factor Alpha Expression Both Locally and Systemically in Pigs Undergoing Lung Resection Surgery

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Background: Lung resection surgery is associated with an inflammatory reaction. The use of 1-lung ventilation (OLV) seems to increase the likelihood of this reaction. Different prophylactic and therapeutic measures have been investigated to prevent lung injury secondary to OLV. Lidocaine, a commonly used local anesthetic drug, has antiinflammatory activity. Our main goal in this study was to investigate the effect of IV lidocaine on tumor necrosis factor alpha (TNF-α) expression during lung resection surgery with OLV.

Methods: Eighteen pigs underwent left caudal lobectomy. The animals were divided into 3 groups: control, lidocaine, and sham. All animals received general anesthesia. In addition, the lidocaine group received a continuous IV infusion of lidocaine during surgery (1.5 mg/kg/h). Animals in the sham group only underwent thoracotomy. Samples of bronchoalveolar lavage (BAL) fluid and plasma were collected before initiation of OLV, at the end of OLV, at the end of surgery, and 24 hours after surgery. Lung biopsy specimens were collected from the left caudal lobe (baseline) before surgery and from the mediastinal lobe and the left cranial lobe 24 hours after surgery. Samples were flash-frozen and stored to measure levels of the following inflammatory markers: interleukin (IL-1β, IL-2, IL-10, TNF-α), nuclear factor κB, monocyte chemoattractant protein-1, inducible nitric oxide synthase, and endothelial nitric oxide synthase. Markers of apoptosis (caspase 3, caspase 9, Bad, Bax, and Bcl-2) were also measured. In addition, levels of metalloproteinases and nitric oxide metabolites were determined in BAL fluid and in plasma samples. A nonparametric test was used to examine statistical significance.
RESULTS: OLV caused lung damage with increased TNF-α expression in BAL, plasma, and lung samples. Other inflammatory (IL-1, nuclear factor κB, monocyte chemoattractant protein-1) and apoptosis (caspase 3, caspase 9, and BAX) markers were also increased. With the use of IV lidocaine there was a significant decrease in the levels of TNF-α in the same samples compared with the control group. Lidocaine administration also reduced the inflammatory and apoptotic changes observed in the control group. Hemodynamic values, blood gas values, and airway pressure were similar in all groups.

CONCLUSIONS: Our results suggest that lidocaine can prevent OLV-induced lung injury through reduced expression of proinflammatory cytokines and lung apoptosis. Administration of lidocaine may help to prevent lung injury during lung surgery with OLV.

A Novel Index of Hypoxemia for Assessment of Risk During Procedural Sedation
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BACKGROUND: Procedural sedation is essential for many procedures. Sedation has an excellent safety profile; however, it is not without risks. Assessment of risk using clinical outcomes in clinical studies is difficult due to their rare occurrence. Therefore, surrogate endpoints are frequently used in a clinical study in lieu of clinical outcomes. As a clinician integrates multiple aspects of a physiological variable to determine potential risk, a surrogate endpoint should consider a similar approach. In this study, we identified and tested the appropriateness of a new surrogate endpoint that may be used in clinical studies, area under the curve of oxygen...
desaturation (AUCDesat). A review of patient sedation records by anesthesiologists was conducted to assess its relationship to the anesthesia professional perception of risk.

METHODS: This study was a post hoc analysis and assessment of perceived risk by anesthesiologists. It consisted of 13 U.S.-trained board-certified anesthesiologists ranking physiological variables as indicators of risk and then reviewing 204 records from 3 completed sedation studies involving the SEDASYS® System. After review, each anesthesiologist assigned a Likert score based on his or her perception of risk for oversedation-related sequelae in each record. These scores were analyzed to determine their relationship to desaturation presence/absence, duration, depth, number of events, and AUCDesat that incorporates each component.

RESULTS: Anesthesiologists ranked arterial oxygenation to be the most important factor in assessing risk post hoc (mean rank of 4.69 of 5, $P = 0.0007$ compared with next highest ranked factor—respiratory rate, $N = 13$). AUCDesat was better correlated to the Likert scores ($r_s = 0.85$) when compared with the individual elements of AUCDesat, binary assessment of desaturation ($r_s = 0.73$), desaturation depth ($r_s = -0.70$), desaturation duration ($r_s = 0.70$), and incidence of desaturations ($r_s = 0.55$) (all 4 comparisons versus $r_s = 0.85$, $P < 0.0001$).

CONCLUSIONS: Anesthesiologists determined arterial oxygenation to be the most important physiological variable in assessing sedation risk and the potential for adverse clinical outcomes. AUCDesat, a composite index that incorporates duration, incidence, and depth of oxygen desaturation, was better correlated to the Likert scores. AUCDesat, given that it is a single numerical variable, is an ideal end point for assessment of risk of adverse clinical outcomes in clinical sedation studies. Future studies using AUCDesat and actual physiological outcomes may be useful in further defining this end point.

Optimal Nasopharyngeal Temperature Probe Placement

Lee, Jeongwoo MD*; Lim, Hyungsun MD*; Son, Kyung-geun MD*; Ko, Seonghoon MD, PhD*†

Anesthesia & Analgesia 2014 119 848–856

**Optimal Nasopharyngeal Temperature Probe Placement**

Lee, Jeongwoo MD*; Lim, Hyungsun MD*; Son, Kyung-geun MD*; Ko, Seonghoon MD, PhD*†

Anesthesia & Analgesia 2014 119 848–856

背景：鼻咽部是全麻手术期间最常用来监测体温的部位，但并不清楚麻醉医生盲目放置鼻咽温度探头的位置是否恰当, 本文研究目的为 1) 探究鼻咽黏膜最接近颈内动脉(ICA)的位置，2) 评估麻醉住院医生和麻醉护士摆放鼻咽温度探头的尖端位置。

方法：研究第一阶段回顾了100名患者的增强轴向CT图像来确定鼻咽黏膜最接近左或右颈内动脉的位置，随后在矢状位图像上测量此点至鼻孔的距离。研究第二阶段用内窥镜评估由麻醉住院医生（224名患者）或麻醉护士（116名患者）放置的鼻咽温度探头位置。位置不佳时将探头重新定位到最佳的位置，并记录两者的温度差异。

结果：CT图像显示，分别有60%、38%及2%的患者，其黏膜最接近颈内动脉的最佳位置在鼻咽部的上部，中部及下部。颈内动脉和上部鼻咽部黏膜的平均距离较与下部之间的要更短（女：9.4 vs 16.8 mm，p<0.001；男：12.4 vs 18.8 mm，p<0.001）。通过下鼻道从鼻孔至鼻咽部上部的平均距离（95%预测区间）女性为9.1（8.1-10.2）cm，男性为9.7（8.6-10.3）cm。由住院医生和护士正确地将温度探头放置在鼻咽部上部或中部的概率分别为43%（95%的可信区间，37%-49%）和41%（95%的可信区间，36%-50%）。当温度探头在鼻腔位置不佳时，测得鼻咽部上部的体温中位数差异（95%CI）为0.2℃（0.15℃—0.25℃）。

结论：鼻咽黏膜最接近颈内动脉的位置为鼻咽腔上部或中部，鼻孔至鼻咽上 1/3 的深度大致为10cm，医生盲目地放置鼻咽部温度探头，其最佳位置的放置率低于50%。
BACKGROUND: Although the nasopharynx is a commonly used temperature-monitoring site during general anesthesia, it is unknown whether the position of nasopharyngeal temperature probes placed blindly by anesthesia practitioners is optimal. The purposes of this study were (1) to determine where the nasopharyngeal mucosa is in closest proximity to the internal carotid artery (ICA) and (2) to evaluate the tip position of nasopharyngeal temperature probes that were placed by anesthesiology residents and nurse anesthetists.

METHODS: In the first phase of the study, we reviewed enhanced axial computed tomography images of 100 patients to determine where the nasopharyngeal mucosa was in closest proximity to the left or the right ICA. The distance from this point to the nares was then measured in the sagittal image. In the second phase of the study, nasendoscopy was used to evaluate the positioning of nasopharyngeal temperature probes placed by anesthesiology residents (244 patients) or nurse anesthetists (116 patients). Malpositioned probes were repositioned to an optimal location, and the temperature differences were recorded.

RESULTS: In the computed tomography images, the mucosa in closest proximity to the ICA was in the upper, mid-, and lower nasopharynx in 60%, 38%, and 2% of patients, respectively. The average distances between the ICA and the nasopharyngeal mucosa in the upper portion were significantly shorter than those in the lower portion (female: 9.4 vs 16.8 mm, P < 0.001; male: 12.4 vs 18.8 mm, P < 0.001). The average distances (95% prediction interval) from the nares to the upper portion of the nasopharynx through the inferior meatus were 9.1 (8.1–10.2) cm in females and 9.7 (8.6–10.8) cm in males. Temperature probes were correctly positioned in the upper or mid-nasopharynx by residents and nurses in 43% (95% confidence interval [CI], 37%–49%) and 41% (95% CI, 36%–50%), respectively. When the probe was inadvertently placed in the nasal cavity, the median (95% CI) temperature difference from the upper nasopharynx was 0.2°C (0.15°C–0.25°C).

CONCLUSIONS: The closest portion of the nasopharyngeal mucosa to the ICA is within the upper or mid-nasopharynx. The depth from the nares to the upper one-third of the nasopharynx is approximately 10 cm. Less than half of nasopharyngeal temperature probes placed blindly by practitioners were optimally positioned.

