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# Pain and Analgesic Mechanisms

Research Report

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## **室性心动过速消融：一项给予麻醉医生的系统综述**

### **Ventricular Tachycardia Ablation: A Comprehensive Review for Anesthesiologists**

Mittnacht, Alexander J. C. MD<sup>\*</sup>; Dukkupati, Srinivas MD<sup>†</sup>; Mahajan, Aman MD, PhD<sup>‡</sup>

*Anesthesia & Analgesia* 2015 120 737–748

经皮导管消融术越来越多运用于药物治疗无效的反复发作室性心动过速（ventricular tachycardia, VT）的患者。对于此类患者最佳的管理包括谨慎考虑潜在心脏疾病的严重程度，麻醉药物相互作用以及在 VT 标测和消融过程中的技术问题。目标在于选择一种致心律失常性最小的麻醉技术，这样可以使得在电生理操作室内 VT 的发生具有可重复性。麻醉药可以直接通过对于离子通道和缝隙连接作用，或间接通过对于自主神经系统作用改变动作电位和心室去极化过程。此外，在操作过程中维持血流动力学稳定以及监测终末器官灌注是另一项挑战。本综述全面地更新了当今 VT 消融的实施过程中的麻醉处理方法。

（俞芳 译 陈杰 校）

Percutaneous catheter ablation is being increasingly performed in patients with recurrent ventricular tachycardia (VT) unresponsive to medical treatment. Optimal management of patients requires careful consideration of the severity of the underlying cardiac disease, the anesthetic drug interactions, and the procedural technique during VT mapping and ablation. The goal is to choose an anesthetic technique that has the least effect on arrhythmogenicity, allowing reproducibility of the VT in the electrophysiology laboratory. Anesthetics can alter action potential and ventricular depolarization directly through their effects on ion channels and gap junctions, as well as indirectly via their effects on the autonomic nervous system. Furthermore, maintaining hemodynamic stability and monitoring for adequate end-organ perfusion are additional challenges. In this review, we provide a comprehensive update on the currently performed VT ablation procedures and their anesthetic considerations.

## **丙泊酚对于高糖诱导的人脐静脉内皮细胞凋亡和功能障碍的保护作用**

### **Propofol Protects Against High Glucose-Induced Endothelial Apoptosis and Dysfunction in Human Umbilical Vein Endothelial Cells**

Zhu, Minmin MD; Wen, Meilin MD; Sun, Xia MD; Chen, Wankun MD; Chen, Jiawei MD, PhD; Miao, Changhong MD, PhD

Anesthesia & Analgesia 2015 120 781–789

**背景：**围术期高血糖症是临床上常见的一种代谢紊乱疾病。高血糖诱导内皮细胞凋亡和功能障碍。丙泊酚是一种临床上广泛使用的静脉麻醉药物。本研究检测丙泊酚是否及如何减轻高糖诱导的人脐静脉内皮细胞（HUVECs）凋亡和功能障碍。**方法：**用不同浓度（5，10，15 和 25 mM）的血糖体外培养 HUVEC，时间分别是 4，8，12 和 24 小时。为了研究丙泊酚的效应，用不同浓度（0.2，1，5 和 25 $\mu$ M）的丙泊酚孵育 2 小时。在平行实验中，细胞在 5 mM 葡萄糖中孵育作为对照。用硝酸还原酶法测定产生的一氧化氮（NO）。用细胞计数试剂盒-8 测定细胞活性。用 Western blot 法检测 caspase 3、细胞色素 C、内皮型一氧化氮合酶（eNOS）、p-eNOS-Thr495、p66Shc、蛋白激酶 C  $\beta$ II（PKC $\beta$ II）和 p-PKC $\beta$ II-Ser660。用亚铁细胞色素 c 减少法测定超氧阴离子（O $_2^{\cdot-}$ ）累积。用末端脱氧核苷酸转移酶介导 dUTP 缺口末端标记染色法测定细胞凋亡。

**结果：**与对照组相比，高糖减少 HUVEC 的 NO 产生（ $P < 0.0001$ ，降低细胞活性（ $P < 0.0001$ ）。与高糖处理相比，丙泊酚预处理细胞（5 $\mu$ M，2 h）减少了高浓度葡萄糖诱导的抑制性 p-eNOS-Thr495 磷酸化（ $P < 0.0001$ ），增加 NO 的产生（ $P = 0.0007$ ），降低高血糖诱导的 p66Shc 的表达（ $P < 0.0001$ ）和 p66Shc 线粒体易位（ $P < 0.0001$ ），O $_2^{\cdot-}$ 蓄积（ $P < 0.0001$ ），线粒体细胞色素 C 释放（ $P < 0.0001$ ），活化 Caspase 3 的表达（ $P < 0.0001$ ）和增强内皮细胞活性（ $P < 0.0001$ ）。此外，异丙酚抑制高糖诱导的 PKC- $\beta$ II 的表达（ $P = 0.0002$ ）和 p-PKC $\beta$ II-ser660 磷酸化（ $P < 0.0001$ ）。丙泊酚的保护作用与 PKC $\beta$ II 抑制剂十分相似。

**结论：**丙泊酚通过降低高糖诱导 PKC $\beta$ II 的表达和 p-PKC $\beta$ II-ser660 磷酸化的机制，抑制高糖诱导的 p66Shc 线粒体易位。因此保护人脐静脉内皮细胞免受高糖诱导的内皮细胞功能障碍和细胞凋亡。

（徐欢译 陈杰校）

**BACKGROUND:** Perioperative hyperglycemia is a common clinical metabolic disorder. Hyperglycemia could induce endothelial apoptosis and dysfunction. Propofol is a widely used IV anesthetic drug in clinical settings. In the present study, we examined whether and how propofol reduced high glucose-induced endothelial apoptosis and dysfunction in human umbilical vein endothelial cells (HUVECs).

**METHODS:** HUVECs were cultured with different concentrations (5, 10, 15, and 25 mM) of glucose for different times (4, 8, 12, and 24 hours). To study the effect of propofol, cells were incubated with different concentrations (0.2, 1, 5, and 25  $\mu$ M) of propofol for 2 hours. In parallel experiments, cells were incubated in 5 mM glucose as control. Nitric oxide (NO) production was measured with a nitrate reductase assay. Cell viability was determined with a Cell Counting Kit-8. Protein expression of active caspase 3, cytochrome c, endothelial NO synthase (eNOS), p-eNOS-Thr495, p66Shc, protein kinase C  $\beta$ II (PKC $\beta$ II), and p-PKC $\beta$ II-Ser660 was measured by Western blot analysis. Accumulation of superoxide anion (O $_2^{\cdot-}$ ) was measured with the reduction of ferricytochrome c. Cell apoptosis was determined with terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling staining.

**RESULTS:** Compared with control, high glucose decreased NO production ( $P < 0.0001$ ) and reduced cells viability ( $P < 0.0001$ ) in HUVECs. Compared with high glucose treatment, pretreatment of cells with propofol (5  $\mu$ M, 2 hours) reduced high glucose-induced inhibitory p-eNOS-Thr495 phosphorylation ( $P < 0.0001$ ), increasing NO production ( $P = 0.0007$ ), decreased high glucose-induced p66Shc expression ( $P < 0.0001$ ) and p66Shc mitochondrial translocation ( $P < 0.0001$ ), O $_2^{\cdot-}$  accumulation ( $P < 0.0001$ ), mitochondrial cytochrome c release ( $P < 0.0001$ ), active caspase 3 expression ( $P < 0.0001$ ), and enhancing endothelial viability ( $P < 0.0001$ ). Furthermore, propofol inhibited high glucose-induced PKC $\beta$ II expression ( $P = 0.0002$ ) and p-

PKC $\beta$ II-Ser660 phosphorylation ( $P < 0.0001$ ). Moreover, the observed protective effect of propofol was quite similar to that of PKC $\beta$ II inhibitor.

**CONCLUSIONS:** Propofol, by a mechanism of decreasing high glucose-induced PKC $\beta$ II expression and p-PKC $\beta$ II-Ser660 phosphorylation, inhibits high glucose-induced p66Shc mitochondrial translocation, therefore protecting HUVECs from high glucose-induced endothelial dysfunction and apoptosis.

## 金黄色葡萄球菌在麻醉工作区域传播的流行病学

### The Epidemiology of Staphylococcus aureus Transmission in the Anesthesia Work Area

Loftus, Randy W. MD<sup>\*</sup>; Koff, Matthew D. MS, MD<sup>\*</sup>; Brown, Jeremiah R. MS, PhD<sup>†</sup>; Patel, Hetal M. BS<sup>‡</sup>; Jensen, Jens T. MS<sup>\*</sup>; Reddy, Sundara MD<sup>‡</sup>; Ruoff, Kathryn L. PhD<sup>§</sup>; Heard, Stephen O. MD<sup>||</sup>; Yeager, Mark P. MD<sup>\*</sup>; Dodds, Thomas M. MD<sup>\*</sup>

Anesthesia & Analgesia 2015 120 807-818

**背景:**关于术中金黄色葡萄球菌传播的流行病学所知甚少。本研究主要目的是检查麻醉工作区域常见的金葡萄球菌(表型)的传播方式、传染源、传播路径以及抗生素敏感性。次要研究目标是检查表型与术后 30 天病人培养、表型增长率和表型分离的危险因素之间的关系。

**方法:**先前通过病原学分类、时态关联以及 API 系统确认金葡萄球菌可引起术中细菌性传播事件,需进行抗生素纸片扩散法敏感性检测。结合这些技术确认金葡萄球菌传播事件,并将之分类(发生于术中或术间)。金葡萄球菌传播源可以通过已证实的实验模型以及对术后 30 天病人的培养结果进行脉冲凝胶电泳来证实。通过时间-阳性分析来评估增长率,通过 logistic 回归对孤立的风险因素进行评估。

