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[室性心動過速消融：一項給予麻醉醫生的系統綜述](#)

Ventricular Tachycardia Ablation: A Comprehensive Review for Anesthesiologists

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Anesthesia & Analgesia 2015 120 737–748

經皮導管消融術越來越多運用於藥物治療無效的反復發作室性心動過速（ventricular tachycardia, VT）的患者。對於此類患者最佳的管理包括謹慎考慮潛在心臟疾病的嚴重程度，麻醉藥物相互作用以及在 VT 標測和消融過程中的技術問題。目標在於選擇一種致心律失常性最小的麻醉技術，這樣可以使得在電生理操作室內 VT 的發生具有可重複性。麻醉藥可以直接通過對於離子通道和縫隙連接作用，或間接通過對於自主神經系統作用改變動作電位和心室去極化過程。此外，在操作過程中維持血流動力學穩定以及監測終末器官灌注是另一項挑戰。本綜述全面地更新了當今 VT 消融的實施過程中的麻醉處理方法。

(俞芳 譯 陳傑 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.

[丙泊酚對於高糖誘導的人臍靜脈內皮細胞凋亡和功能障礙的保護作用](#)

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

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背景：圍術期高血糖症是臨床上常見的一種代謝紊亂疾病。高血糖誘導內皮細胞凋亡和功能障礙。丙泊酚是一種臨床上廣泛使用的靜脈麻醉藥物。本研究檢測丙泊酚是否及如何減輕高糖誘導的人臍靜脈內皮細胞（HUVECs）凋亡和功能障礙。**方法：**用不同濃度（5，10，15 和 25 mM）的血糖體外培養 HUVEC，時間分別是 4，8，12 和 24 小時。爲了研究丙泊酚的效應，用不同濃度（0.2，1，5 和 25 μ M）的丙泊酚孵育 2 小時。在平行實驗中，細胞在 5 mM 葡萄糖中孵育作爲對照。用硝酸還原酶法測定產生的一氧化氮（NO）。用細胞計數試劑盒-8 測定細胞活性。用 Western blot 法檢測 caspase 3、細胞色素 C、內皮型一氧化氮合酶（eNOS）、p-eNOS-Thr495、p66Shc、蛋白激酶 C β II（PKC β II）和 p-PKC β II-Ser660。用亞鐵細胞色素 c 減少法測定超氧陰離子（O $_2^{\cdot-}$ ）累積。用末端去氧核苷酸轉移酶介導 dUTP 缺口末端標記染色法測定細胞凋亡。

結果：與對照組相比，高糖減少 HUVEC 的 NO 產生（ $P < 0.0001$ ，降低細胞活性（ $P < 0.0001$ ）。與高糖處理相比，丙泊酚預處理細胞（5 μ M，2 h）減少了高濃度葡萄糖誘導的抑制性 p-eNOS-Thr495 磷酸化（ $P < 0.0001$ ），增加 NO 的產生（ $P = 0.0007$ ），降低高血糖誘導的 p66Shc 的表達（ $P < 0.0001$ ）和 p66Shc 線粒體易位（ $P < 0.0001$ ），O $_2^{\cdot-}$ 蓄積（ $P < 0.0001$ ），線粒體細胞色素 C 釋放（ $P < 0.0001$ ），活化 Caspase 3 的表達（ $P < 0.0001$ ）和增強內皮細胞活性（ $P < 0.0001$ ）。此外，異丙酚抑制高糖誘導的 PKC- β II 的表達（ $P = 0.0002$ ）和 p-PKC β II-ser660 磷酸化（ $P < 0.0001$ ）。丙泊酚的保護作用與 PKC β II 抑制劑十分相似。

結論：丙泊酚通過降低高糖誘導 PKC β II 的表達和 p-PKC β II-ser660 磷酸的機制，抑制高糖誘導的 p66Shc 線粒體易位。因此保護人臍靜脈內皮細胞免受高糖誘導的內皮細胞功能障礙和細胞凋亡。

（徐歡 譯 陳傑 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 μ 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 β II (PKC β II), and p-PKC β 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 μ 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 β II expression ($P = 0.0002$) and p-

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

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

金黃色葡萄球菌在麻醉工作區域傳播的流行病學

The Epidemiology of Staphylococcus aureus Transmission in the Anesthesia Work Area

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Anesthesia & Analgesia 2015 120 807–818

背景:關於術中金黃色葡萄球菌傳播的流行病學所知甚少。本研究主要目的是檢查麻醉工作區域常見的金葡萄球菌（表型）的傳播方式、傳染源、傳播路徑以及抗生素敏感性。次要研究目標是檢查表型與術後 30 天病人培養、表型增長率和表型分離的危險因素之間的關係。