血清孕酮浓度与麻醉镇痛需求的关系：一个关于接受剖宫产分娩产妇的前瞻性观察研究

The Relationship Between Serum Progesterone Concentration and Anesthetic and Analgesic Requirements: A Prospective Observational Study of Parturients Undergoing Cesarean Delivery

Lee, Jeongwoo MD, PhD*; Lee, Junho MD*; Ko, Seonghoon MD, PhD†

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结果：平均血清孕酮浓度为 128.2±83 ng/mL。每小时七氟醚用量与血清孕酮浓度之间存在显著的负相关（Pearson 相关系数 r = −0.26；95% 置信区间，0.44 到 −0.05，P = 0.01）。累计镇痛药物用量在术后第 2 小时（R = −0.20，P = 0.05），第 24 小时（R = −0.25，P = 0.02），和第 48 小时（R = −0.28，P = 0.01）与血清孕酮浓度呈负相关。高孕酮水平妇女（高于中位数值）相对于低孕酮水平妇女（低于中位数值），每小时七氟醚用量（P = 0.02）和术后 48 小时累积镇痛药物用量（P = 0.02）更少。

结论：近足月产妇对麻醉和镇痛药物需求降低可能部分取决于血清孕酮浓度。

在儿科围术期患者中无创血红蛋白监测的趋势和准确性

Trending and Accuracy of Noninvasive Hemoglobin Monitoring in Pediatric Perioperative Patients

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背景：Rainbow Pulse CO-Oximetry 技术® (Masimo Corporation, Irvine, CA) 提供了对动脉血红蛋白浓度的连续无创监测方法（SpHb）。在接受可能失血手术的儿童中，对比由该创新监测仪得到的 SpHb 与普通实验室得到的血红蛋白浓度（Hb）来评估该设备的趋势和准确性。

方法：Hb 浓度分别由 Pulse CO-Oximetry 和传统血红蛋白分析仪记录。使用回归分析和四象限散点图来评估 SpHb 和 Hb 测定值的变化趋势（ΔSpHb 和 ΔHb）。
BACKGROUND: Rainbow Pulse CO-Oximetry technology® (Masimo Corporation, Irvine, CA) provides continuous and noninvasive measurement of arterial hemoglobin concentration (SpHb). We assessed the trending and accuracy of SpHb by this innovative monitoring compared with Hb concentration obtained with conventional laboratory techniques (Hb) in children undergoing surgical procedures with potential for substantial blood loss.

METHODS: Hb concentrations were recorded from Pulse CO-Oximetry and a conventional hematology analyzer. Regression analysis and 4-quadrant plot were used to evaluate the trending for changes in SpHb and Hb measurements (ΔSpHb and ΔHb). Bias, precision, and limits of agreement of SpHb and of in vivo adjusted SpHb (SpHb – first bias to HB) compared with Hb were calculated.

RESULTS: One hundred fifty-eight SpHb–Hb data pairs and 105 delta pairs (ΔSpHb and ΔHb) from 46 patients aged 2 months to 17 years with Hb ranging from 16.7 to 7.9 g/dL were collected. To evaluate trending, the delta pairs (ΔSpHb and ΔHb) were plotted, which revealed a positive correlation (ΔSpHb = 0.022 + 0.76ΔHb) with correlation coefficient r = 0.76, 95% CI [confidence interval] = 0.57–0.86. The bias and precision of SpHb to Hb and in vivo adjusted SpHb were 0.4 ± 1.3 g/dL and 0.1 ± 1.2 g/dL, respectively; the limits of agreement were −2.0 to 3.2 g/dL before in vivo adjustment and −2.4 to 2.2 g/dL after in vivo adjustment (P value = 0.04). The mean percent bias (from the reference Hb concentration) decreased from 4.1% ± 11.9% to 0.7% ± 11.3% (P value = 0.01). No drift in bias over time was observed during the study procedure. Of patient demographic and physiological factors tested for correlation with the SpHb, only perfusion index at sensor site showed a weak correlation.

CONCLUSIONS: The accuracy of SpHb in children with normal Hb and mild anemia is similar to that previously reported in adults and is independent of patient demographic and physiological states except for a weak correlation with perfusion index. The trending of SpHb and Hb in children with normal Hb and mild anemia showed a positive correlation. Further studies are necessary in children with moderate and severe anemia.
BACKGROUND: We hypothesized that preconditioning (PC) with a short exposure to isoflurane (ISO) would reduce neurodegeneration induced by prolonged exposure to ISO in neonatal rats, as previously shown in neuronal cell culture.

METHODS: We randomly divided 7-day-old Sprague-Dawley rats into 3 groups: control, 1.5% ISO, and PC + 1.5% ISO. The control group was exposed to carrier gas (30% oxygen balanced in nitrogen) for 30 minutes and then to carrier gas again for 6 hours the following day. The 1.5% ISO group was exposed to carrier gas for 30 minutes and then to 1.5% ISO for 6 hours the following day. The PC + 1.5% ISO group was preconditioned with a 30-minute 1.5% ISO exposure and then exposed to 1.5% ISO for 6 hours the following day. Blood and brain samples were collected 2 hours after the exposures for determination of neurodegenerative biomarkers, including caspase-3, S100β, caspase-12, and an autophagy biomarker Beclin-1.

RESULTS: Prolonged exposure to ISO significantly increased cleaved caspase-3 expression in the cerebral cortex of 7-day-old rats compared with the group preconditioned with ISO and the controls using Western blot assays. However, significant differences were not detected for other markers of neuronal injury.

CONCLUSIONS: The ISO-mediated increase in cleaved caspase-3 in the postnatal day 7 rat brain is ameliorated by PC with a brief anesthetic exposure, and differences were not detected in other markers of neuronal injury.

**What Epidural Opioid Results in the Best Analgesia Outcomes and Fewest Side Effects After Surgery?: A Meta-Analysis of Randomized Controlled Trials**

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背景：硬膜外阿片类药物被广泛用于椎管神经阻滞和术后镇痛。然而，阿片类药物的镇痛疗效和副作用的个体差异仍有争议。
方法：此项随机对照试验的 meta 分析，比较至少 2 种急性术后连续硬膜外输注镇痛方式至少 24 小时以上。个体研究数据使用反向方差法加权。主要结果为疼痛视觉模拟评分量表(VAS)评分。次要结果包括阿片类药物的副作用，如瘙痒、术后恶心呕吐(PONV)、镇静、低血压和呼吸抑制。

结果：24 项试验中有 19 项包含比较以下阿片类药物中的两种：吗啡、芬太尼或舒芬太尼。研究对象共 1513 名。对手术类型进行汇集分析发现在术后任何时候 VAS 疼痛评分并无临床显著差异。与芬太尼相比，吗啡术后 PONV(OR = 1.91，95% 可信区间，1.14 - -3.18；P = 0.014)、瘙痒(OR = 1.64，95% 可信区间，0.98 - -2.76；P = 0.162)发生率更高。阿片类药物消耗总量仅在于吗啡和芬太尼的研究中有差异，吗啡组的患者药物需要量减少 1.2mg（相当于吗啡）(95% CI, 0.27–2.18)。除两个研究外其余试验组使用辅助镇痛剂相似。

结论：根据 VAS 疼痛评分，硬膜外阿片类药物之间的镇痛效果是相似的。这些镇痛药的相似之处可能反映了同时使用硬膜外局麻药和阿片类药物镇痛的通常方法，根据患者的疼痛状况确定注入速率。关于副作用方面，尽管这些组之间阿片类药物消耗总量相似，吗啡的 PONV 和瘙痒发生率可能比芬太尼更高。

（张帆 译 陈杰 校）

BACKGROUND: Epidural opioids are widely used for central neuraxial blockade and postoperative analgesia. However, differences in analgesic efficacy and side effect rates among individual opioids remain controversial.

METHODS: We conducted a random-effects meta-analysis of randomized controlled trials that compared at least 2 continuous epidural infusions for acute postoperative analgesia over at least 24 hours. Individual study data were weighted by the inverse-variance method. Visual analog scale (VAS) pain scores were the primary outcome. Secondary outcomes included opioid side effects, such as pruritus, postoperative nausea and vomiting (PONV), sedation, hypotension, and respiratory depression.

RESULTS: Nineteen of the 24 trials included compared 2 of the following opioids: morphine, fentanyl, or sufentanil. The total subjects studied were 1513. Pooled analysis by type of surgery showed no clinically significant differences in VAS pain scores at any time after surgery. There were more PONV (OR = 1.91; 95% CI, 1.14–3.18; P = 0.014) and perhaps pruritus (OR = 1.64; 95% CI, 0.98–2.76; P = 0.162) with morphine compared to fentanyl. Total opioid consumption differed only in the trials comparing morphine and fentanyl, where patients in the morphine group required 1.2 mg (of morphine equivalent) less (95% CI, 0.27–2.18). Use of analgesic adjuncts was similar for all but 2 studies.

CONCLUSIONS: Analgesic outcome, in terms of VAS pain score, was similar between the epidural opioids studied. These similarities in analgesia may reflect the common practices of concurrently using epidural local anesthetics with the opioids and titrating infusion rates according to a patient’s pain status. With respect to side effects, the incidence of PONV and possibly pruritus was higher with morphine compared with fentanyl, despite there being similar total opioid consumption between those groups.