**结果:**对从先前术中传播事件中分离出的 170 例金葡萄球菌,通过 API 表型进一步细分。两个表型:表型 P(病人)和表型 H(手),占分离株的 65%。表型 P 和表型 H 分别确认为在 39%和 28%的病例中至少 1 次传播事件的致病菌。患者皮肤表面(优势比[OR],8.40;95%可信区间(CI),2.30 -30.73)和环境(优势比,10.89;95%置信区间,1.29 - 92.13)样本的表型 P 阳性率比医护人员手部(参照物)的更高。与表型 H 相比,表型 P 更耐甲氧西林(优势比,4.38;95%置信区间,4.38 - 1.59; $P = 0.004$ ),与术后 30 天病人培养结果相关性更大(风险比 36.63, 风险差异,0.174;95%置信区间,0.174 - 0.019, $P < 0.001$ )。与表型 H 相比,表型 P 对甲氧西林耐药和甲氧西林敏感表现出更快的增长率(表型 P:中位数 10.32 H,四分位区间,10.08 - -10.56;表型 H:中位数,10.56 H,四分位区间,10.32 -10.8;  $P = 0.012$ )。分离表型 P 的风险因素包括年龄(优势比,14.11;95%置信区间,3.12 - -63.5; $P = 0.001$ )和病人是否在医院病房暴露(优势比,41.11; 95%置信区间,5.30 -318.78;  $P < 0.001$ )。

**结论:**两种表型的金葡萄球菌都常在麻醉工作区域内传播。与医护人员手部来源表型相比,病人和环境相关表型抗生素耐药性风险增大,术后 30 天病人培养结果阳性率增高。未来工作方向应该是改善患者进入围术期区域时金葡萄球菌的筛查并增强手术室环境清洁以减少相关术后感染。

(池晓颖 译 陈杰 校)

**BACKGROUND:** Little is known regarding the epidemiology of intraoperative Staphylococcus aureus transmission. The primary aim of this study was to examine the mode of transmission, reservoir of origin, transmission locations, and antibiotic susceptibility for frequently encountered S aureus strains (phenotypes) in the anesthesia work area. Our secondary aims were to examine phenotypic associations with 30-day postoperative patient cultures, phenotypic growth rates, and risk factors for phenotypic isolation.

**METHODS:** S aureus isolates previously identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and analytical profile indexing

were subjected to antibiotic disk diffusion sensitivity. The combination of these techniques was then used to confirm *S aureus* transmission events and to classify them as occurring within or between operative cases (mode). The origin of *S aureus* transmission events was determined via use of a previously validated experimental model and links to 30-day postoperative patient cultures confirmed via pulsed-field gel electrophoresis. Growth rates were assessed via time-to-positivity analysis, and risk factors for isolation were characterized via logistic regression.

**RESULTS:** One hundred seventy *S aureus* isolates previously implicated as possible intraoperative transmission events were further subdivided by analytical profile indexing phenotype. Two phenotypes, phenotype P (patients) and phenotype H (hands), accounted for 65% of isolates. Phenotype P and phenotype H contributed to at least 1 confirmed transmission event in 39% and 28% of cases, respectively. Patient skin surfaces (odds ratio [OR], 8.40; 95% confidence interval [CI], 2.30–30.73) and environmental (OR, 10.89; 95% CI, 1.29–92.13) samples were more likely than provider hands (referent) to have phenotype P positivity. Phenotype P was more likely than phenotype H to be resistant to methicillin (OR, 4.38; 95% CI, 1.59–12.06;  $P = 0.004$ ) and to be linked to 30-day postoperative patient cultures (risk ratio, 36.63 [risk difference, 0.174; 95% CI, 0.019–0.328];  $P < 0.001$ ). Phenotype P exhibited a faster growth rate for methicillin resistant and for methicillin susceptible than phenotype H (phenotype P: median, 10.32H; interquartile range, 10.08–10.56; phenotype H: median, 10.56H; interquartile range, 10.32–10.8;  $P = 0.012$ ). Risk factors for isolation of phenotype P included age (OR, 14.11; 95% CI, 3.12–63.5;  $P = 0.001$ ) and patient exposure to the hospital ward (OR, 41.11; 95% CI, 5.30–318.78;  $P < 0.001$ ).

**CONCLUSIONS:** Two *S aureus* phenotypes are frequently transmitted in the anesthesia work area. A patient and environmentally derived phenotype is associated with increased risk of antibiotic resistance and links to 30-day postoperative patient cultures as compared with a provider hand-derived phenotype. Future work should be directed toward improved screening and decolonization of patients entering the perioperative arena and improved intraoperative environmental cleaning to attenuate postoperative health care–associated infections.

## 麻醉医生的手卫生学知识和观念

### Hand Hygiene Knowledge and Perceptions Among Anesthesia Providers

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**背景：**医护人员服从手卫生指南是卫生保健相关感染预防的重要措施，但医疗系统总体依从性仍然较低。关于 4 项手消毒指征相关问题（根据接触类型）能提供完全正确答案的从业者，与答错 1 项以上的从业者相比，他们的手卫生依从性更佳。更好地理解麻醉科从业者知识缺乏情况促使进行手卫生的改进策略。这项研究的主要目的是描述和确认麻醉医师中手卫生知识不足的现状。

**方法：**对国内和多中心团队的 5 个时刻的手卫生知识改良此项问卷，来测试麻醉医生对手卫生的了解情况。完全了解定义为答对 5 项关于手卫生知识的 5 个时刻的问题，评分为 1 分。不完全了解定义为是为答错一个或者更多的问题，评分为 0 分。采用一个多层次的随机效应 XTMELOGIT logistic 模型分析回答者知识不足和地理分布，以及逐步前进后退 logistic 回归分析来确认不完全了解的预测因素。

**结果：**多中心和全国性调查研究组调查应答率分别为 55.8% 和 18.2%。至少一项知识错误发生于 81.6% 的受访者中，正确答案的中位数是 2.89（95% 置信区间，2.78–2.99）。对在接触环境和接触病人前进行手卫生的认识不足是较低的正确中位数的原因。一些认知因素

与减少不完全知识相关，包括在接触环境后积极响应洗手（比值比[OR] 0.23，0.14–0.37， $P < 0.001$ ），在对病人护理中消毒环境（比值比 0.54，0.35–0.82， $P = 0.004$ ），相信他们可以影响同事（比值比 0.43，0.27–0.68， $P < 0.001$ ），并打算坚持准则（比值比 0.56，0.36–0.86， $P = 0.008$ ）。这些协变量与受试者特征曲线下面积相关性为 0.79（95% 置信区间，0.74–0.83）。**结论：**麻醉医生在手卫生准则方面的知识缺乏频繁发生，往往由于没有认识到手卫生在于与污染的病人接触和环境接触后。术中手卫生改进方案应解决这些知识缺陷。本研究证实的不完备知识的相关预测因素应在未来的研究中进一步验证。

（李慧 译 陈杰 校）

**BACKGROUND:** Health care worker compliance with hand hygiene guidelines is an important measure for health care-associated infection prevention, yet overall compliance across all health care arenas remains low. A correct answer to 4 of 4 structured questions pertaining to indications for hand decontamination (according to types of contact) has been associated with improved health care provider hand hygiene compliance when compared to those health care providers answering incorrectly for 1 or more questions. A better understanding of knowledge deficits among anesthesia providers may lead to hand hygiene improvement strategies. In this study, our primary aims were to characterize and identify predictors for hand hygiene knowledge deficits among anesthesia providers.

**METHODS:** We modified this previously tested survey instrument to measure anesthesia provider hand hygiene knowledge regarding the 5 moments of hand hygiene across national and multicenter groups. Complete knowledge was defined by correct answers to 5 questions addressing the 5 moments for hand hygiene and received a score of 1. Incomplete knowledge was defined by an incorrect answer to 1 or more of the 5 questions and received a score of 0. We used a multilevel random-effects XTMELOGIT logistic model clustering at the respondent and geographic location for insufficient knowledge and forward/backward stepwise logistic regression analysis to identify predictors for incomplete knowledge.

**RESULTS:** The survey response rates were 55.8% and 18.2% for the multicenter and national survey study groups, respectively. One or more knowledge deficits occurred with 81.6% of survey respondents, with the mean number of correct answers 2.89 (95% confidence interval, 2.78–2.99). Failure of providers to recognize prior contact with the environment and prior contact with the patient as hand hygiene opportunities contributed to the low mean. Several cognitive factors were associated with a reduced risk of incomplete knowledge including providers responding positively to washing their hands after contact with the environment (odds ratio [OR] 0.23, 0.14–0.37,  $P < 0.001$ ), disinfecting their environment during patient care (OR 0.54, 0.35–0.82,  $P = 0.004$ ), believing that they can influence their colleagues (OR 0.43, 0.27–0.68,  $P < 0.001$ ), and intending to adhere to guidelines (OR 0.56, 0.36–0.86,  $P = 0.008$ ). These covariates were associated with an area under receiver operator characteristics curve of 0.79 (95% confidence interval, 0.74–0.83).

**CONCLUSIONS:** Anesthesia provider knowledge deficits around to hand hygiene guidelines occur frequently and are often due to failure to recognize opportunities for hand hygiene after prior contact with contaminated patient and environmental reservoirs. Intraoperative hand hygiene improvement programs should address these knowledge deficits. Predictors for incomplete knowledge as identified in this study should be validated in future studies.

### 来源于麻醉工作区域的细菌传播事件的动态和影响

## The Dynamics and Implications of Bacterial Transmission Events Arising from the Anesthesia Work Area

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卫生保健相关感染被认为是与病人发病率、死亡率和医疗成本显著增加的一项医院范围内的问题。来源于手术室环境内麻醉工作区域的细菌传播是术后 30 天感染的根源之一，影响高达 16% 接受手术的病人。对麻醉相关细菌传播动态更好的理解有助于产生改善术中感染控制和改善病人安全的方案。

(秦懿译 陈杰校)

Health care-associated infections are a hospital-wide concern associated with a significant increase in patient morbidity, mortality, and health care costs. Bacterial transmission in the anesthesia work area of the operating room environment is a root cause of 30-day postoperative infections affecting as many as 16% of patients undergoing surgery. A better understanding of anesthesia-related bacterial transmission dynamics may help to generate improvements in intraoperative infection control and improve patient safety.