方法:先前通過病原學分類、時態關聯以及 API 系統確認金葡萄球菌可引起術中細菌性傳播事件，需進行抗生素紙片擴散法敏感性檢測。結合這些技術確認金葡萄球菌傳播事件，並將之分類（發生於術中或術間）。金葡萄球菌傳播源可以通過已證實的實驗模型以及對術後 30 天病人的培養結果進行脈衝凝膠電泳來證實。通過時間-陽性分析來評估增長率，通過 logistic 回歸對孤立的風險因素進行評估。

結果:對從先前術中傳播事件中分離出的 170 例金葡萄球菌，通過 API 表型進一步細分。兩個表型：表型 P(病人)和表型 H(手)，占分離株的 65%。表型 P 和表型 H 分別確認為在 39%和 28%的病例中至少 1 次傳播事件的致病菌。患者皮膚表面(優勢比[OR],8.40;95%可信區間(CI),2.30 -30.73)和環境(優勢比,10.89;95%置信區間,1.29 - 92.13)樣本的表型 P 陽性率比醫護人員手部(參照物)的更高。與表型 H 相比，表型 P 更耐甲氧西林(優勢比,4.38;95%置信區間,4.38 - 1.59;P = 0.004)，與術後 30 天病人培養結果相關性更大(風險比 36.63，風險差異,0.174;95%置信區間,0.174 - 0.019,P < 0.001)。與表型 H 相比，表型 P 對甲氧西林耐藥和甲氧西林敏感表現出更快的增長率(表型 P:中位數 10.32 H,四分位區間,10.08 - -10.56;表型 H:中位數,10.56 H,四分位區間,10.32 -10.8 ; P = 0.012)。分離表型 P 的風險因素包括年齡(優勢比,14.11;95%置信區間,3.12 - -63.5;P = 0.001)和病人是否在醫院病房暴露(優勢比,41.11 ; 95%置信區間,5.30 -318.78 ; P < 0.001)。

結論:兩種表型的金葡萄球菌都常在麻醉工作區域內傳播。與醫護人員手部來源表型相比，病人和環境相關表型抗生素耐藥性風險增大，術後 30 天病人培養結果陽性率增高。未來工作方向應該是改善患者進入圍術期區域時金葡萄球菌的篩查並增強手術室環境清潔以減少相關術後感染。

(池曉穎 譯 陳傑 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.

麻醉醫生的手衛生學知識和觀念

Hand Hygiene Knowledge and Perceptions Among Anesthesia Providers

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背景：醫護人員服從手衛生指南是衛生保健相關感染預防的重要措施，但醫療系統總體依從性仍然較低。關於 4 項手消毒指征相關問題（根據接觸類型）能提供完全正確答案的從業者，與答錯 1 項以上的從業者相比，他們的手衛生依從性更佳。更好地理解麻醉科從業者知識缺乏情況促使進行手衛生的改進策略。這項研究的主要目的是描述和確認麻醉醫師中手衛生知識不足的現狀。

方法：對國內和多中心團隊的 5 個時刻的手衛生知識改良此項問卷，來測試麻醉醫生對手衛生的瞭解情況。完全瞭解定義為答對 5 項關於手衛生知識的 5 個時刻的問題，評分為 1 分。不完全瞭解定義為是為答錯一個或者更多的問題，評分為 0 分。採用一個多層次的隨機效應 XTMELOGIT logistic 模型分析回答者知識不足和地理分佈，以及逐步前進後退 logistic 回歸分析來確認不完全瞭解的預測因素。

結果：多中心和全國性調查研究組調查應答率分別為 55.8% 和 18.2%。至少一項知識錯誤發生於 81.6% 的受訪者中，正確答案的中位數是 2.89（95% 置信區間，2.78–2.99）。對在接觸環境和接觸病人前進行手衛生的認識不足是較低的正確中位數的原因。一些認知因素

與減少不完全知識相關，包括在接觸環境後積極回應洗手（比值比[OR] 0.23，0.14–0.37， $P < 0.001$ ），在對病人護理中消毒環境（比值比 0.54，0.35–0.82， $P = 0.004$ ），相信他們可以影響同事（比值比 0.43，0.27–0.68， $P < 0.001$ ），並打算堅持準則（比值比 0.56，0.36–0.86， $P = 0.008$ ）。這些協變數與受試者特徵曲線下面積相關性為 0.79（95% 置信區間，0.74–0.83）。**結論：**麻醉醫生在手衛生準則方面的知識缺乏頻繁發生，往往由於沒有認識到手衛生在於與污染的病人接觸和環境接觸後。術中手衛生改進方案應解決這些知識缺陷。本研究證實的不完備知識的相關預測因素應在未來的研究中進一步驗證。

（李慧 譯 陳傑 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.