全髋关节置换术中局部浸润镇痛后罗哌卡因的药代动力学

Ropivacaine Pharmacokinetics After Local Infiltration Analgesia in Hip Arthroplasty

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本研究纳入15名择期行全髋关节置换手术的病人，在其局部浸润镇痛后30小时期间通过液相质谱法检测血浆中罗哌卡因的浓度。罗哌卡因血浆浓度的95%预测范围的上界值为0.032mg/L。有报道显示当副作用明显需停止静脉注射的罗哌卡因动脉血中浓度0.34-0.85mg/L。在局部浸润镇痛的第一个24小时，α-1酸性糖蛋白与未结合罗哌卡因部分没有相关性。在本研究中未发现全身麻醉毒性等症状或反应。出现不良反应的Clopper-Pearson95%置信区间的上限为0.218。

吸入麻醉后的低通气可发生再麻醉
Hypoventilation After Inhaled Anesthesia Results in Reanesthetization

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背景：自从吸入麻醉以来，发生低通气的原因很多。在本研究中，我们研究了吸入麻醉在导致低通气中发挥的作用以及再麻醉发生的机制。

方法：针对体重为70公斤的模拟人，分别利用地氟醚，七氟醚和异氟醚行吸入麻醉，利用Gas Man®计算机模拟系统监测麻醉气体的摄取和排泄。对挥发罐进行设置和调整，从而使得吸入麻醉分布容积丰富的组织(VRG)包括脑，麻醉深度能够迅速达到0.75 MAC（最低肺泡有效浓度），1.0 MAC和1.5 MAC，并可保持此麻醉深度1，2，4，6小时。在模拟吸入麻醉结束前，将挥发罐刻度调整为0，并且新鲜气体流量设置为8L/min。肺泡通气量(VA)保持为4L/min，直到VRG达到苏醒麻醉深度，约为0.33 MAC。然后将VA调整为近乎窒息流量0.1 L/min和窒息流量0.0 L/min，并监测VRG麻醉深度，若达到0.5 MAC或者大于0.5 MAC，判断为重度再麻醉；若VRG麻醉深度达到0.33 MAC并小于0.5 MAC，判断为轻度再麻醉。此外VRG在麻醉深度达到0.33 MAC时，研究判断为最低VA从而可防止重度再麻醉的发生。

结果：吸入麻醉1h后，所有模拟患者在达到0.75 MAC和1.0 MAC时均未发生轻度和重度再麻醉。吸入麻醉4h到6h后，不同麻醉气体使模拟患者达到1.0 MAC和1.5 MAC，并且在接近窒息和窒息VA时均发生重度再麻醉。利用最小肺泡VA可防止重度再麻醉发生，比如6h的0.75 MAC麻醉，VA可小至0.5 L/min；6h的1.0 MAC麻醉，VA可小至0.5 L/min；6h的1.5 MAC麻醉，VA可小至1.2 L/min。对于所有不同类型吸入麻醉的模拟患者，导致再麻醉的来源是肌肉组织，4h吸入麻醉可达到0.8 MAC，其中2h地氟烷吸入麻醉可达到0.75 MAC。吸入麻醉6h后，脂肪组织麻醉深度小于0.15 MAC。

结论：吸入麻醉后低通气可能导致再麻醉。肌肉组织是麻醉和再麻醉气体的储存分布部位，脂肪组织则亦是麻醉气体的容器并可促使再麻醉的发生。不同麻醉气体包括地氟烷，七氟醚和异氟醚，吸入麻醉4h达到1.0 MAC后，如果发生严重低通气，则由于肌肉中麻醉气体的释放，导致不同程度的再麻醉。

（隋永恒 译 陈杰 校）
BACKGROUND: During emergence from volatile anesthesia, hypoventilation may result from many causes. In this study, we examined the effect of hypoventilation after initial emergence from volatile anesthesia and the potential for reanesthetization.

METHODS: The uptake and excretion of desflurane (Des), sevoflurane, and isoflurane were studied using the Gas Man® computer simulation program for a 70-kg simulated patient. The vaporizer setting was adjusted so that a VRG (vessel-rich tissue group, including brain) level of 0.75 minimum alveolar concentration (MAC), 1.0 MAC, and 1.5 MAC was rapidly achieved and maintained within tight limits for a 1-, 2-, 4-, and 6-hour period of anesthesia.

At the end of the simulated period of anesthesia, the vaporizer was set to 0 and fresh gas flow was set to 8 L/min. Ventilation (VA) was continued at 4 L/min until the anesthetic level in the VRG reached MAC awake, equal to 0.33 MAC for each drug. Then, the VA was adjusted to 0.1 L/min to simulate near-apnea and 0.0 L/min to simulate true apnea. Severe reanesthetization was said to occur if the VRG level increased to or above 0.5 MAC. Mild reanesthetization was said to occur if VRG increased from its value of 0.33 MAC but did not reach 0.5 MAC. The minimum VA required to avoid severe reanesthetization was studied by trials of decreased VA beginning at the time the VRG reached 0.33 MAC.

RESULTS: After emergence from 1 hour of anesthesia, all simulated patients were protected against mild and severe reanesthetization if anesthesia was at 0.75 or 1.0 MAC. After 4 or 6 hours of anesthesia, severe reanesthetization occurred with all drugs with near or true apnea if anesthesia was at 1.0 or 1.5 MAC. The minimum alveolar VA to protect against severe reanesthetization after 6 hours of anesthesia was no more than 0.5 L/min for all drugs at 0.75 MAC, no more than 0.5 L/min at 1.0 MAC, and no more than 1.2 L/min at 1.5 MAC. In all simulated cases, the source of anesthetic drug that allowed reanesthetization was muscle (MUS), which reached a value of 0.8 MAC within 4 hours with all drugs and reached a value of 0.75 MAC with desflurane after 2 hours. Fat levels of anesthetic remained less than 0.15 MAC for all drugs up to the 6 hours tested.

CONCLUSIONS: Reanesthetization from hypoventilation after inhaled anesthesia is possible. After initial emergence, muscle is a source of anesthetic and predisposes to reanesthetization while fat is a sink for anesthetic and fosters continued emergence. Severe hypoventilation will cause some degree of reanesthetization from anesthetic released from muscle after 4 hours of 1 MAC inhaled anesthesia with desflurane, sevoflurane, or isoflurane.

根治性前列腺切除术后结局：用芬太尼进行全身麻醉和区域麻醉镇痛比较：配对队列研究

Outcomes after radical prostatectomy for cancer: a comparison between general anesthesia and epidural anesthesia with fentanyl analgesia: a matched cohort study

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背景：肿瘤手术应用区域麻醉能改善肿瘤预后。其中一个可能的机制是静脉应用阿片类药物可能引起免疫抑制的减少。我们设计了一项回顾性队列配对研究。全身麻醉静脉应用芬太尼，硬膜外麻醉时硬膜外使用芬太尼镇痛，比较二者根治性前列腺切除术后的长期结局。
BACKGROUND: The use of regional anesthesia for cancer surgery has been associated with improved oncologic outcomes. One of the proposed mechanisms is a reduction in the use of systemic opioids that may cause immunosuppression. We used a retrospective matched cohort design to compare long-term oncologic outcomes after prostatectomy for cancer performed under general anesthesia with systemic opioids or with epidural anesthesia with epidural fentanyl analgesia. Since epidural fentanyl is quickly reabsorbed systemically, we hypothesized that there would be no difference in long-term oncologic outcomes between the 2 groups.

METHODS: There were 486 men who underwent prostatectomy performed under epidural anesthesia between January 1, 1991, and January 31, 1996. They were 1:1 matched based on age (±5 years), surgical year (±1 year), and baseline prostate cancer pathology to patients who had general anesthesia with systemic opioids. Long-term cancer outcomes and all-cause mortality were examined. Analyses were performed using stratified proportional hazards regression models, with hazard ratios >1 indicating worse outcome for general anesthesia only compared with epidural anesthesia and fentanyl analgesia.

RESULTS: After adjusting for positive surgical margins and adjuvant therapies, patients in the general anesthesia group were found not to be at increased risk of prostate cancer recurrence (hazard ratio [HR] = 0.79, 95% confidence interval [CI], 0.60-1.04), systemic tumor progression (HR = 0.92, 95% CI, 0.46-1.84), cancer-specific mortality (HR = 0.53, 95% CI, 0.18-1.58), or overall mortality (HR = 1.23, 95% CI 0.93-1.63) when compared with patients who received epidural anesthesia.