### 氟哌啶醇抑制小鼠树突状细胞成熟和辅助 T1 细胞免疫反应的启动

#### Haloperidol Suppresses Murine Dendritic Cell Maturation and Priming of the T Helper 1-Type Immune Response

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**背景：**氟哌啶醇常用于治疗精神分裂症，或在重症监护室用于镇静重症病人，它同时有免疫调节作用。尽管氟哌啶醇影响免疫功能的机制尚不清楚，但有一种可能性是它改变了树突细胞(DC)的功能。DCs 是强有力的抗原递呈细胞，它影响了 T 淋巴细胞的激活和成熟。此项研究通过体内和体外实验考察了氟哌啶醇对 DC 介导的免疫反应的免疫调节作用。

**方法：**使用从骨髓提取的 DCs 进行细胞培养，检测氟哌啶醇对共刺激分子 (CD80 和 CD86)、II 型主要组织相容性复合体分子和 DC 成熟标志物 CD83 的表达的影响。DC 培养的上清液检测白介素-12 p40 水平。另外分析了氟哌啶醇对混合培养的 DCs 和淋巴细胞的影响，并检测了培养上清液中  $\gamma$  干扰素的分泌。在体内试验中评估了氟哌啶醇对半抗原诱导的接触性超敏反应的影响。

**结果：**氟哌啶醇抑制了 CD80、CD86、II 型主要组织相容性复合体和 DC 细胞上的 CD83 的表达,并抑制了 DC 培养上清液中白介素-12p40 分泌。在含有 T 细胞 (CD4<sup>+</sup>和 CD8 $\alpha$ <sup>+</sup>) 和 DCs 的混合培养物中，氟哌啶醇处理过的 DCs 抑制了同种异体 T 细胞的增殖，并有效抑制了  $\gamma$  干扰素的产生。在体实验中，氟哌啶醇减少半抗原诱导的接触性超敏反应。此外，D2 样受体拮抗剂抑制了 DCs 成熟的方式类似于氟哌啶醇。

**结论：**研究表明，在动物中氟哌啶醇抑制了 DCs 的功能成熟，并在抑制 DC 介导的辅助 T1 细胞免疫反应中起着重要作用。此外，氟哌啶醇对 DCs 的作用可能是通过多巴胺 D2 样受体所介导。总之这些结果表明，氟哌啶醇抑制了 DC 介导的免疫反应。

(王筱婧译 陈杰校)

**BACKGROUND:** Haloperidol has immunomodulatory effects when used to treat patients with schizophrenia and also is used to sedate critically ill patients in the intensive care unit. Although the mechanism by which haloperidol affects immune function is unclear, one possibility is that it alters dendritic cell (DC) function. DCs are potent antigen-presenting cells that influence the activation and maturation of T lymphocytes. In this study, we investigated the in vitro and in vivo immunomodulatory effects of haloperidol on DC-mediated immune responses.

**METHODS:** Using bone marrow–derived DCs in cell culture, we evaluated the effect of haloperidol on expression of costimulatory molecules (CD80 and CD86), major histocompatibility complex class II molecules, and the DC maturation marker CD83. DC culture supernatants also were evaluated for interleukin-12 p40 levels. In addition, we analyzed the effect of haloperidol on a mixed cell culture containing DCs and lymphocytes and measured the secretion of interferon- $\gamma$  in the culture supernatants. We also assessed the in vivo effects of haloperidol on hapten-induced contact hypersensitivity responses.

**RESULTS:** Haloperidol inhibited the expression of CD80, CD86, major histocompatibility complex class II, and CD83 molecules on DCs and the secretion of interleukin-12p40 in DC culture supernatants. In mixed cell cultures containing both T cells (CD4+ and CD8 $\alpha$ +) and DCs, haloperidol-treated DCs suppressed the proliferation of allogeneic T cells and effectively inhibited the production of interferon- $\gamma$ . In vivo, haloperidol reduced hapten-induced contact hypersensitivity responses. Furthermore, an antagonist to D2-like receptor suppressed the maturation of DCs in a manner similar to haloperidol.

**CONCLUSIONS:** The results of our study suggest that haloperidol suppresses the functional maturation of DCs and plays an important role in the inhibition of DC-induced T helper 1 immune responses in the whole animal. Furthermore, the effect of haloperidol on DCs may be mediated by dopamine D2–like receptors. Together, these results demonstrate that administration of haloperidol suppresses DC-mediated immune responses.

### 儿茶酚氧位甲基转移酶 (COMT) 基因单倍型与术后病人芬太尼用量有紧密联系

#### COMT Gene Haplotypes Are Closely Associated with Postoperative Fentanyl Dose in Patients

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**背景:** 芬太尼的镇痛效应个体差异较大, COMT 的单核苷酸多态性 (SNPs) 能调节疼痛敏感性。然而, 现在还不清楚, COMT 的基因多态性是否能影响行根治性胃大部分切除术患者的术后芬太尼镇痛效果。

**方法:** 将全麻下择期行根治性胃大部分切除术共 115 例、ASA 为 I–III 级的患者纳入研究。在手术结束后的 48 小时内, 患者使用芬太尼自控静脉输注镇痛。患者的疼痛视觉模拟量表得分维持在  $\leq 30$ mm, 在术后 24h 和 48h, 记录芬太尼的使用量与副作用。通过聚合酶链反应扩增 DNA 或聚合酶链反应限制性片段长度多态性的 DNA 序列分析测出所有患者的 COMT 的 SNPs (rs6269, rs4633, rs4818, 和 rs4680)。

**结果:** 拥有不同 COMT 的 SNPs (rs6269, rs4633, rs4818, 和 rs4680) 的患者在术后 24 小时 ( $P > 0.207$ ) 和 48 小时 ( $P > 0.148$ ) 的芬太尼总用量无差异。然而, COMT 基因单倍型联合 COMT rs6269, rs4633, rs4818, 和 rs4680 却显著影响患者在术后 24 小时 ( $P = 0.029$ ) 和 48 小时 ( $P = 0.032$ ) 的芬太尼的使用量。在 COMT 基因的单倍型中, 携带单倍型 ACCG 的患者在术后 24h 和 48h 的芬太尼使用量要高于 GCGG 和 ATCA 单倍型 ( $P < 0.042$ )。恶心, 呕吐和眩晕的发生率在 4 个不同 COMT 的 SNPs 中无显著差别 ( $P > 0.482$ )。

**结论:** 含有 rs6269, rs4633, rs4818, 和 rs4680 的 COMT 基因单倍型对术后芬太尼镇痛的个体差异性有影响。携带 COMT 基因单倍型 ACCG 的患者在术后 24h 和 48h 需要更多的药量。

(殷文译 陈杰校)

**BACKGROUND:** Fentanyl's analgesic efficacy varies widely among individuals. The single-nucleotide polymorphisms (SNPs) of catechol-O-methyltransferase (COMT) modulate

sensitivity to pain. It remains unclear, however, whether COMT genetic variability affects postoperative fentanyl analgesia in patients undergoing radical gastrectomy.

**METHODS:** One hundred fifteen patients, ASA physical status I–III, who were scheduled for radical gastrectomy under general anesthesia, were enrolled in this study. Patient-controlled IV analgesia with fentanyl was administered during the first 48 hours after surgery. Visual analog scale score for patients' pain was maintained at  $\leq 30$  mm. The amount of fentanyl consumed and side effects were recorded for the first 24 and 48 hours postoperatively. The SNPs of COMT (rs6269, rs4633, rs4818, and rs4680) of all patients were screened by DNA sequence analysis of polymerase chain reaction–amplified DNA or polymerase chain reaction–restriction fragment length polymorphism.

**RESULTS:** There were no significant differences in the doses of fentanyl used among patients possessing different SNPs of COMT rs6269, rs4633, rs4818, and rs4680 at 24 (all  $P > 0.207$ ) and 48 (all  $P > 0.148$ ) hours after surgery. COMT gene haplotypes combined by COMT rs6269, rs4633, rs4818, and rs4680, however, significantly affected fentanyl consumption at 24 ( $P = 0.029$ ) and 48 ( $P = 0.032$ ) hours after surgery. Among the haplotypes of COMT gene, patients with haplotype ACCG consumed more fentanyl than GCGG and ATCA haplotypes during the first 24 and 48 hours (all  $P < 0.042$ ) after surgery. No significant differences were found in the incidence of nausea, vomiting, and dizziness among the 4 SNPs of COMT gene (all  $P > 0.079$ ) and their haplotypes (all  $P > 0.482$ ).

**CONCLUSIONS:** COMT gene haplotype constructed by rs6269, rs4633, rs4818, and rs4680 contributes to the individual variation of postoperative analgesia with fentanyl. Patients carrying the COMT gene haplotype ACCG consumed the most drug during the first 24 and 48 hours postoperatively.

### 体外膜式氧合引起高分子量血管性血友病因子多聚体短暂缺失

#### Extracorporeal Membrane Oxygenation Induces Short-Term Loss of High-Molecular-Weight von Willebrand Factor Multimers

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**背景:** 高分子量 (HMW) 血管性血友病因子 (vWF) 多聚体在初期的止血过程中起重要作用。心室辅助装置带来的剪切力增加导致 HMW vWF 多聚体过早降解。但是体外膜式氧合 (ECMO) 条件下是否同样存在 vWF 多聚体的降解仍然是疑问。

**方法:** 我们在顽固性心功能不全伴/不伴肺功能衰竭并且需要 ECMO 治疗的患者进行了一项观察性研究。观察主要节点是在 ECMO 前, ECMO 中和 ECMO 后的 HMW vWF 的质量和数量。为了进一步研究初期止血的改变, 针对入组的 38 例患者, 在患者接受 ECMO 前 (基础值), 经行 ECMO 24 小时和 48 小时, 以及 ECMO 治疗后 24h, 我们同时检测 vWF 抗原 (vWF-Ag), vWF 瑞斯托菌素辅因子 (vWF-RCo) 和 VIII 因子的水平。