來源於麻醉工作區域的細菌傳播事件的動態和影響

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

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衛生保健相關感染被認為是與病人發病率、死亡率和醫療成本顯著增加的一項醫院範圍內的問題。來源於手術室環境內麻醉工作區域的細菌傳播是術後 30 天感染的根源之一，影響高達 16% 接受手術的病人。對麻醉相關細菌傳播動態更好的理解有助於產生改善術中感染控制和改善病人安全的方案。

(秦懿 譯 陳傑 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.

氟哌啶醇抑制小鼠樹突狀細胞成熟和輔助 T1 細胞免疫反應的啓動

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

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背景：氟哌啶醇常用於治療精神分裂症，或在重症監護室用於鎮靜重症病人，它同時有免疫調節作用。儘管氟哌啶醇影響免疫功能的機制尚不清楚，但有一種可能性是它改變了樹突細胞(DC)的功能。DCs 是強有力的抗原遞呈細胞，它影響了 T 淋巴細胞的啓動和成熟。此項研究通過體內和體外實驗考察了氟哌啶醇對 DC 介導的免疫反應的免疫調節作用。

方法：使用從骨髓提取的 DCs 進行細胞培養，檢測氟哌啶醇對共刺激分子 (CD80 和 CD86)、II 型主要組織相容性複合體分子和 DC 成熟標誌物 CD83 的表達的影響。DC 培養的上清液檢測白介素-12 p40 水準。另外分析了氟哌啶醇對混合培養的 DCs 和淋巴細胞的影響，並檢測了培養上清液中 γ 干擾素的分泌。在體內試驗中評估了氟哌啶醇對半抗原誘導的接觸性超敏反應的影響。

結果：氟哌啶醇抑制了 CD80、CD86、II 型主要組織相容性複合體和 DC 細胞上的 CD83 的表達，並抑制了 DC 培養上清液中白介素-12p40 分泌。在含有 T 細胞 (CD4⁺和 CD8 α ⁺) 和 DCs 的混合培養物中，氟哌啶醇處理過的 DCs 抑制了同種異體 T 細胞的增殖，並有效抑制了 γ 干擾素的產生。在體實驗中，氟哌啶醇減少半抗原誘導的接觸性超敏反應。此外，D2 樣受體拮抗劑抑制了 DCs 成熟的方式類似於氟哌啶醇。

結論：研究結果表明，在動物中氟哌啶醇抑制了 DCs 的功能成熟，並在抑制 DC 介導的輔助 T1 細胞免疫反應中起著重要作用。此外，氟哌啶醇對 DCs 的作用可能是通過多巴胺 D2 樣受體所介導。總之這些結果表明，氟哌啶醇抑制了 DC 介導的免疫反應。

(王筱婧 譯 陳傑 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- γ 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 α +) and DCs, haloperidol-treated DCs suppressed the proliferation of allogeneic T cells and effectively inhibited the production of interferon- γ . 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.

兒茶酚氧位甲基轉移酶 (COMT) 基因單倍型與術後病人芬太尼用量有緊密聯繫

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

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背景：芬太尼的鎮痛效應個體差異較大，COMT 的單核苷酸多態性 (SNPs) 能調節疼痛敏感性。然而，現在還不清楚，COMT 的基因多變性是否能影響行根治性胃大部分切除術患者的術後芬太尼鎮痛效果。

方法：將全麻下擇期行根治性胃大部分切除術共 115 例、ASA 為 I–III 級的患者納入研究。在手術結束後的 48 小時內，患者使用芬太尼自控靜脈輸注鎮痛。患者的疼痛視覺類比量表得分維持在 ≤ 30 mm，在術後 24h 和 48h，記錄芬太尼的使用量與副作用。通過聚合酶鏈反應擴增 DNA 或聚合酶鏈反應限制性片段長度多態性的 DNA 序列分析測出所有患者的 COMT 的 SNPs (rs6269, rs4633, rs4818, 和 rs4680)。

結果：擁有不同 COMT 的 SNPs (rs6269, rs4633, rs4818, 和 rs4680) 的患者在術後 24 小時 (P>0.207) 和 48 小時 (P>0.148) 的芬太尼總用量無差異。然而，COMT 基因單倍型聯合 COMT rs6269, rs4633, rs4818, 和 rs4680 卻顯著影響患者在術後 24 小時 (P=0.029) 和 48 小時 (P=0.032) 的芬太尼的使用量。在 COMT 基因的單倍型中，攜帶單倍型 ACCG 的患者在術後 24h 和 48h 的芬太尼使用量要高於 GCGG 和 ATCA 單倍型 (P<0.042)。噁心，嘔吐和眩暈的發生率在 4 個不同 COMT 的 SNPs 中無顯著差別 (P>0.482)。

結論：含有 rs6269, rs4633, rs4818, 和 rs4680 的 COMT 基因單倍型對術後芬太尼鎮痛的個體差異性有影響。攜帶 COMT 基因單倍型 ACCG 的患者在術後 24h 和 48h 需要更多的藥量。

(殷文譯 陳傑校)

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 ≤ 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.