CONCLUSIONS: Compared with general anesthesia with systemic opioids, epidural anesthesia and analgesia with fentanyl were not associated with improvement in oncologic outcomes in patients undergoing radical prostatectomy for cancer.
背景：骨髓衰竭和严重血小板减少的病人通常在操作前预先输注血小板。尽管如此，这样的输注在临床上的效果还没有确定。我们在行中心静脉穿刺前预先输注血小板的骨髓衰竭病人中做了一个前瞻性观察研究，我们的目的是评估骨髓衰竭致血小板减少的病人行中心静脉穿刺前预先输注血小板的效果和持续时间。

方法：39个血小板计数低于50 × 10/L的骨髓衰竭成年病人在预先输注血小板前依次登记，他们均行锁骨下中心静脉穿刺。分别在输注血小板前、输注后1小时和输注后4小时三个时间点取血液标本。利用常规血液学检查、转动栓塞弹力测定法（EXTEM 和 FIBTEM）、多重电极集合度测定法来评估凝血情况，包括磷酸腺苷、胶原蛋白和凝血酶受体激动多肽，同时用流式细胞术检测P-选择素CD62P和活化糖蛋白PAC-1在血小板的表达。根据对不良反应常用的术语标准把出血并发症分为五个等级。

结果：此项研究包括17位女性和22位男性。输注后1小时血小板计数从24 × 10/L（18-32）增加到42 × 10/L（31-50），但在输注后4小时并没有明显不同（40 × 10/L（29-50））。血栓弹力测定EXTEM得出最大凝血块强度在输注后1小时从38mm（32-45）增加到46mm（41-52），并且在输注后4小时没有变化。凝血时间在输注后1小时从58.5秒（50-78）降至53秒（45-61），在输注后4小时（57秒）也没有明显不同。FIBTEM得出的输注后的结果完全没有变化。所有的多平台分析结果在输注后1小时明显增加，在4小时没有变化。流式细胞术分析显示出不同的结果，却没有总体趋势。

结论：在血小板减少的骨髓衰竭病人中预先输注血小板可以通过增加血小板的数量而不是增强血小板的功能来改善血液凝集参数。改善的凝血参数和血小板聚集会持续存在输注后1-4小时。

吕越昌译 薛张纲校

BACKGROUND: Patients with bone marrow failure and severe thrombocytopenia are frequently given prophylactic platelet transfusion before interventions. The clinical effects of such transfusions, however, are poorly defined. We performed a prospective observational study on patients with bone marrow failure scheduled for prophylactic platelet transfusion before the insertion of a central venous catheter. The objectives were to evaluate the effect and duration of prophylactic platelet transfusions on central venous catheter insertion in thrombocytopenic patients with bone marrow failure.

METHODS: Thirty-nine adult patients with bone marrow failure and platelet counts below 50 × 10/L were consecutively enrolled before prophylactic platelet transfusion for subclavian central venous catheter insertion. Blood samples were drawn from the patients before platelet transfusion, 1 hour, and 4 hours after completion of the transfusion. The coagulation profile was assessed by conventional hematological tests, thromboelastometry (ROTEM) assays (EXTEM and FIBTEM), multiple electrode aggregometry (Multiplate) assays including adenosine diphosphate, collagen, and thrombin receptor agonist peptide, and by flow cytometry for the platelet expression of P-selectin (CD62P) and activated glycoprotein IIb-IIIa (PAC-1). Bleeding complications were classified with a 5-grade scale, according to the Common Terminology Criteria for Adverse Events.

RESULTS: Seventeen women and 22 men were included in the study. Platelet count was increased from 24 × 10/L (18-32) before to 42 × 10/L (31-50) 1 hour after transfusion (P < 0.0001) and was not significantly different 4 hours after transfusion (40 × 10/L (29-50), P = 0.047). Maximal clot firmness EXTEM was increased from 38 mm (32-45) before to 46 mm (41-52) 1 hour after transfusion (P < 0.0001) and did not change 4 hours after transfusion. Clotting time EXTEM was decreased from 58.5 seconds (50-78) beforehand to 53 seconds (45-61) 1 hour after transfusion (P = 0.0006) and was not significantly different 4 hours after transfusion (57 seconds (52-70, P = 0.025). FIBTEM results were all unchanged after transfusion. All Multiplate
analyses were significantly increased after 1 hour and were not diminished 4 hours after transfusion. Four grade 1 bleeding episodes occurred, but no grade 2 to 5 bleeding could be detected. Flow cytometry analyses showed mixed results with no overall trend.

**CONCLUSIONS:** Prophylactic platelet transfusions in thrombocytopenic patients with bone marrow failure improve hemostatic parameters on ROTEM and Multiplate by increasing the number of platelets, and not through enhancement of platelet function. Improved clotting parameters on ROTEM and platelet aggregation on Multiplate appear to persist between 1 and 4 hours after transfusion.

美国大学附属医院产科麻醉产后出血预案使用情况的研究
The use of postpartum hemorrhage protocols in United States academic obstetric anesthesia units.

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背景：产后出血（PPH）是导致产妇在住院和分娩中发生严重产后并发症、心跳骤停以及死亡的重要原因。计划性诊疗已被证实可在多种情况下改善患者预后。National Partnership for Maternal Safety 推荐在美国所有的妇产科机构都应实施 PPH 预案。这项研究旨在确定在在美国的大学附属医院的产科中，PPH 预案的使用的情况。我们假设大部分 (>80%) 的大学附属医院的产科麻醉拥有合适的 PPH 预案。

方法：调查由一个专家小组实施。调查的内容包括医院的特点，PPH 预案的可行性、计划开展这份预案以及预案包含的内容，包括即将来临的国家妇产科安全协会关于产后出血的安全倡议。电子调查问卷通过电子邮件发放给美国 104 位大学附属医院产科麻醉的负责人。回复的问卷按照 PPH 预案的使用进行适当的分层。单因素分析用来统计描述问卷答复的特征，二项分布用来评价 PPH 预案使用的分布概率。

结果：问卷的答复率为 58%。在回复中，拥有 PPH 预案的单位小于预期假设（P=0.03），回复的单位中，约 67% 拥有 PPH 预案（N=40, 95% 可信区间[CI]: 53%-78%）。在回复问卷的单位中，有 PPH 预案的单位的年分娩量中位数为 3900，而无 PPH 预案的单位的年分娩量中位数为 2300，但二者在剖宫产率（P = 0.73）及产后出血发生率（P = 0.69）上没有差别。回复及未回复问卷单位的年分娩量没有显著差别（P = 0.06），提示每年分娩量 >3200 的大学附属医院分娩量较小的医院更有可能有适当的 PPH 预案（比数比 3.16 (95% CI: 1.01-9.90)。研究中，在校正未回复医院中的分娩量后，所有学术中心的产科麻醉中 67%（95% CI: 55%-77%）拥有合适的 PPH 预案。医院的规模扩大与 PPH 预案的存在并不相关。95% 拥有 PPH 预案的医院以及 90% 没有 PPH 预案的医院中都有大量输血的常规（95% CI of difference: -7% to 7%）。在回复问卷的医院中，57% 拥有产后出血的急救小组，这个比率在有或无 PPH 预案的单位中没有差别[均差: 4%，95% CI (-24% to 32%)]。

结论：尽管对国家患者安全质量改进的强调越来越多，在美国，仍然有至少 20% 的产科麻醉中心没有 PPH 预案。分娩量是最重要的预测 PPH 预案是否存在的变量。通过关注小分娩量的单位，可以使国家努力实施在所有大学附属医院中广泛应用 PPH 预案的计划获得巨大收益。未来的工作需要在非大学附属医院中评估和推行 PPH 预案。

(杜芳译 薛张纲校)
BACKGROUND: Postpartum hemorrhage (PPH) is the leading cause of severe maternal morbidity, cardiac arrest, and death during the hospitalization for childbirth. Protocol-driven care has been associated with improved outcomes in many settings; the National Partnership for Maternal Safety now recommends that PPH protocols be implemented in every labor and delivery unit in the United States. In this study, we sought to identify the level of PPH protocol availability in academic United States obstetric units. We hypothesized that the majority (>80%) of academic obstetric anesthesia units would have a PPH protocol in place.

METHODS: A survey was developed by an expert panel. Domains included hospital characteristics, availability of PPH protocol or plans to develop such a protocol, and protocol components included in the upcoming National Partnership for Maternal Safety obstetric hemorrhage safety bundle initiative. The electronic survey was emailed to the 104 directors of United States academic obstetric anesthesia units. Responses were stratified by PPH protocol availability as appropriate. Univariate statistics were used to characterize survey responses and the probability distribution for PPH protocol availability was estimated using the binomial distribution.

RESULTS: The survey response rate was 58%. The percentage of responding units with a PPH protocol was lower than hypothesized (P = 0.03); there was a PPH protocol in 67% of responding units (N = 40, 95% confidence interval [CI]: 53%-78%). The median annual delivery volume for responding units with PPH protocol was 3900 vs 2300 for units without PPH protocol (P = 0.002), with no difference in cesarean delivery rate (P = 0.73) or observed PPH rate (P = 0.69). There was no difference in annual delivery volume between responding and nonresponding hospitals (P = 0.06), suggesting that academic centers with delivery volume >3200 births per year are more likely than smaller volume hospitals to have a PPH protocol in place (odds ratio 3.16 (95% CI: 1.01-9.90). Adjusting for delivery volume among nonresponding hospitals, we estimate that 67% (95% CI: 55%-77%) of all academic obstetric anesthesia units had a PPH protocol in place at the time of this survey. Institutional processes for escalation do not correlate with the presence of a PPH protocol. There was a massive transfusion protocol in 95% of units with a PPH protocol and in 90% of units without (95% CI of difference: -7% to 7%). A PPH code team or rapid response team was available in 57% of responding institutions, with no difference between units with or without a PPH protocol [mean difference 4%, 95% CI (-24% to 32%)].

CONCLUSIONS: Despite increasing emphasis on national quality improvement in patient safety, there are no PPH protocols in at least 20% of U.S. academic obstetric anesthesia units. Delivery volume is the most important variable predicting the presence of a PPH protocol. National efforts to ensure universal presence of a PPH protocol in all academic centers will achieve the greatest impact by focusing on small-volume facilities. Future work is needed to evaluate and facilitate PPH implementation in nonacademic obstetric units.