**结果:** 与基础水平相比, 经过 24h ECMO 治疗后, vWF-Ag 和 vWF-RCo 水平明显下降 (平均数  $\pm$  标准差, vWF-Ag, 307%  $\pm$  152% 到 261%  $\pm$  138%,  $P = 0.002$ ; vWF-RCo 282%  $\pm$  145% 到 157%  $\pm$  103%,  $P < 0.0001$ )。同样在后续治疗过程中 vWF-Ag 和 vWF-RCo 水平亦明显下降 (vWF-Ag 265%  $\pm$  128%,  $P = 0.025$ ; vWF-RCo 163%  $\pm$  94%,  $P < 0.0001$ )。在终止 ECMO 治疗后, vWF-Ag 高于基础水平 (359%  $\pm$  131%,  $P = 0.004$ ), 而 vWF-RCo 与基础水平持平 (338%  $\pm$  142%,  $P = 0.046$ )。与基础值相比, vWF-RCo/vWF-Ag 比值在 24h ECMO 治疗后明显下降 (0.96  $\pm$  0.23 至 0.61  $\pm$  0.17,  $P \leq 0.0001$ ), 在 48h ECMO 治疗后该比值亦明显下降 (0.63  $\pm$  0.18,  $P \leq 0.0001$ )。在终止治疗后, 该比值迅速与基础值持平 (0.94  $\pm$  0.19,  $P = 0.437$ )。HMW vWF 多聚体的数量在 24h (21  $\pm$  1.4 至 14



$\pm 1.8$ ,  $P \leq 0.0001$ ) 和 48h ( $15 \pm 2.1$ ,  $P \leq 0.0001$ ) 治疗后均明显下降。在 ECMO 治疗终止 24h 后, HMW vWF 多聚体水平恢复到基础水平 ( $21 \pm 1.8$ ,  $P = 0.551$ )。

**结论:** HMW vWF 多聚体在 ECMO 治疗后出现减少, 在治疗终止后逐渐恢复。虽然凝血筛查试验无阳性表现, 但是在 ECMO 治疗中 vWF:RCo/vWF:Ag 比值小于 0.7 仍然提示 HMW vWF 多聚体的丢失。我们的研究在一定程度上解释了 ECMO 治疗中患者出血倾向增加的现象。在 ECMO 治疗给予 vWF 治疗有助于改善出血倾向, 帮助止血功能的恢复。

(王嘉兴 译 薛张纲 校)

**BACKGROUND:** High-molecular-weight (HMW) von Willebrand factor (vWF) multimers are crucial for primary hemostasis. Increased shear stress from ventricular assist devices can provoke premature degradation of HMW vWF multimers. Whether similar loss of vWF multimers occurs during extracorporeal membrane oxygenation (ECMO) is not clear.

**METHODS:** We conducted a prospective observational study in a clinical cohort of patients who required ECMO for intractable cardiac and/or respiratory failure. The primary end point was the quantity and quality of HMW vWF multimer bands before, during, and after ECMO support. To investigate further changes in primary hemostasis, we also measured vWF antigen activity (vWF:Ag), vWF ristocetin cofactor activity (vWF:RCo), and factor VIII in 38 patients who required ECMO support before initiation of ECMO (baseline), after 24 and 48 hours on ECMO, and 24 hours after termination of ECMO therapy.

**RESULTS:** Compared with baseline, vWF:Ag and vWF:RCo decreased after 24 hours of ECMO (mean  $\pm$  SD, vWF:Ag,  $307\% \pm 152\%$  to  $261\% \pm 138\%$ ,  $P = 0.002$ ; vWF:RCo  $282\% \pm 145\%$  to  $157\% \pm 103\%$ ,  $P < 0.0001$ ) and remained lower during ongoing support (vWF:Ag  $265\% \pm 128\%$ ,  $P = 0.025$ ; vWF:RCo  $163\% \pm 94\%$ ,  $P < 0.0001$ ). After termination of ECMO, vWF:Ag was greater than baseline ( $359\% \pm 131\%$ ,  $P = 0.004$ ) and vWF:RCo was similar to baseline levels ( $338\% \pm 142\%$ ,  $P = 0.046$ ). Compared with baseline, the calculated vWF:RCo/vWF:Ag ratio decreased after 24 hours on support ( $0.96 \pm 0.23$  to  $0.61 \pm 0.17$ ,  $P \leq 0.0001$ ) and remained lower during 48 hours on ECMO ( $0.63 \pm 0.18$ ,  $P \leq 0.0001$ ). After termination of ECMO support ( $0.94 \pm 0.19$ ,  $P = 0.437$ ), values rapidly returned to baseline. The number of HMW vWF multimers (n) decreased from baseline after 24 hours on ECMO ( $21 \pm 1.4$  to  $14 \pm 1.8$ ,  $P \leq 0.0001$ ) and after 48 hours on ECMO ( $15 \pm 2.1$ ,  $P \leq 0.0001$ ). Twenty-four hours after termination of ECMO support, HMW vWF multimeric pattern had returned to baseline values ( $21 \pm 1.8$ ,  $P = 0.551$ ).

**CONCLUSIONS:** Loss of HMW vWF multimer bands occurred in patients undergoing ECMO support and resolved after the termination of ECMO. Although not detectable with coagulation screening tests, a vWF:RCo/vWF:Ag ratio  $< 0.7$  during ECMO was highly indicative for loss of HMW vWF multimers. Our findings may at least in part explain increased bleeding tendency during ECMO therapy. Administration of vWF concentrates may support restoration of primary hemostasis in patients with relevant bleeding during ECMO support.

## Remimazolam 和咪达唑仑在上消化道内镜的镇静中的 IIa 期随机双盲研究

### A Phase IIa, Randomized, Double-Blind Study of Remimazolam (CNS 7056) Versus Midazolam for Sedation in Upper Gastrointestinal Endoscopy

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**背景:** 这项探索性研究是评估不同单次剂量 remimazolam 用于镇静的安全性和有效性的首次研究。

**方法：**病人按计划行诊断性上消化道内镜检查，随机、双盲给予 3 种剂量中的 1 种的 remimazolam 或者咪达唑仑，每组 25 位病人。给予单次的药物镇静满意后，病人行胃镜检查。我们评价检查的成功与否、镇静效果、苏醒和安全性。

**结果：**低剂量组（0.10mg/kg）、中剂量组（0.15mg/kg）和高剂量组（0.20mg/kg）给予单次剂量 remimazolam 后的胃镜检查成功率分别是 32%、56%、64%，咪达唑仑组（0.075mg/kg）的成功率是 44%。Remimazolam 组的镇静起效时间是 1.5-2.5 分钟，而咪达唑仑组是 5 分钟。因为这项研究是给予单次剂量，必要时给予咪达唑仑或丙泊酚以维持镇静状态完成检查。所有治疗组病人镇静后的苏醒都非常迅速，但受单次剂量后选择的追加药物的影响。在 remimazolam 和咪达唑仑的安全性上没有明显的不同。

**结论：**这项剂量探索性研究表明在诊断性上消化道内镜检查中给予病人单次剂量 remimazolam（0.10-0.20mg/kg）能够快速镇静和快速苏醒。Remimazolam 的安全性良好，与咪达唑仑相似，保证了这个起效迅速的药物的进一步发展。

（吕越昌 译 薛张纲 校）

**BACKGROUND:** This exploratory study was the first study of remimazolam in patients to assess the safety and efficacy of different single doses for procedural sedation.

**METHODS:** Patients scheduled to undergo a diagnostic upper gastrointestinal endoscopy were randomized to receive 1 of 3 doses of remimazolam or midazolam(25 per group) in a double-blind manner. After a single dose of study drug to achieve sedation, patients underwent gastroscopy. We assessed the success of the procedure, sedation levels, recovery from sedation, and safety.

**RESULTS:** A single dose of remimazolam resulted in a successful procedure in 32%, 56%, and 64% of patients in the low (0.10), middle (0.15), and high (0.20 mg/kg) dose groups compared with 44% of patients in the midazolam (0.075 mg/kg) dose group. The onset of sedation was 1.5 to 2.5 minutes in there mimazolam dose groups compared with 5 minutes for midazolam. Because this was a single administration study, sedation could be maintained for as long as necessary to complete the procedure, using rescue midazolam or propofol. Recovery from sedation was rapid for all treatment groups but was influenced by the choice of rescue medication. There were no obvious differences in the safety profiles of remimazolam and midazolam.

**CONCLUSIONS:** This exploratory dose-finding study showed that a single administration of remimazolam (0.10-0.20 mg/kg) was capable of inducing rapid sedation with a quick recovery profile in patients undergoing a diagnostic upper gastrointestinal endoscopy. The safety profile was favorable and appeared to be similar to that of midazolam, warranting further development of this short-acting compound.

### 无针连接组件大量减少了快速输液时晶体及红细胞的流速

#### Needleless Connectors Substantially Reduce Flow of Crystalloid and Red Blood Cells During Rapid Infusion

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尽管无针连接组件（NC）被广泛地用于围术期，但现代无针连接组件减低输注液体的速度的可能性并未被彻底研究。我们研究了 Level 1 通过不同的静脉导管输液的 5 种装置及无针连接组件在加压输注晶体液以及红细胞时的流速特点。在大于 18 号的导管中，晶体液的速度降低 29% to 85%，在这些导管中，红细胞输注流速下降 22% to 76%（P < 0.0050）。我们建议临床实践者在使用大管径静脉导管经行快速输液时去除无针连接组件。

(吴赤译 薛张纲校)

Although needleless connectors (NC) are frequently used in the perioperative setting, the potential of modern NCs to slow delivery of IV fluids has not been thoroughly studied. We examined flow characteristics of 5 NC models during pressurized delivery of crystalloid and banked red blood cells from a Level 1 warmer through various IV catheters. Crystalloid flow rates were reduced by 29% to 85% from control in catheters >18 gauge, while red blood cell flow reductions ranged from 22% to 76% in these catheters (all  $P < 0.0050$ ). We suggest that practitioners consider eliminating NCs when large IV catheters are inserted for rapid fluid administration.