儿科病人使用高/低新鲜气体流量以及是否使用热湿交换器对 dräger Primus 麻醉工作站湿度的影响

The humidity in a dräger primus anesthesia workstation using low or high fresh gas flow and with or without heat and moisture exchanger in pediatric patients.

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背景：全麻下预防干燥气体对气道上皮有害影响的最低绝对湿度被认为是 20mgH₂O/L。由于儿童分钟通气量小，我们假定儿童与成人相比呼吸回路湿度较低。Primus 麻醉工作站
站（Dräger Medical, Lübeck, Germany）具有一个内置的加热器来加热病人呼出的气体。热湿交换器（HME）是一种可以用来进一步加湿和加热吸入气体的装置。为了评价小儿麻醉时呼吸回路的加湿性能，我们比较了低或新鲜气体流量（FGF）以及是否使用热湿交换器时吸入气体的温度和湿度。

方法：根据Primus麻醉工作站呼吸回路中的肺通气方式的不同，将四十名儿童随机分为4组，分别是低FGF（1 L/min）HME（Pall BB25FS, Pall Biomedical, East Hills, NY）组、低FGF无HME组、高FGF（3 L/min）HME组、高FGF无HME组。我们分别在病人连接呼吸回路10、20、40、60、80分钟后测定吸入气体的温度和湿度。

结果：研究发现，吸入气体平均温度HME组（HME1L: 30.3°C ± 1.1°C; HME3L: 29.3°C ± 1.2°C）与无HME组（1L: 27.0°C ± 1.2°C; 3L: 27.1°C ± 1.5°C; P < 0.0001）相比较高。吸入气体的平均绝对湿度HME与无HME组相比较高，低流量组与高流量组相比较高（[HME1L: 25 ± 1 mg H₂O/L] > [HME3L: 23 ± 2 mg H₂O/L] > [1L: 17 ± 1 mg H₂O/L] > [3L: 14 ± 1 mg H₂O/L]; P < 0.0001）。

结论：小儿呼吸回路中低或高FGF都不能满足降低呼吸道失水风险的最低湿度水平。使用HME可以增加吸入气体的湿度和温度，使其更接近生理值。低FGF可以提高HME的效率从而增加吸入气体的湿度值。因此，小儿麻醉期间低FGF并联合使用HME是保存吸入气体温度和湿度的最有效方式。

（江凌慧译 薛张纲校）

BACKGROUND: An inhaled gas absolute humidity of 20 mg H₂O·L is the value most considered as the threshold necessary for preventing the deleterious effects of dry gas on the epithelium of the airways during anesthesia. Because children have small minute ventilation, we hypothesized that the humidification of a circle breathing system is lower in children compared with adults. The Primus anesthesia workstation (Dräger Medical, Lübeck, Germany) has a built-in hotplate to heat the patient’s exhaled gases. A heat and moisture exchanger (HME) is a device that can be used to further humidify and heat the inhaled gases during anesthesia. To evaluate the humidifying properties of this circle breathing system during pediatric anesthesia, we compared the temperature and humidity of inhaled gases under low or high fresh gas flow (FGF) conditions and with or without an HME.

METHODS: Forty children were randomly allocated into 4 groups according to the ventilation of their lungs by a circle breathing system in a Dräger Primus anesthesia workstation with low (1 L·min) or high (3 L·min) FGF without an HME (1L and 3L groups) or with an HME (Pall BB25FS, Pall Biomedical, East Hills, NY; HME1L and HME3L groups). The temperature and absolute humidity of inhaled gases were measured at 10, 20, 40, 60, and 80 minutes after connecting the patient to the breathing circuit.

RESULTS: The mean inhaled gas temperature was higher in HME groups (HME1L: 30.3°C ± 1.1°C; HME3L: 29.3°C ± 1.2°C) compared with no-HME groups (1L: 27.0°C ± 1.2°C; 3L: 27.1°C ± 1.5°C; P < 0.0001). The mean inhaled gas absolute humidity was higher in HME than no-HME groups and higher in low-flow than high-flow groups ([HME1L: 25 ± 1 mg H₂O·L] > [HME3L: 23 ± 2 mg H₂O·L] > [1L: 17 ± 1 mg H₂O·L] > [3L: 14 ± 1 mg H₂O·L]; P < 0.0001).

CONCLUSIONS: In a pediatric circle breathing system, the use of neither high nor low FGF provides the minimum humidity level of the inhaled gases thought to reduce the risk of dehydration of airways. Insertion of an HME increases the humidity and temperature of the inhaled gases, bringing them closer to physiological values. The use of a low FGF enhances the HME efficiency and consequently increases the inhaled gas humidity values. Therefore, the association of an HME with low FGF in the breathing circuit is the most efficient way to conserve the heat and the moisture of the inhaled gas during pediatric anesthesia.
Serum Anticholinergic Activity and Postoperative Cognitive Dysfunction in Elderly Patients

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BACKGROUND: Cerebral cholinergic transmission plays a key role in cognitive function, and anticholinergic drugs administered during the perioperative phase are a hypothetical cause of postoperative cognitive dysfunction (POCD). We hypothesized that perioperative increase in serum anticholinergic activity (SAA) is associated with POCD in elderly patients.

METHODS: Seventy-nine patients aged >65 years undergoing elective major surgery under standardized general anesthesia (thiopental, sevoflurane, fentanyl, and atracurium) were investigated. Cognitive functions were assessed preoperatively and 7 days postoperatively using the extended version of the CERAD-Neuropsychological Assessment Battery. POCD was defined as a postoperative decline >1 z-score in at least 2 test variables. SAA was measured preoperatively and 7 days postoperatively at the time of cognitive testing. Hodges-Lehmann median differences and their 95% confidence intervals were calculated for between-group comparisons.
RESULTS: Of the patients who completed the study, 46% developed POCD. Patients with POCD were slightly older and less educated than patients without POCD. There were no relevant differences between patients with and without POCD regarding gender, demographically corrected baseline cognitive functions, and duration of anesthesia. There were no large differences between patients with and without POCD regarding SAA preoperatively (pmol/mL, median [interquartile range]/median difference [95% CI], P; 1.14 [0.72, 2.37] vs 1.13 [0.68, 1.68]/0.12 [-0.31, 0.57], P = 0.56), SAA 7 days postoperatively (1.32 [0.68, 2.59] vs 0.97 [0.65, 1.83]/0.35 [-0.26, 0.81], P = 0.37), or changes in SAA (0.08 [-0.50, 0.70] vs -0.02 [-0.53, 0.41]/0.1 [-0.31, 0.52], P = 0.62). There was no significant relationship between changes in SAA and changes in cognitive function (Spearman rank correlation coefficient preoperatively of 0.03 [95% CI, -0.21, 0.26] and postoperatively of -0.002 [95% CI, -0.24, 0.23]).

CONCLUSIONS: In this panel of patients with low baseline SAA and clinically insignificant perioperative anticholinergic burden, although a relationship cannot be excluded in some patients, our analysis suggests that POCD is probably not a substantial consequence of anticholinergic medications administered perioperatively but rather due to other mechanisms.

糖原合酶激酶-3β抑制剂通过调节AMPA受体的表达和功能来抑制瑞芬太尼诱导的术后痛觉过敏

Glycogen Synthase Kinase-3β Inhibition Prevents Remifentanil-Induced Postoperative Hyperalgesia via Regulating the Expression and Function of AMPA Receptors.


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背景：很多研究证实单纯应用瑞芬太尼可提高痛觉敏感性。我们之前报道了激活糖原合酶激酶-3β可通过调节脊髓背角内N-甲基-D天冬氨酸受体的可塑性来促进瑞芬太尼诱导的痛觉过敏。本研究中，我们证实了糖原合酶激酶-3β抑制剂通过调节脊髓背角内AMPA受体的表达和功能来抑制瑞芬太尼诱导的术后痛觉过敏。

方法：首先，我们建立瑞芬太尼诱导的痛觉过敏模型，在开始输注瑞芬太尼前1天、后2小时、6小时、1天、2天、3天、5天以及7天时测定切口模型的机械痛以及热痛情况。应用western blot法测定脊髓背角内AMPAR亚单位（Glu-R1和Glu-R2）运输、AMPAR亚单位磷酸化情况以及糖原合酶激酶-3β活性。另外，我们应用全细胞膜片钳记录法来分析抑制糖原合酶激酶-3β对脊髓背角内AMPA受体诱发电位的影响情况。

结论：瑞芬太尼诱导的术后痛觉过敏的裸鼠脊髓背角AMPA受体亚单位Glu-R1上调(275 ± 36.54 [mean ± SD] vs 100 ± 9.53, P = 0.0009)。应用选择性糖原合酶激酶-3β抑制剂，如氯化锂和TDZD，可改善瑞芬太尼诱导的术后痛觉过敏，并使AMPA受体亚单位Glu-R1下调(254 ± 23.51 vs 119 ± 14.74, P = 0.0027; 254 ± 23.51 vs 124 ± 9.35, P = 0.0032)。另外，瑞芬太尼孵育可提高背角神经元内AMPA受体诱发电位的频率和幅值(61.09 ± 9.34 pA vs 32.56 ± 6.44 pA, P = 0.0009; 118.32 ± 20.33 ms vs 64.37 ± 43.29 ms, P = 0.0002)，而氯化锂和TDZD均可抑制该效果。瑞芬太尼诱导的术后疼痛可促进pGluR1 Ser845和Rab5的表达，该效果同样可被氯化锂或TDZD抑制。

总结：上述结果表明抑制糖原合酶激酶-3β导致瑞芬太尼诱导的术后痛觉过敏症状改善是通过下调细胞膜上AMPA受体Glu-R1的表达以及脊髓背角内pGluR1和Rab5的表达来实现的。

（郝光伟译 薛张纲校）

BACKGROUND: Many studies have confirmed that brief remifentanil exposure can enhance pain sensitivity. We previously reported that activation of glycogen synthase kinase-3β (GSK-3β)
contributes to remifentanil-induced hyperalgesia via regulating N-methyl-D-aspartate receptor plasticity in the spinal dorsal horn. In this study, we demonstrated that GSK-3β inhibition prevented remifentanil-induced postoperative hyperalgesia via regulating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) expression and function in the spinal dorsal horn.