### 麻醉操作导致的肠球菌易位的传播动力学

#### The Dynamics of Enterococcus Transmission from Bacterial Reservoirs Commonly Encountered by Anesthesia Providers

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**背景：**肠球菌是医疗操作相关感染的第二大病因，该细菌从无害的正常菌群逐步进化为大大增加病人感染率和死亡率的多重耐药微生物。预防该微生物在医院内部以及医院之间蔓延至关重要。本研究主要关注全麻常规操作导致肠球菌易位的传播动力学。

**方法：**我们从三大医疗中心内麻醉师经常接触的肠球菌生存部位（病人鼻咽和腋窝、麻醉师的手、麻醉机限压阀和调节按钮）分离肠球菌并按病原种类、短暂接触以及表型分析（族群分析指数）分别保存，并将麻醉过程中各部位肠球菌的接触鉴定为可能导致术中细菌传播的主要事件。然后通过抗生素圆盘内细菌扩散以及细菌对抗生素的敏感性分析来确认传播事件的发生。最终通过对传播事件中的接触分析以确认该事件发生的频率、方式、起源、传播部位以及病原菌对抗生素的敏感性。

**结果：**通过大体形态以及简单的快速实验确认麻醉过程中常见细菌储存部位分离出来的细菌（共 389 例）为肠球菌。进一步通过族群分析参数分析以及短暂接触鉴定其中 43%（166/389）为可能的术中细菌传播事件。其中，30%（49/166）通过了抗生素敏感性确认。其中，80%（39/49）为表型 E5 或 E7。在所有两种表型的细菌中，麻醉师的手均为该细菌的主要来源（E7 96%[72/75];E5 89%[50/56]）以及传播部位（E7 94%[16/17];E5 89%[19/22]）。

**结论：**麻醉师的手为麻醉操作过程中导致肠球菌传播事件的主要细菌来源以及传播部位。下一步研究方向为提高操作过程中手卫生对术中肠球菌传播事件的影响。

(郝光伟译 薛张纲校)

**BACKGROUND:** Enterococci, the second leading cause of health care-associated infections, have evolved from commensal and harmless organisms to multidrug-resistant bacteria associated with a significant increase in patient morbidity and mortality. Prevention of ongoing spread of this organism within and between hospitals is important. In this study, we characterized Enterococcus transmission dynamics for bacterial reservoirs commonly encountered by anesthesia providers during the routine administration of general anesthesia.

**METHODS:** Enterococcus isolates previously obtained from bacterial reservoirs frequently encountered by anesthesiologists (patient nasopharynx and axilla, anesthesia provider hands, and the adjustable pressure-limiting valve and agent dial of the anesthesia machine) at 3 major academic medical centers were identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and phenotypic analysis (analytical profile indexing).

They were then subjected to antibiotic disk diffusion sensitivity for transmission event confirmation. Isolates involved in confirmed transmission events were further analyzed to characterize the frequency, mode, origin, location of transmission events, and antibiotic susceptibility of transmitted pathogens.

**RESULTS:** Three hundred eighty-nine anesthesia reservoir isolates were previously identified by gross morphology and simple rapid tests as Enterococcus. The combination of further analytical profile indexing analysis and temporal association implicated 43% (166/389) of those isolates in possible intraoperative bacterial transmission events. Approximately, 30% (49/166) of possible transmission events were confirmed by additional antibiotic disk diffusion analysis. Two phenotypes, E5 and E7, explained 80% (39/49) of confirmed transmission events. For both phenotypes, provider hands were a common reservoir of origin proximal to the transmission event (96% [72/75] hand origin for E7 and 89% [50/56] hand origin for E5) and site of transmission (94% [16/17] hand transmission location for E7 and 86% [19/22] hand transmission location for E5).

**CONCLUSIONS:** Anesthesia provider hand contamination is a common proximal source and transmission location for Enterococcus transmission events in the anesthesia work area. Future work should evaluate the impact of intraoperative hand hygiene improvement strategies on the dynamics of intraoperative Enterococcus transmission

在静脉通路中留下的不只是你的指纹：一项关于异丙酚麻醉和可能存在三通污染的前瞻性研究

### Leaving More Than Your Fingerprint on the Intravenous Line: A Prospective Study on Propofol Anesthesia and Implications of Stopcock Contamination

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**背景：**在麻醉和手术中对静脉通路中的三通进行操作时可能会导致静脉管路的污染。在异丙酚这种营养丰富的催眠药物广泛应用的情况下，我们提出这样的假说：异丙酚麻醉增加了静脉三通管的细菌污染，使用过异丙酚的静脉三通继续使用时可能会存在安全隐患。

**方法：**我们的体外试验是从当天使用过和未使用过异丙酚的患者的静脉通路上拆下三通器，并立即作为试验样本收集起来。这些三通器在室温下被分别保存 6,24,48 小时。每个时间间隔（6h、24h、48h）我们分别取两组（使用过异丙酚和未使用过异丙酚）的 50 个样本进行培养。我们抽取静脉三通器中死角的残余物并将其接种于血平板中进行菌落计数和菌种鉴定来实现细菌的定量培养。

**结果：**细菌培养阳性率在异丙酚三通组为 17.3% (26/150)而在非异丙酚三通组为 18.6% (28/150)。6 小时点，异丙酚组中：有可见残留异丙酚的三通的平均细菌计数为 44CFU/ml，无可见残留异丙酚的三通的平均细菌计数为 41 CFU/mL；在非异丙酚组该值为 37 CFU/mL。异丙酚麻醉后 48 小时，在被污染的三通死角中细菌数增殖 100 倍。无可见残留异丙酚的三通和非异丙酚组三通比较，无可见残留异丙酚的三通的细菌计数也存在显著差异(P = 0.034)。

**结论：**麻醉过程中特别是异丙酚麻醉中存在静脉三通细菌污染的隐患。异丙酚麻醉可能增加术后感染的风险，因为细菌会在静脉三通的死角中繁殖。

(盖晓冬 译 薛张纲 校)

**BACKGROUND:** Acute care handling of IV stopcocks during anesthesia and surgery may result in contaminated IV tubing sets. In the context of widespread propofol use, a nutrient-rich hypnotic drug, we hypothesized that propofol anesthesia increases bacterial contamination of IV



stopcocks and may compromise safety of IV tubing sets when continued to be used after propofol anesthesia.

**METHODS:** We conducted an in vitro trial by collecting IV tubing sets at the time of patient discharge from same-day ambulatory procedures performed with and without propofol anesthesia. These extension sets were then held at room temperature for 6, 24, or 48 hours. We cultured 50 samples at each interval for both cohorts. Quantitative cultures were done by aspirating the IV stopcock dead space and plating the aspirate on blood agar for colony count and speciation.

**RESULTS:** Positive bacterial counts were recovered from 17.3% of propofol anesthesia stopcocks (26/150) and 18.6% of nonpropofol stopcocks (28/150). At 6 hours, the average bacterial counts from stopcocks with visible residual propofol was 44 colony forming units (CFU)/mL, compared with 41 CFU/mL with no visible residual propofol and 37 CFU/mL in nonpropofol anesthesia stopcocks. There was a 100-fold increase in bacterial number in contaminated stopcock dead spaces at 48 hours after propofol anesthesia. This difference remained significant when comparing positive counts from stopcocks with no visible residual propofol and nonpropofol anesthesia ( $P = 0.034$ ).

**CONCLUSIONS:** There is a covert incidence and degree of IV stopcock bacterial contamination during anesthesia which is aggravated by propofol anesthetic. Propofol anesthesia may increase risk for postoperative infection because of bacterial growth in IV stopcock dead spaces.

#### 应用新技术对手术室内病原菌传播机制的研究

### The Use of a Novel Technology to Study Dynamics of Pathogen Transmission in the Operating Room

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手术环境中发现的致病菌具有潜在的致感染风险，并可导致一定的致病率和致死率。为了研究手术室内麻醉人员作为带菌者引起病人感染的机制，我们利用最新的实验技术在模拟手术室环境内利用高仿真的模拟病人实施了此项研究。

（潘艳 译 薛张纲 校）

Pathogenic organisms have been found in the intraoperative environment, potentially posing a risk of infection that could cause morbidity and mortality. In an effort to understand how a patient's bacteria can be spread throughout the operating room with the anesthesia provider as a vector, we conducted a study using recently developed experimental technology in a simulated operating room environment with a high-fidelity human patient simulator.

#### 应用呼气相辅助通气的方法通过一根小口径的气管导管对严重低氧血症猪的急救性通气

### Rescue Ventilation Through a Small-Bore Transtracheal Cannula in Severe Hypoxic Pigs Using Expiratory Ventilation Assistance

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Anesthesia & Analgesia: 2015 120 890–894

**背景：**抽吸产生的呼气相辅助通气（EVA）的方法使得通过一根小口径的气管导管进行双向通气成为可能。本研究中我们通过急性低氧血症猪的模型来研究 EVA 在恢复氧和以及通气的效率。

**方法：**对六只体重在 61-76kg 的猪进行麻醉，利用带套囊的气管导管进行间断性正压通气。接好监测后，给这些猪置入一根长 75mm，内径 2mm 的气管导管。记录好基础生命体征后，断开呼吸机。缺氧 2 分钟后，通过应用辅助呼气相通气的方法进行再氧合并且持续 15 分钟，这期间气管导管都是封闭的。本研究中的第二阶段，我们将气管导管半开半闭或者完全开放重复上述实验过程。实验中我们实时监测气道压力，血流动力学参数及动脉血气，并进行描述性统计学分析。

**结果：**在上呼吸道完全或部分梗阻的动物模型中，应用呼气相辅助通气的方法能使所有的动物在 20 秒内恢复氧合。在完全梗阻的气道中，二氧化碳的分压在 15 分钟内能保持稳定。在气道梗阻程度稍轻的情况下，再氧合的时间被延迟。在气道完全开放的情况下，这一方法的有效性很有限，其中的 2 只猪在 15 分钟的通气后动脉氧分压依然低于 85mmHg，并且二氧化碳分压上升到 90mmHg。

**结论：**在严重低氧血症猪的模型中，在气道完全封闭及部分封闭情况下通过辅助呼气相通气的方法能使缺氧快速恢复，而在上呼吸道完全开放的情况下，这种方法在恢复氧合和辅助通气方面就显得无能为力。

（王飞译 薛张纲校）

**BACKGROUND:** Suction-generated expiratory ventilation assistance (EVA) has been proposed as a way to facilitate bidirectional ventilation through a small-bore transtracheal cannula (TC). In this study, we investigated the efficiency of ventilation with EVA for restoring oxygenation and ventilation in a pig model of acute hypoxia.

**METHODS:** Six pigs (61–76 kg) were anesthetized and ventilated (intermittent positive pressure ventilation) via a cuffed endotracheal tube (ETT). Monitoring lines were placed, and a 75-mm long, 2-mm inner diameter TC was inserted. After the baseline recordings, the ventilator was disconnected. After 2 minutes of apnea, reoxygenation with EVA was initiated through the TC and continued for 15 minutes with the ETT occluded. In the second part of the study, the experiment was repeated with the ETT either partially obstructed or left open. Airway pressures and hemodynamic data were recorded, and arterial blood gases were measured. Descriptive statistical analysis was performed.

**RESULTS:** With a completely or partially obstructed upper airway, ventilation with EVA restored oxygenation to baseline levels in all animals within 20 seconds. In a completely obstructed airway, PaCO<sub>2</sub> remained stable for 15 minutes. At lesser degrees of airway obstruction, the time to reoxygenation was delayed. Efficacy probably was limited when the airway was completely unobstructed, with 2 of 6 animals having a PaO<sub>2</sub> <85 mm Hg even after 15 minutes of ventilation with EVA and a mean PaCO<sub>2</sub> increased up to 90 mm Hg.

**CONCLUSIONS:** In severe hypoxic pigs, ventilation with EVA restored oxygenation quickly in case of a completely or partially obstructed upper airway. Reoxygenation and ventilation were less efficient when the upper airway was completely unobstructed.

对于行门诊手术的父母和孩子术前准备的基于网络简明的干预研究（WebTIPS）：形成性评价和随机对照试验

**Web-Based Tailored Intervention for Preparation of Parents and Children for Outpatient Surgery (WebTIPS): Formative Evaluation and Randomized Controlled Trial**

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**背景：**这项 2 阶段的项目的目的是为了对一项新开发的基于网络的简明干预在父母和儿童术前准备的程序进行形成性评价和初步疗效的测试(WebTIPS)。

**方法：**第 1 阶段入组了 13 个接受门诊择期外科手术的 2 - 7 岁儿童和他们的父母，对其进行 WebTIPS 的形成性评价。在定性研究中，家长参与集中研讨小组是非常普遍的，而且这是询问研究参与者的一个产品或概念看法和态度的一个方法。在第 2 阶段中，来自两个医疗中心的 2–7 岁儿童被随机分配接受 WebTIPS (n = 38)和标准护理(n = 44)。第二阶段的主要结果是孩子和家长的术前焦虑。

**结果：**在第二阶段，父母认为 WebTIPS 有效( $P < 0.001$ )并且易于使用( $P < 0.001$ )。在第二阶段，在进入手术室时( $P = 0.02$ ；Cohen  $d = 0.59$ )和介绍麻醉面罩时(分别为  $43.5 \pm 21.7$  与  $57.0 \pm 57.0$ ,  $P = 0.01$ ；Cohen  $d = 0.63$ )，WebTIPS 组的儿童( $36.2 \pm 14.1$ )与标准护理组的儿童( $46.0 \pm 19.0$ )相比，焦虑程度较低。术前等候区，WebTIPS 组的父母( $32.1 \pm 7.4$ )较对照组父母( $36.8 \pm 7.1$ )经历更少的焦虑( $P = 0.004$ ；Cohen  $d = 0.65$ )。

**结论：**WebTIPS 受到了家长和孩子的广泛认可，其可减少术前焦虑。

(黄文惠 译 薛张纲 校)

**BACKGROUND:** The purpose of this 2-phase project was to conduct a formative evaluation and to test the preliminary efficacy of a newly developed Web-based Tailored Intervention for Preparation of parents and children undergoing Surgery (WebTIPS).

**METHODS:** Phase 1 enrolled 13 children 2 to 7 years of age undergoing outpatient elective surgery and their parents for formative evaluation of WebTIPS. Parent participation focus groups are common in qualitative research and are a method of asking research participants about their perceptions and attitudes regarding a product or concept. In phase 2, children 2 to 7 years of age in 2 medical centers were assigned randomly to receive the WebTIPS program (n = 38) compared with children receiving the standard of care (n = 44). The primary outcome of phase II was child and parent preoperative anxiety.

**RESULTS:** In phase 2, parents reported WebTIPS to be both helpful ( $P < 0.001$ ) and easy to use ( $P < 0.001$ ). In phase 2, children in the WebTIPS group ( $36.2 \pm 14.1$ ) were less anxious than children in the standard of care group ( $46.0 \pm 19.0$ ) at entrance to the operating room ( $P = 0.02$ ; Cohen  $d = 0.59$ ) and introduction of the anesthesia mask ( $43.5 \pm 21.7$  vs  $57.0 \pm 21.2$ , respectively,  $P = 0.01$ ; Cohen  $d = 0.63$ ). Parents in the WebTIPS group ( $32.1 \pm 7.4$ ) also experienced less anxiety compared with parents in the control group ( $36.8 \pm 7.1$ ) in the preoperative holding area ( $P = 0.004$ ; Cohen  $d = 0.65$ ).

**CONCLUSIONS:** WebTIPS was well received by parents and children and led to reductions in preoperative anxiety.

### 体外循环期间的麻醉管理：一项系统回顾

#### Anesthetic Management During Cardiopulmonary Bypass: A Systematic Review

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心脏手术期间所必需的体外循环目前对于麻醉医生的特殊挑战主要在于以下 3 个方面：麻醉、镇痛和肌松。

在体外循环期间特殊的病理生理变化会导致药代动力学的改变，这一改变则会影响静脉麻醉药的血清和组织中的浓度。简单地说，体外循环期间引起药效学的改变将会影响麻醉效

果。而这些改变所带来的临床意义则代表了一种“移动目标”，就像临床实践的不断演变和体外循环技术的不断进步一样。另外，灌注技术的选择、修正并维持体外循环回路和膜式氧合器。

因此，他们的意义不仅仅是被麻醉医生所赞赏。这些技术将会对病人的麻醉状态产生深远的影响。体外循环期间的输送和维持面临着独特的挑战。在体外循环期间。灌注师将直接对麻醉的维持负责，而对于心脏循环来说这是一种特殊的状态。

另外，麻醉深度的监测，包括临床指征的评估、血流动力学指标、脑电双频指数、呼气末麻醉药物浓度的监测以及肌张力的监测等在体外循环期间都将是缺失的、不可信的、甚至直接被这种特殊的病理生理学因素所影响。在心脏手术期间，这些监测不足所带来的困难将会大大增加术中知晓的发生率。

更复杂的是，医疗器械的规格缺少具体的临床指南以及国际政策的不断变化将会增加医疗机构内甚至是国家之间更多的复杂医疗纠纷并引入新的实践变化。

因此我们对文献进行了一些列系统的调查来确定体外循环期间的麻醉操作是否有证可循，从而发现了文献中存在的差异，这一调查为我们今后的研究提供了指导，并且探索了不断发展的手术操作、灌注技术以及国际政策对于体外循环期间麻醉、镇痛和肌松所带来的影响。

（王慧娟 译，李士通 审校）

Cardiopulmonary bypass (CPB) required for cardiac surgery presents unique challenges to the cardiac anesthesiologist responsible for providing the 3 most basic facets of any anesthetic: amnesia, analgesia, and muscle relaxation. Unique pathophysiologic changes during CPB result in pharmacokinetic alterations that impact the serum and tissue concentrations of IV and volatile anesthetics. Similarly, CPB causes pharmacodynamic alterations that impact anesthetic efficacy. The clinical significance of these alterations represents a “moving target” as practice evolves and the technology of CPB circuitry advances. In addition, perfusionists choose, modify, and maintain the CPB circuitry and membrane oxygenator. Thus, their significance may not be fully appreciated by the anesthesiologist. These issues have a profound impact on the anesthetic state of the patient. The delivery and maintenance of anesthesia during CPB present unique challenges. The perfusionist may be directly responsible for the delivery of anesthetic during CPB, a situation unique to the cardiac suite. In addition, monitors of anesthetic depth—assessment of clinical signs, hemodynamic indicators, the bispectral index monitor, end-tidal anesthetic concentration, or twitch monitoring—are often absent, unreliable, or directly impacted by the unique pathophysiology associated with CPB. The magnitude of these challenges is reflected in the higher incidence of intraoperative awareness during cardiac surgery. Further complicating matters are the lack of specific clinical guidelines and varying international policies regarding medical device specifications that add further layers of complexity and introduce practice variability both within institutions and among nations. We performed a systematic survey of the literature to identify where anesthetic practice during CPB is evidence based (or not), identify gaps in the literature to guide future investigations, and explore the implications of evolving surgical practice, perfusion techniques, and national policies that impact amnesia, analgesia, and muscle relaxation during CPB.

曲马多及其代谢产物 M1 会选择性的抑制瞬态电压感受器阳离子通道受体 1 (TRPV1) 的活性，而不是瞬时受体电位香草酸受体 1 (TRPA1)

**Tramadol and Its Metabolite M1 Selectively Suppress Transient Receptor Potential Ankyrin 1 Activity, but Not Transient Receptor Potential Vanilloid 1 Activity**

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**背景：**瞬时受体电位香草酸受体 1(TRPV1)和瞬态电压感受器阳离子通道受体 1(TRPV1)都在感觉神经元处表达，他们是负责感受伤害性刺激的多形态非选择性阳离子通道。最近的报道指出这些通道在炎性、神经病理性以及癌性疼痛中有非常重要的影响，从而在镇痛药的药理学目标的研究方面起到了积极的作用。曲马多是在临床实践中使用的一种有效的镇痛药。据研究，曲马多和它的代谢产物 M1 和  $\mu$  阿片受体结合从而抑制单胺类受体在中枢神经系统的再摄取，从而激活下行抑制系统。然而，曲马多在疼痛控制方面的作用机制目前尚未研究清楚。TRPV1 和 TRPA1 也许是曲马多的作用靶点，但是目前没有被广泛研究。

**方法：**我们通过运用钙离子成像检测和全细胞膜片钳记录的方法研究了曲马多和它的代谢产物 M1 对于人胚胎性肾 293 细胞是否以及如何表达瞬时受体电位香草酸受体 1(hTRPV1)和瞬态电压感受器阳离子通道受体 1 (hTRPA1)。

**结果：**分别与辣椒素组（一种 TRPV1 激动剂）和异硫氰酸烯丙酯组（一种 TRPA1 激动剂）相比，曲马多和它的代谢产物 M1 在人胚胎性肾 293 细胞中表达 hTRPV1 和 hTRPA1 的同时本身并不增加细胞内钙离子浓度。而且，在辣椒素的作用下，人胚胎性肾 293 细胞表达的 hTRPV1，经过曲马多或它的代谢产物 M1 预处理 5 分钟后，也不会影响细胞内钙离子浓度的增加。反过来，在异硫氰酸烯丙酯的预处理后，曲马多和它的代谢产物 M1 在人胚胎性肾 293 细胞表达 hTRPA1 的同时，则明显抑制了细胞内钙离子浓度的增加。另外，膜片钳的研究发现，在异硫氰酸烯丙酯的作用下，曲马多和它的代谢产物 M1 则降低了细胞的内向电流。

**结论：**这些数据表明了曲马多和它的代谢产物 M1 会选择性的抑制 hTRPA1 的作用，而对 hTRPV1 无影响，而且 hTRPA1 在镇痛药的化合物中起到了重要的作用。

（王慧娟译，李士通 审校）

**BACKGROUND:** The transient receptor potential vanilloid 1 (TRPV1) and the transient receptor potential ankyrin 1 (TRPA1), which are expressed in sensory neurons, are polymodal nonselective cation channels that sense noxious stimuli. Recent reports showed that these channels play important roles in inflammatory, neuropathic, or cancer pain, suggesting that they may serve as attractive analgesic pharmacological targets. Tramadol is an effective analgesic that is widely used in clinical practice. Reportedly, tramadol and its metabolite (M1) bind to  $\mu$ -opioid receptors and/or inhibit reuptake of monoamines in the central nervous system, resulting in the activation of the descending inhibitory system. However, the fundamental mechanisms of tramadol in pain control remain unclear. TRPV1 and TRPA1 may be targets of tramadol; however, they have not been studied extensively.