METHODS: Using a rat model of remifentanil-induced incision hyperalgesia, mechanical and thermal pain was tested 1 day before infusion and 2 hours, 6 hours, 1 day, 2 days, 3 days, 5 days, and 7 days after infusion. Western blot analysis was used to detect AMPAR subunit (GluR1 and GluR2) trafficking, AMPAR phosphorylation status, and GSK-3β activity in the spinal dorsal horn. Furthermore, whole-cell patch-clamp recording was used to analyze the effect of GSK-3β inhibition on AMPAR-induced current in the spinal dorsal horn.

RESULTS: Membrane AMPAR subunit GluR1 was upregulated in the spinal cord in remifentanil-induced postoperative hyperalgesia rats (275 ± 36.54 [mean ± SD] vs 100 ± 9.53, P = 0.0009). Selective GSK-3β inhibitors, LiCl and TDZD, treatment ameliorates remifentanil-induced postoperative hyperalgesia, and this was associated with the downregulated GluR1 subunit in the membrane fraction (254 ± 23.51 vs 119 ± 14.74, P = 0.0027; 254 ± 23.51 vs 124 ± 9.35, P = 0.0032). Moreover, remifentanil incubation increased the amplitude and the frequency of AMPAR-induced current in dorsal horn neurons (61.09 ± 9.34 pA vs 32.56 ± 6.44 pA, P = 0.0009; 118.32 ± 20.33 milliseconds vs 643.67 ± 43.29 milliseconds, P = 0.0002), which was prevented with the application of LiCl and TDZD, respectively. Remifentanil-induced postoperative pain induced an increase in pGluR1 Ser845 and Rab5, which was prevented with the application of LiCl and TDZD.

CONCLUSIONS: These results indicate that amelioration of remifentanil-induced postoperative hyperalgesia by GSK-3β inhibition is attributed to downregulated AMPAR GluR1 expression in the membrane fraction and inhibition of AMPAR function via altering pGluR1 and Rab5 expression in the spinal dorsal horn.

血红蛋白氧载体 HBOC-201 在非心脏手术病人中使用时的安全性和有效性的随机多中心研究
A Safety and Efficacy Evaluation of Hemoglobin-Based Oxygen Carrier HBOC-201 in a Randomized, Multicenter Red Blood Cell Controlled Trial in Noncardiac Surgery Patients
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背景：我们介绍的是1998-1999年血红蛋白氧载体未公开发表的研究结果。
方法：在一个多中心、随机的、单盲的对比研究中，HBOC-201 对比同种异体的红细胞灌注，非心脏手术患者接受最多7个单位 HBOC-201（n=83）或红细胞（n=77）。患者可能转化红细胞更安全或者其他推论。同种异体红细胞输注的有效作用终点被消除和/或减少需要28天。
结果：在 HBOC-201 组避免红细胞输注的患者比例是 0.427（95% 可信区间，0.321-0.533）。HBOC-201 组被试者平均接受 3.2 个单位红细胞，而对照组为 4.4 个单位（P=0.004）。29名（95.2%）HBOC-201组被试者和72名（93.5%）红细胞组被试者出现不良反应，认为分别与59名（77.1%）和18名（23.4%）被试者研究性治疗有关。HBOC-201组和红细胞输注组30天死亡数分别是5名（6.0%）和4名（5.2%）患者（P=1.00），严重不良反应发生率分别是24（28.9%）和20（26.0%），而监护室停留时间（对数秩 P=0.15）和出院时间（对数秩 P=0.53）两组则相近。
BACKGROUND: We present the results of a previously unpublished hemoglobin-based oxygen carrier (HBOC) study conducted in 1998-1999.

METHODS: In a multicenter, randomized, single-blind, comparative study of HBOC-201 versus allogeneic red blood cell (RBC) transfusions, no-cardiac surgery patients received HBOC-201 to a maximum of 7 units (n = 83) or RBCs (n = 77). Patients could be switched to RBCs for safety or any other reason. The efficacy end points were elimination and/or reduction of allogeneic RBC transfusions for 28 days.

RESULTS: The proportion of patients in the HBOC-201 group that avoided RBC transfusion was 0.427 (95% confidence interval, 0.321 - 0.533). Subjects in the HBOC-201 group received on average 3.2 units of RBCs versus 4.4 units in the control arm (P = 0.004). Seventy-nine (95.2%) subjects in the HBOC-201 group and 72 (93.5%) in the RBC group experienced adverse events (AEs), judged to be associated with study treatment in 59 (71.1%) and 18 (23.4%) subjects, respectively. Thirty-day mortality, 5 (6.0%) vs 4 (5.2%) patients (P = 1.00), incidence of serious AEs, 24 (28.9%) vs 20 (26.0%) (P = 0.73), or time to intensive care unit (log-rank P = 0.15) or hospital discharge (log-rank P = 0.53) were similar for the HBOC-201 and RBC groups, respectively.

CONCLUSIONS: Up to 7 units of HBOC-201 infused over the course of 6 days resulted in RBC transfusion avoidance in 43% of patients. There were no notable differences in mortality and serious AEs incidence. The use of HBOC-201 was associated with a notable excess of nonserious AEs.
BACKGROUND: Drug-induced sleep endoscopy (DISE) uses sedative-hypnotics to induce moderate obstruction in sleep apnea patients, thereby facilitating anatomic assessment of obstructive physiology. Implementation of DISE with propofol requires a dosing strategy that reliably and efficiently produces obstruction while minimizing oxygen desaturation.

METHODS: The surgeon in a prospective study of transoral robotic resection of the tongue base enrolled 97 patients with obstructive sleep apnea confirmed by polysomnography who failed continuous positive airway pressure. All patients were screened by DISE. Propofol dose was determined using custom software written in MATLAB, which has been previously described. Studies were performed in an operating room with standard monitors and resuscitation equipment. No topical anesthesia was used, and no IV drugs other than propofol were used. All patients received 2 L/min supplemental oxygen via a nasal cannula placed in the mouth. After initiation of propofol sedation, a pediatric bronchoscope was positioned via the naris to observe the velopharynx. The sedation sequence was continued until the clinical end point of obstruction onset was noted. Observation of the pharynx was performed for a sufficient period to obtain images of the anatomic site(s) of obstruction. The infusion was then terminated. Statistical analysis was performed with MATLAB (MathWorks, version 2012b). Comparison of saturation nadirs between DISE and subject sleep studies was performed with both the paired and unpaired Student t test.

RESULTS: The subject population was characterized by a median body mass index of 32.1 (interquartile range [IQR] 6.8) kg/m and apnea-hypopnea index of 48 (IQR 32). All patients demonstrated obstruction within the design variables. Obstruction was observed after 236 (±57.9) seconds at an estimated effect-site concentration of 4.2 ± 1.3 mcg/mL. The median saturation nadir during DISE was significantly higher (91.4% (IQR 5.1)) than that during standard sleep studies (81.0% [IQR 11.2], P < 0.0001). Ninety-five percent confidence intervals for correlations between DISE saturation nadir and body mass index, age, apnea-hypopnea index, or administered propofol dose included zero in all cases.

CONCLUSIONS: A propofol infusion strategy that requires limited experience with propofol dose selection and only 1 pump dosing change reliably produced airway obstruction in patients with severe sleep apnea. Clinical obstruction was achieved faster than target-controlled infusion-based systems for similar procedures reported in the literature. The observed degree of oxygen desaturation in the model system was within a clinically acceptable range.