**METHODS:** We examined whether and how tramadol and M1 act on human embryonic kidney 293 (HEK293) cells expressing human TRPV1 (hTRPV1) or hTRPA1 by using a  $\text{Ca}^{2+}$  imaging assay and whole-cell patch-clamp recording.

**RESULTS:** Tramadol and M1 (0.01–10  $\mu\text{M}$ ) alone did not increase in intracellular  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_i$ ) in HEK293 cells expressing hTRPV1 or hTRPA1 compared with capsaicin (a TRPV1 agonist) or the allyl isothiocyanate (AITC, a TRPA1 agonist), respectively. Furthermore, in HEK293 cells expressing hTRPV1, pretreatment with tramadol or M1 for 5 minutes did not change the increase in  $[\text{Ca}^{2+}]_i$  induced by capsaicin. Conversely, pretreatment with tramadol (0.1–10  $\mu\text{M}$ ) and M1 (1–10  $\mu\text{M}$ ) significantly suppressed the AITC-induced  $[\text{Ca}^{2+}]_i$  increases in HEK293 cells expressing hTRPA1. In addition, the patch-clamp study showed that pretreatment with tramadol and M1 (10  $\mu\text{M}$ ) decreased the inward currents induced by AITC.

**CONCLUSIONS:** These data indicate that tramadol and M1 selectively inhibit the function of hTRPA1, but not that of hTRPV1, and that hTRPA1 may play a role in the analgesic effects of these compounds.

## 麻醉工作中 G-细菌病原体的传播动力学研究

### Transmission Dynamics of Gram-Negative Bacterial Pathogens in the Anesthesia Work Area

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**背景：**革兰氏阴性菌是感染及社区传播病原体健康护理的主要关注对象。我们的主要目的是描述麻醉工作环境（AWE）中常见 G-细菌的传播动力学。并研究这些传播事件与术后 30 天护理相关感染（HCLs）之间的关系。

**方法：**从三个主要的学术医疗中心的 AWE（病人鼻咽部和腋部，麻醉实施者手部，麻醉机的可调式限压阀和代理拨号？）得到 G-细菌的分离株，并通过对细菌病原体吧、类型，事件关系，及表型分析定义可能书中细菌感染事件。前 5 中常见事件采用抗生素纸片扩散敏感性试验来确定流行病学相关传播事件。流行病学相关传播事件中，同病例及病例间传播的相互作用采用多因素回归分析比例二项检验统计学分析进行研究。研究包括纳入及未纳入在一个给定研究单位下同一菌属的重复感染（所观察的每个手术室的第一个及第二个病例）来检验统计学依赖的潜在影响。传播的菌株通过凝胶电泳进行比较区别术后 30 天 HCLs 致病细菌。

**结果：**最常见的 5 中 G-菌属包括，不动杆菌，假单胞菌，短波单胞菌，肠杆菌属，和莫拉菌，共占可能感染事件的 81%(767/945)。通过抗生素药敏试验检验，22%的可能感染事件被为流行病学相关性并有待进一步传播动力学研究。20 例涉及同病例及病例间传播，其中 19%与流行病学相关。作为流行病学相关传染源，麻醉实施者的手部比对病人或环境污染存在更低的传染可能性。暴露于 HALs 及存在术中 G-暴露的病人中，同病例及病例间的传播发生率相同。凝胶电泳发现 8%（2/23）的 G-与感染致病微生物相连。术后 30 天护理相关感染中，发现病人及麻醉实施者的手部为传染来源，病例间传播事件中环境是载体。

**结论：**病例间及同病例间的 G-细菌传播经常发生，通过脉冲凝胶电泳可以术后 30 天感染相关。污染环境及病人皮肤表面比麻醉实施者手部更容易成为细菌感染源。

（王慧娟译，李士通 审校）

**BACKGROUND:** Gram-negative organisms are a major health care concern with increasing prevalence of infection and community spread. Our primary aim was to characterize the transmission dynamics of frequently encountered gram-negative bacteria in the anesthesia work area environment (AWE). Our secondary aim was to examine links between these transmission events and 30-day postoperative health care-associated infections (HCAIs).

**METHODS:** Gram-negative isolates obtained from the AWE (patient nasopharynx and axilla, anesthesia provider hands, and the adjustable pressure-limiting valve and agent dial of the anesthesia machine) at 3 major academic medical centers were identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and phenotypic analysis (analytical profile indexing). The top 5 frequently encountered genera were subjected to antibiotic disk diffusion sensitivity to identify epidemiologically related transmission events. Complete multivariable logistic regression analysis and binomial tests of proportion were then used to examine the relative contributions of reservoirs of origin and within- and between-case modes of transmission, respectively, to

epidemiologically related transmission events. Analyses were conducted with and without the inclusion of duplicate transmission events of the same genera occurring in a given study unit

(first and second case of the day in each operating room observed) to examine the potential effect of statistical dependency. Transmitted isolates were compared by pulsed-field gel electrophoresis to disease-causing bacteria for 30-day postoperative HCAs.

**RESULTS:** The top 5 frequently encountered gram-negative genera included Acinetobacter, Pseudomonas, Brevundimonas, Enterobacter, and Moraxella that together accounted for 81% (767/945) of possible transmission events. For all isolates, 22% (167/767) of possible transmission events were identified by antibiotic susceptibility patterns as epidemiologically related and underwent further study of transmission dynamics. There were 20 duplicates involving within- and between-case transmission events. Thus, approximately 19% (147/767) of isolates excluding duplicates were considered epidemiologically related. Contaminated provider hand reservoirs were less likely (all isolates, odds ratio 0.12, 95% confidence interval 0.03-0.50,  $P = 0.004$ ; without duplicate events, odds ratio 0.05, 95% confidence interval 0.01-0.49,  $P = 0.010$ ) than contaminated

patient or environmental sites to serve as the reservoir of origin for epidemiologically related transmission events. Within- and between-case modes of gram-negative bacilli transmission occurred at similar rates (all isolates, 7% between-case, 5.2% within-case, binomial  $P$  value 0.176; without duplicates, 6.3% between-case, 3.7% within-case, binomial  $P$  value 0.036). Overall, 4.0% (23/548) of patients suffered from HCAs and had an intraoperative exposure to gram-negative isolates. In 8.0% (2/23) of those patients, gram-negative bacteria were linked by pulsed-field gel electrophoresis to the causative organism of

infection. Patient and provider hands were identified as the reservoirs of origin and the environment confirmed as a vehicle for between-case transmission events linked to HCAs.

**CONCLUSIONS:** Between- and within-case AWE gram-negative bacterial transmission occurs frequently and is linked by pulsed-field gel electrophoresis to 30-day postoperative infections. Provider hands are less likely than contaminated

environmental or patient skin surfaces to serve as the reservoir of origin for transmission events.

### 双层手套，一个减少手术室污染的简单策略评估的随机对照试验

#### Double Gloves: A Randomized Trial to Evaluate a Simple Strategy to Reduce Contamination in the Operating Room

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**背景：**对于病人和医护人员，口腔菌群失调，血源性病原体和细菌污染造成感染的直接风险，。我们采用新验证的技术在模拟手术室环境中，研究是否使用 2 层手套，并在气管插管后立即脱去外层手套可减少这种风险。

**方法：**41 位麻醉住院医师（培训 2-4 年）被纳入研究（包括个人及团体模拟）。进入模拟手术室后，住院医师行麻醉诱导及气管插管（定时约 6 分钟），他们并不知研究设计。22 个模拟试验中，11 位住院医师在气管插管时佩戴单层手套，11 位佩戴双层手套并在插管完成后立即脱去外层。在模拟实验开始前，我们在模型的嘴唇及口腔涂抹荧光标记的胶体替代病原体。实验后，观察者手持紫外线灯检查手术环境的 40 处，来确认替代病原体是否转移到病人或病人所处环境中。佩戴双层手套的住院医师在护士的引导下于完成气管插管后立即脱去外层手套，40 个潜在病原体传播地点确定并分级。

**结果：**两组的污染率存在临床及统计学显著差异。单层手套组污染处数量为  $20.3 \pm 1.4$  (mean $\pm$ SE); 双层手套组污染处数量为  $5.0 \pm 0.7$  ( $P < 0.001$ )。

**结论：**当麻醉师佩戴两层手套进行诱导及插管，并与完成插管后立即脱去外层手套，可显著减少手术环境的污染。

（许红娇译，李士通 审校）

**BACKGROUND:** Oral flora, blood-borne pathogens, and bacterial contamination pose a direct risk of infection to patients and health care workers. We conducted a study in a simulated operating room using a newly validated technology to determine whether the use of 2 sets of gloves, with the outer set removed immediately after endotracheal intubation, may reduce this risk.