The Antihypersensitive and Antiinflammatory Activities of a Benzofuranone Derivative in Different Experimental Models in Mice: The Importance of the Protein Kinase C Pathway

The Antihypersensitive and Antiinflammatory Activities of a Benzofuranone Derivative in Different Experimental Models in Mice: The Importance of the Protein Kinase C Pathway

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**方法**：试验中用瑞士老鼠。通过内脚趾注射角叉胶，缓激肽，前列腺素，肾上腺素，脂多糖或者弗氏佐剂或者用神经疼痛模型 (von Frey 纤维 0.6g) 来诱导高敏反应。通过角叉胶，PGE2，BK 诱导的爪水肿模型引发抗炎反应。PKC 用于佛波醇导致的伤害模型。

**结果**：BF1 抑制高敏反应和脚底注射角叉胶，BK，PGE2（P<0.001）引起的水肿模型，并且减少弗氏佐剂和肾上腺素（P<0.001）引起的超敏反应是有效的，而不是脂多糖（P<0.257）引起的。BF1 抑制佛波醇诱导的舔的行为，表明涉及到 PKC 通路。试验中还观察到降低结扎部分坐骨神经（P<0.001）导致的超敏反应，抑制嗜中性粒细胞迁移和进入脊髓的白介素-1β 的产生。BF1 治疗不会影响运动功能（P=0.0783），这是其他止痛药的严重副作用。

**结论**：在急性和慢性疼痛和炎症模型，BF1 有剂量依赖的抗高敏反应和抗炎反应，可能通过 PKC 通路的激活来。这种容易快速合成的复合物，低成本，低浓度，每天一次的药物表明可以有望用于未来的临床研究。

（王雪译 李士通审校）

**BACKGROUND:** Benzofuranone (BF1) was synthesized and its effects evaluated on mechanical hypersensitivity and paw edema models induced by different agents and on neuropathic pain induced by partial ligation of the sciatic nerve. An attempt was also made to elucidate the mechanism of action.

**METHODS:** Swiss mice were used for the tests. Hypersensitivity was induced by intraplantar injection of carrageenan, bradykinin (BK), prostaglandin E2 (PGE2), epinephrine, lipopolysaccharide, or complete Freund adjuvant or by using a neuropathic pain model (evaluated with von Frey filament 0.6 g). The antiinflammatory effects were investigated in a paw edema model induced by carrageenan, PGE2, and BK (measured with a plethysmometer). The involvement of protein kinase C (PKC) was investigated through a noiception model induced by phorbol myristate acetate.

**RESULTS:** BF1 inhibited the hypersensitivity and paw edema induced by intraplantar injection of carrageenan, BK, and PGE2 (P < 0.001), and it was effective in reducing the hypersensitivity evoked by complete Freund adjuvant or epinephrine (P < 0.001) but not by lipopolysaccharide (P = 0.2570). BF1 inhibited the licking behavior induced by phorbol myristate acetate (P < 0.001), suggesting involvement of the PKC pathway. A reduction in hypersensitivity of mice submitted to partial ligation of the sciatic nerve (P < 0.001) was observed, with inhibition of neutrophil migration and interleukin-1β production into the spinal cord. BF1 treatment did not interfere with locomotor activity (P = 0.0783) and thermal withdrawal threshold (P = 0.5953), which are important adverse effects of other analgesics.

**CONCLUSIONS:** BF1 has dose-dependent antihypersensitive and antiinflammatory effects in both acute and chronic models of pain and inflammation, possibly mediated through interference with the PKC activation pathway. The easy and fast synthesis of this compound, low-cost, low-concentration-requirement, and once-daily-administration drug suggest it as a candidate for future clinical studies.

**小儿应用硝普钠进行控制性降压的预测因素**

Predictors of Arterial Blood Pressure Control During Deliberate Hypotension with Sodium Nitroprusside in Children

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背景：硝普钠用于特定手术降低动脉血压。关于硝普钠控制血压效果的数据有限。但没有关于病人和临床医生影响动脉血压的数据。我们评估了行大手术的婴儿和儿童应用硝普钠的剂量反应效应以及进行血压控制的定量评估。

方法：153例患者在进行控制性降压的手术操作时注射标记过的硝普钠。持续输注硝普钠，滴定进行控制血压（MAP界定为临床标准的10%）通过动脉导管记录血压。用定量统计法统计血压控制情况。多元法评估病人和方法的效果。

结果：45.4%（SD 23.9%；95%可信区间41.5%–49.18%）的手术时间进行控制血压。在输注速率方面，较大的变化与更严重的血压控制有关（少控制7.99%的血压速率为1μg/kg/min增加平均滴注量，P=0.0009）。病人基础血压与目标血压很大的差异预示更多的血压控制（每mmHg多控制0.93%的血压增加MAP的差异性，P=0.0013）。这两种效果都出现在多元模型中。

结论：硝普钠降低血压是有效的。然而，血压维持目标血压的时间不到一半的。临床医生和病人因素不能预测血压，虽然确认了2种相反的关系。弄清这些关系需要进一步的研究，并且最好应用模型，建议用于小儿控制性降压时增加剂量。

（王雪 译，李士通 审校）

BACKGROUND: Sodium nitroprusside (SNP) is used to decrease arterial blood pressure (BP) during certain surgical procedures. There are limited data regarding efficacy of BP control with SNP. There are no data on patient and clinician factors that affect BP control. We evaluated the dose-response relationship of SNP in infants and children undergoing major surgery and performed a quantitative assessment of BP control.

METHODS: One hundred fifty-three subjects at 7 sites received a blinded infusion followed by open-label SNP during operative procedures requiring controlled hypotension. SNP was administered by continuous infusion and titrated to maintain BP control (mean arterial BP [MAP] within ±10% of clinician-defined target). BP was recorded using an arterial catheter. Statistical process control methodology was used to quantify BP control. A multivariable model assessed the effects of patient and procedural factors.

RESULTS: BP was controlled an average 45.4% (SD 23.9%; 95% CI, 41.5%–49.18%) of the time. Larger changes in infusion rate were associated with worse BP control (7.99% less control for 1 μg·kg·min increase in average titration size, P = 0.0009). A larger difference between a patient’s baseline and target MAP predicted worse BP control (0.93% worse control per 1-mm Hg increase in MAP difference, P = 0.0013). Both effects persisted in multivariable models.

CONCLUSIONS: SNP was effective in reducing BP. However, BP was within the target range less than half of the time. No clinician or patient factors were predictive of BP control, although 2 inverse relationships were identified. These relationships require additional study and may be best coupled with exposure-response modeling to propose improved dosing strategies when using SNP for controlled hypotension in the pediatric population.

术前使用他汀类药物不能使高风险患者免受术后发生早期急性呼吸窘迫综合征的回顾性队列研究

Preoperative Statin Administration Does Not Protect Against Early Postoperative Acute Respiratory Distress Syndrome: A Retrospective Cohort Study

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BACKGROUND: Statins have been shown to possess antiinflammatory and immunomodulatory effects. In this study, we sought to determine if preoperative statin therapy is associated with a reduced frequency of postoperative acute respiratory distress syndrome (ARDS) in surgical populations at increased risk of developing ARDS.

METHODS: We performed a retrospective cohort evaluation of the association between preoperative statin therapy and early postoperative ARDS in patients undergoing elective high-risk thoracic and aortic vascular surgery. The association between preoperative statin therapy and postoperative ARDS was assessed using propensity-adjusted analyses to control for indication bias and confounding factors.

RESULTS: Of 1845 patients, 722 were receiving preoperative statin therapy. One hundred twenty patients developed postoperative ARDS. Frequencies of ARDS among those receiving statin therapy versus those who were not was 7.2% and 6.1%, respectively (OR = 1.20; 95% CI, 0.83-1.75; P = 0.330). Neither the stratified propensity score analysis (pooled OR 0.93; 95% CI, 0.60-1.43) nor matched analysis (OR = 0.78; 95% CI, 0.48-1.27) identified a statistically significant association between preoperative statin administration and postoperative ARDS. When compared to matched controls, patients who developed postoperative ARDS did not differ in mortality (7.7% vs 8.8%, P = 0.51), hospital length of stay (21 days vs 15 days, P = 0.21), or ventilator-free days (24 days vs 25 days, P = 0.62).

CONCLUSIONS: In patients undergoing high-risk surgery, preoperative statin therapy was not associated with a statistically significant reduction in postoperative ARDS. These results do not support the use of statins as prophylaxis against ARDS in patients undergoing high-risk surgery.
BACKGROUND: The Agency for Healthcare Research and Quality (AHRQ) has established multiple sets of indicators for quality monitoring and improvement. One such set is the patient safety indicators (PSIs), which focuses on potentially preventable hospital complications after surgeries, procedures, and childbirth. Our objective in this study was to determine the prevalence of childbirth-related anesthesia complications by method of delivery and to evaluate the variation in complication rates across hospitals using the AHRQ PSI methodology and a modification specific to childbirth with the goal of determining the relevance of tracking anesthesia complications as a potential PSI for childbirth.

METHODS: The technical specifications of the experimental Anesthesia Complication Quality Indicator, one of the PSI defined by AHRQ, were modified to create a childbirth-specific indicator that included all childbirth admissions (vaginal and cesarean deliveries) and complications from general and neuraxial anesthesia/analgesia. Using California hospital discharge data, we calculated hospital-specific rates, adjusting for age, race/ethnicity, and pregnancy complications.

RESULTS: A total of 508,842 deliveries occurred in 254 hospitals in California in 2009. Hospitals with <200 annual deliveries (N = 12) were excluded from analyses. Among 242 hospitals, the rate of anesthesia complications was 0.13% for the standard AHRQ study population (adult surgical admissions, which included cesarean deliveries). The childbirth-specific rate of anesthesia complications was 0.31%. When stratified by method of delivery, complication rates were 0.49% for cesarean delivery and 0.22% for vaginal delivery (P < 0.0001). The unadjusted mean (SD) was 0.34% (0.34%), with range (0%~2.46%). The rates of 13 hospitals (including their 95% confidence limits) remained in the upper quartile as outliers, with adjusted rates from 0.52% to 2.13%.