**METHODS:** Forty-one anesthesiology residents (PGY 2-4) were enrolled in a study consisting of individual or group simulation sessions. On entry to the simulated operating room, the residents were asked to perform an anesthetic induction and

tracheal intubation timed to approximately 6 minutes; they were unaware of the study design. Of the 22 simulation sessions, 11 were conducted with the intubating resident wearing single gloves, and 11 with the intubating resident using double gloves with the outer pair removed after verified intubation. Before the start of the scenario, we coated the lips and inside of the mouth of the mannequin with a fluorescent marking gel as a surrogate pathogen. After the simulation, an observer examined 40 different sites using a handheld ultraviolet light in the operating room to determine the transfer of surrogate pathogens to the patient and the patient's environment. Residents who wore double gloves were instructed by a confederate nurse to remove the outer set immediately after completion of the intubation. Forty sites of potential intraoperative pathogen spread were identified and assigned a score.

**RESULTS:** The difference in the rate of contamination between anesthesiology residents who wore single gloves versus those with double gloves was clinically and statistically significant. The number of sites that were contaminated in the operating room when the intubating resident wore single gloves was  $20.3 \pm 1.4$  (mean  $\pm$  SE); the number of contaminated sites when residents wore double gloves was  $5.0 \pm 0.7$  ( $P < 0.001$ ).

**CONCLUSIONS:** The results of this study suggest that when an anesthesiologist wears 2 sets of gloves during laryngoscopy and intubation and then removes the outer set immediately after intubation, the contamination of the intraoperative environment is dramatically reduced.

### 专为孩子和父母定制的门诊手术前准备网络版的运行操作（网络贴士）

#### Web-Based Tailored Intervention for Preparation of Parents and Children for Outpatient Surgery (WebTIPS): Development

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**背景：**由于费用控制的强制，目前的门诊手术前准备程序无法应用于大多数孩子与父母。最近网上流行了一种教孩子和父母术前准备的好方法。在这篇文章中，我们主要讲述网络版门诊手术前准备的运行操作（网络小贴士）。

**程序运行：**一个多学科工作组认为基于网络的干预首先是由输入，矩阵，输出三大模块组成。接下来，输入的各种变量的内容，矩阵的逻辑及输出的内容是发展的。输出产品有一个大人模块和一个小孩模块，详见 <http://surgerywebtips.com/about.php>。小孩模块使用的准备策略是信息提供，建模，玩耍和应对技能训练。贴士的大人模块提供的策略是信息提供，应对技能训练，放松及分散注意力技能。著名的动画和网页设计公司开发出一种安全的连网产品基于上述描述。



**结论：**在这篇文章中我们讲述了术前准备程序网络版的原理与操作步骤，父母和孩子在手术前后可多次访问这个程序网站。在 *Anesthesia & Analgesia* 杂志上有后续文章对此有标准化的评估及网络版术前准备的初步效果。

（许红娇译，李士通审校）

**BACKGROUND:**As a result of cost-containment efforts, preparation programs for outpatient surgery are currently not available to the majority of children and parents. The recent dramatic growth in the Internet presents a unique opportunity to transform how children and their parents are prepared for surgery. In this article, we describe the development of a Web-based Tailored Intervention for Preparation of parents and children undergoing Surgery (WebTIPS).

**DEVELOPMENT OF PROGRAM:**A multidisciplinary task force agreed that a Web-based tailored intervention consisting of intake, matrix, and output modules was the preferred approach. Next, the content of the various intake variables, the matrix logic, and the output content was developed. The output product has a parent component and a child component and is described in <http://surgerywebtips.com/about.php>. The child component makes use of preparation strategies such as information provision, modeling, play, and coping skills training. The parent component of WebTIPS includes strategies such as information provision, coping skills training, and relaxation and distraction techniques. A reputable animation and Web design company developed a secured Web-based product based on the above description.

**CONCLUSIONS:**In this article, we describe the development of a Web-based tailored preoperative preparation program that can be accessed by children and parents multiple times before and after surgery. A follow-up article in this issue of *Anesthesia & Analgesia* describes formative evaluation and preliminary efficacy testing of this Web-based tailored preoperative preparation program.

### **EN3427：一种新型阳离子氨基苄型长效局部麻醉药的性能**

#### **EN3427: A Novel Cationic Aminoindane with Long-Acting Local Anesthetic Properties**

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**背景：**目前批准的局部麻醉药物提供了相对简单的局部麻醉，在某些情况下是合适的，甚至是有优势的，但药物作用时间不足将影响其临床情况的使用。我们试图找出新的局部麻醉剂的分子，具体论证了一种长效药物发现计划，在伤害感受器感觉传入表示瞬时受体电位（TRP）通道的优先激动。我们测试的假设是基于相对浸透膜局部麻醉药分子可以持久的麻醉效果，假如神经元的访问是由 TRP 通道的激活。当前的工作描述了从发现，铅分子体内研究 en3427，到建立一些啮齿类动物疼痛模型。

**方法：**雄性 SD 大鼠，采用急性机械手爪夹 2 模型诱发和针刺诱发疼痛的表现。对伤害性刺激的行为反应进行了评估，在基线，任何药物干预前、后在不同的时间点，一个单一的神经周围或皮下注射 en3427 单独或联合利多卡因。缩爪阈值或皮肤 trunci 反射进行量化，和前药后的值进行方差分析，然后 Dunnett 多范围检验进行统计学分析。

**结果：**注射利多卡因（2%）产生的爪子拯救诱发疼痛，是从基线到 1 小时的时间点差异显著（ $P = 0.0081$  Dunnett 多重调整后），在同一模型中，产生一个持久的疼痛，疼痛阈值显著高于基线到 18 小时时间点（Dunnett 多重调整后的  $P = 0.0002$ ）；en3427 的组合（0.2%）和利多卡因（2%）产生更持久的镇痛，疼痛阈值显著高于基线通过 24 小时时间点（Dunnett 多重调整  $P = 0.0073$ ）。用针刺的方法得到了相似的结果。单次皮下注射利多卡因（2%）产生了完整的感觉丧失皮肤针刺通过 0.5 小时，但灵敏度阈值是没有什么不同的基线的 1 小时的时间点，一个类似的 en3427 单独注射（0.2%）产生的一种感觉丧

失，明显不同于基线通过的 8 小时时间点（Dunnett 多重调整后的  $P = 0.0045$ ），和利多卡因的组合（2%）加 en3427（0.2%）的出现进一步增强镇痛持续时间，虽然这是显著不同的从基线只能通过 10 小时时间点（Dunnett 多重调整  $P = 0.0048$ ）。镇痛效果与剂量呈正相关；采用联合注射的方法，我们发现，增加在 en3427 剂量与一个固定的 2%利多卡因 LED 大幅延长镇痛和增加剂量的利多卡因联合固定剂量的 en3427（0.2%）LED 只有小幅增加作用时间。

**结论：**目前的研究表明，一种新的分子实体，en3427 生有效的和持久的对啮齿类动物疼痛模型的镇痛。与利多卡因相比，en3427 镇痛效果明显持久。结果相对于利多卡因 TRP 通道的激活，该药物可能介导和促进神经元的交流而产生随后的诱捕持续时间延长疗效相关。

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**BACKGROUND:** Currently approved local anesthetic drugs provide relatively brief local anesthesia that is appropriate and even desirable in some settings, but an extended duration of action beyond their capabilities would be a distinct benefit in other clinical situations. We implemented a drug discovery program that sought to identify novel local anesthetic molecules that specifically demonstrated a long-acting, preferential action on nociceptor sensory afferents that expressed transient receptor potential (TRP) channels. The hypothesis we tested was whether relatively membrane-impermeant local anesthetic molecules could confer long-lasting anesthesia if neuronal access was facilitated by TRP channel activation. The current work describes in vivo studies on a lead molecule that emerged from the discovery program, EN3427, in several rodent pain models.

**METHODS:** Studies were performed on male Sprague-Dawley rats using 2 models of acute mechanical paw-pinch-evoked and pinprick-evoked nociceptive pain. Behavioral responses to noxious stimuli were assessed at baseline, that is, before any pharmacologic intervention, and at various timepoints after a single perisciatic or subcutaneous administration of either EN3427 alone or in combination with lidocaine. Paw withdrawal thresholds or cutaneous trunci reflexes were quantified, and pre-post drug values were compared statistically with analysis of variance followed by post hoc Dunnett multiple range test.

**RESULTS:** A single perisciatic injection of lidocaine (2%) produced relief of paw-pinch-evoked pain that was significantly different from baseline through to the 1-hour timepoint (Dunnett multiplicity-adjusted  $P = 0.0081$ ), as assessed using paw withdrawal or vocalization end points. EN3427 (0.2%), in the same model, produced a long-lasting block, with pain thresholds being significantly above baseline through to the 18-hour timepoint (Dunnett multiplicity-adjusted  $P = 0.0002$ ); the combination of EN3427 (0.2%) plus lidocaine (2%) produced even longer lasting analgesia, with pain thresholds being significantly above baseline through to the 24-hour timepoint (Dunnett multiplicity-adjusted  $P = 0.0073$ ). Similar results were obtained with use of the pinprick approach. A single subcutaneous injection of lidocaine (2%) produced complete loss of sensation to cutaneous pinprick through 0.5 hours, but sensitivity thresholds were no different to baseline by the 1-hour timepoint, a similar injection of EN3427 alone (0.2%) produced a loss of sensation that was significantly different from baseline through the 8-hour timepoint (Dunnett multiplicity-adjusted  $P = 0.0045$ ), and the combination of lidocaine (2%) plus EN3427 (0.2%) appeared to further enhance duration of analgesia, although this was significantly different from baseline only through the 10-hour timepoint (Dunnett multiplicity-adjusted  $P = 0.0048$ ). Analgesic efficacy was dose related; using the combined injection approach, we found that increases in the dose of EN3427 with a fixed 2% lidocaine led to substantially extended analgesia and increasing doses of lidocaine combined with a fixed dose of EN3427 (0.2%) led to only modestly increased duration of action.

**CONCLUSIONS:** The present studies demonstrate that a new molecular entity, EN3427, produces effective and long-lasting analgesia in 2 rodent pain models. The analgesic effects of EN3427 are significantly longer-lasting than lidocaine and are further extended when EN3427 is combined with lidocaine. The results are discussed with respect to a possible lidocaine-mediated

TRP channel activation and facilitated neuronal access of EN3427, with subsequent entrapment conferring extended-duration efficacy.