CONCLUSIONS: Rates of childbirth-related anesthesia complications may provide an opportunity to identify hospitals with extreme rates that may provide insights into systematic ways to improve patient safety.

QT 延长综合征患儿使用现代麻醉的安全性

The Safety of Modern Anesthesia for Children with Long QT Syndrome
Background: Patients with long QT syndrome (LQTS) may experience a clinical spectrum of symptoms, ranging from asymptomatic, through presyncope, syncope, and aborted cardiac arrest, to sudden cardiac death. Arrhythmias in LQTS are often precipitated by autonomic changes. This patient population is believed to be at high risk for perioperative arrhythmia, specifically torsades de pointes (TdP), although this perception is largely based on limited literature that predates current anesthetic drugs and standards of perioperative monitoring. We present the largest multicenter review to date of anesthetic management in children with LQTS.

Methods: We conducted a multicentered retrospective chart review of perioperative management of children with clinically diagnosed LQTS, aged 18 years or younger, who received general anesthesia (GA) between January 2005 and January 2010. Data from 8 institutions were collated in an anonymized database.

Results: One hundred three patients with LQTS underwent a total of 158 episodes of GA. The median (interquartile range) age and weight of the patients at the time of GA was 9 (3-15) years and 30.3 (15.4-54) kg, respectively. Surgery was LQTS-related in 81 (51%) GA episodes (including pacemaker, implantable cardioverter-defibrillator, and loop recorder insertions and revisions and lead extractions) and incidental in 77 (49%). β-blocker therapy was administered to 76% of patients on the day of surgery and 47% received sedative premedication. Nineteen percent of patients received total IV anesthesia, 30% received total inhaled anesthesia, and the remaining 51% received a combination. No patient received droperidol. There were 5 perioperative episodes of TdP, all in neonates or infants, all in surgery that was LQTS-related.
and none of which was overtly attributable to anesthetic regimen. Thus the incidence (95% confidence interval) of perioperative TdP in incidental versus LQTS-related surgery was 0/77 (0%; 0%-5%) vs 5/81 (6.2%; 2%-14%).

CONCLUSIONS: With optimized perioperative management, modern anesthesia for incidental surgery in patients with LQTS is safer than anecdotal case report literature might suggest. Our series suggests that the risk of perioperative TdP is concentrated in neonates and infants requiring urgent interventions after failed first-line management of LQTS.

Osmolality and respiratory regulation in humans: respiratory compensation for hyperchloremic metabolic acidosis is absent after infusion of hypertonic saline in healthy volunteers.


BACKGROUND:
Several animal studies show that changes in plasma osmolality may influence ventilation. Respiratory depression caused by increased plasma osmolality is interpreted as inhibition of water-dependent thermoregulation because conservation of body fluid predominates at the cost of increased core temperature. Respiratory alkalosis, on the other hand, is associated with a decrease in plasma osmolality and strong ion difference (SID) during human pregnancy. We investigated the hypothesis that osmolality would influence ventilation, so that
increased osmolality will decrease ventilation and decreased osmolality will stimulate ventilation in both men and women.

METHODS: Our study participants were healthy volunteers of both sexes (ASA physical status I). Ten men (mean 28 years; range 20-40) and 9 women (mean 33 years; range 22-43) were included. All women participated in both the follicular and luteal phases of the menstrual cycle. Hyperosmolality was induced by IV infusion of hypertonic saline 3%, and hypoosmolality by drinking tap water. Arterial blood samples were collected for analysis of electrolytes, osmolality, and blood gases. Sensitivity to CO2 was determined by rebreathing tests performed before and after the fluid-loading procedures.

RESULTS: Infusion of hypertonic saline caused hyperchloremic metabolic acidosis with decreased SID in all subjects. Analysis of pooled data showed absence of respiratory compensation. Baseline arterial PCO2 (PaCO2) mean (SD) 37.8 (2.9) mm Hg remained unaltered, with lowest PaCO2 37.8 (2.9) mm Hg after 100 minutes, P = 0.70, causing a decrease in pH from mean (SD) 7.42 (0.02) to 7.38 (0.02), P < 0.001. Metabolic acidosis was also observed during water loading. Pooled results show that PaCO2 decreased from 38.2 (3.3) mm Hg at baseline to 35.7 (2.8) mm Hg after 80 minutes of drinking water, P = 0.002, and pH remained unaltered: pH 7.43 (0.02) at baseline to pH 7.42 (0.02), P = 0.14, mean difference (confidence interval) = pH -0.007 (-0.017 to 0.003).

CONCLUSIONS: Our results indicate that osmolality has an influence on ventilation. Respiratory compensation for hyperchloremic metabolic acidosis was suppressed during hyperosmolality. Water loading caused a decrease in plasma osmolality and metabolic acidosis, and although the decrease in SID was smaller compared with salt loading, the expected respiratory compensation was observed. Ventilation was also stimulated in men, therefore independently of progesterone levels. We propose that the influence of osmolality on ventilation consists mainly as depression in conditions of hyperosmolality and that this depression is absent during hypoosmolality.

甘氨酸转运体抑制剂可减轻癌痛
Relief of Cancer Pain by Glycine Transporter Inhibitors

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背景：近日有研究表明甘氨酸转运体抑制剂在坐骨神经损伤及糖尿病等有神经病理性疼痛的动物模型中具有镇痛作用。复杂的生物学机制表明神经性因素在骨肿瘤引起的剧烈疼痛中起一定作用。骨肿瘤改变了阿片类药物的镇痛作用，限制其有效性。因此急需找到用于缓解骨癌痛的新药。

方法：在 C3H/HeN 小鼠股骨远端髓腔接种溶骨肉瘤细胞 NCTC 2472 建立骨肿瘤小鼠模型。在小鼠股骨肿瘤模型中，我们研究了 GlyT2 抑制剂，ORG 25543 和 ALX 1393,GlyT1 抑制剂，OR 25935，及在异常疼痛、痛阈值、防御行为，和肢体的异常活动等疼痛行为中通过甘氨酸转运体 siRNA 下调脊柱甘氨酸转运蛋白的表达的作用。同时也对吗啡与甘氨酸转运体抑制剂的联合作用进行了研究。

结果：GlyT2 抑制剂，ORG 25543 及 ALX 1393,GlyT1 抑制剂，OR 25935 IV 或口服制剂，下调脊柱甘氨酸转运蛋白表达可改善接种肿瘤细胞 11 天后骨癌痛小鼠的痛行为。这种镇痛效果强大持久。无明显镇痛效果的低剂量吗啡联合 ORG 25543 可以显著提高 ORG 25543 的镇痛效果。小鼠接种肿瘤细胞后第二天，注射 ORG 25543 引起了 3 阶段的疼痛反应，最初痛行为加剧（第 2-4 天），随后基本消失（5-7 天），接着再次出现。在注射
ORG 25543 一天后鞘内注射士的宁，可短暂的拮抗 ORG 25543 的镇痛效果。对照组小鼠中，士的宁提高了注射肿瘤细胞四天后的小鼠痛行为，同时在第 4 到 5 天加剧这一结果。以上证据表明不同机制具有时相依赖性。

结论：甘氨酸转运蛋白抑制剂联合或不联合吗啡可能是用于治疗骨癌痛的新方式，同时也可以进一步研究骨癌痛的发生机制。

（陈凌君 译，李士通 审校）

BACKGROUND: Recent studies have revealed the antinociceptive effects of glycine transporter (GlyT) inhibitors in neuropathic pain models such as sciatic nerve-injured and diabetic animals. Bone cancer can cause the most severe pain according to complex mechanisms in which a neuropathic element is included. Bone cancer modifies the analgesic action of opioids and limits their effectiveness, and thus novel medicament for bone cancer pain is desired.

METHODS: For the femur bone cancer model, NCTC 2472 tumor cells were injected into the medullary cavity of the distal femur of C3H/HeN mice. Effects of GlyT2 inhibitors, ORG 25543 and ALX 1393, and GlyT1 inhibitors, ORG 25935, and knockdown of the expression of spinal GlyTs protein by GlyTs siRNA on pain-like behaviors, such as allodynia, withdrawal threshold, guarding behavior, and limb-use abnormality, were examined in the femur bone cancer model mice. Effects of morphine in combination with GlyT inhibitor were examined.

RESULTS: GlyT2 inhibitors, ORG 25543 and ALX 1393, and GlyT1 inhibitor ORG 25935 by IV or oral administration or knockdown of the expression of spinal GlyTs protein improved pain-like behaviors at 11 days after tumor transplantation. The pain-relief activity was potent and long lasting. Morphine at a dose with no analgesic activity combined with ORG 25543 further promoted the ORG 25543-induced pain-relief activity. Injection of ORG 25543 on the second day after tumor implantation caused 3 phases of pain responses; pain-like behaviors were initially accelerated (at 2-4 days) and subsequently almost disappeared (5-7 days) and then reappeared. Intrathecal injection of strychnine 1 day after injection of ORG 25543 transiently antagonized the pain-relief activity of ORG 25543. In control mice, strychnine improved pain-like behaviors 4 days after tumor implantation and aggravated the behaviors between 4 and 5 days. The evidence suggests that the different mechanisms are phase-dependently involved.

CONCLUSIONS: GlyT inhibitors with or without morphine may be a new strategy for the treatment of bone cancer pain and lead to further investigations of the mechanisms underlying the development of bone cancer pain.