體外膜式氧合引起高分子量血管性血友病因子多聚體短暫缺失

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）多聚體在初期的止血過程中起重要作用。心室輔助裝置帶來的剪切力增加導致 HMW vWF 多聚體過早降解。但是體外膜式氧合（ECMO）條件下是否同樣存在 vWF 多聚體的降解仍然是疑問。

方法：我們在頑固性心功能不全伴/不伴肺功能衰竭並且需要 ECMO 治療的患者進行了一項觀察性研究。觀察主要節點是在 ECMO 前，ECMO 中和 ECMO 後的 HMW vWF 的品質和數量。為了進一步研究初期止血的改變，針對入組的 38 例患者，在患者接受 ECMO 前（基礎值），經行 ECMO 24 小時和 48 小時時，以及 ECMO 治療後 24h，我們同時檢測 vWF 抗原（vWF-Ag），vWF 瑞斯托菌素輔因子（vWF-RCo）和 VIII 因子的水準。

結果：與基礎水準相比，經過 24h ECMO 治療後，vWF-Ag 和 vWF-RCo 水準明顯下降（平均數 \pm 標準差，vWF-Ag，307% \pm 152% 到 261% \pm 138%， $P = 0.002$ ；vWF-RCo 282% \pm 145% 到 157% \pm 103%， $P < 0.0001$ ）。同樣在後續治療過程中 vWF-Ag 和 vWF-RCo 水準亦明顯下降（vWF-Ag 265% \pm 128%， $P = 0.025$ ；vWF-RCo 163% \pm 94%， $P < 0.0001$ ）。在終止 ECMO 治療後，vWF-Ag 高於基礎水準（359% \pm 131%， $P = 0.004$ ），而 vWF-RCo 與基礎水準持平（338% \pm 142%， $P = 0.046$ ）。與基礎值相比，vWF-RCo/vWF-Ag 比值在 24h ECMO 治療後明顯下降（0.96 \pm 0.23 至 0.61 \pm 0.17， $P \leq 0.0001$ ），在 48h ECMO 治療後該比值亦明顯下降（0.63 \pm 0.18， $P \leq 0.0001$ ）。在終止治療後，該比值迅速與基礎值持平（0.94 \pm 0.19， $P = 0.437$ ）。HMW vWF 多聚體的數量在 24h（21 \pm 1.4 至 14

± 1.8 , $P \leq 0.0001$) 和 48h (15 ± 2.1 , $P \leq 0.0001$) 治療後均明顯下降。在 ECMO 治療終止 24h 後, HMW vWF 多聚體水準恢復到基礎水準 (21 ± 1.8 , $P = 0.551$)。

結論: HMW vWF 多聚體在 ECMO 治療後出現減少, 在治療終止後逐漸恢復。雖然凝血篩查試驗無陽性表現, 但是在 ECMO 治療中 vWF:RCo/vWF:Ag 比值小於 0.7 仍然提示 HMW vWF 多聚體的丟失。我們的研究在一定程度上解釋了 ECMO 治療中患者出血傾向增加的現象。在 ECMO 治療給予 vWF 治療有助於改善出血傾向, 幫助止血功能的恢復。

(王嘉興 譯 薛張綱 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 ± 0.23 to 0.61 ± 0.17 , $P \leq 0.0001$) and remained lower during 48 hours on ECMO (0.63 ± 0.18 , $P \leq 0.0001$). After termination of ECMO support (0.94 ± 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 ± 1.4 to 14 ± 1.8 , $P \leq 0.0001$) and after 48 hours on ECMO (15 ± 2.1 , $P \leq 0.0001$). Twenty-four hours after termination of ECMO support, HMW vWF multimeric pattern had returned to baseline values (21 ± 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 和咪達唑侖在上消化道內鏡的鎮靜中的 IIa 期隨機雙盲研究

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: 這項探索性研究是評估不同單次劑量 remimazolam 用於鎮靜的安全性和有效性的首次研究。

方法：病人按計劃行診斷性上消化道內鏡檢查，隨機、雙盲給予 3 種劑量中的 1 種的 remimazolam 或者咪達唑侖，每組 25 位病人。給予單次的藥物鎮靜滿意後，病人行胃鏡檢查。我們評價檢查的成功與否、鎮靜效果、蘇醒和安全性。

結果：低劑量組（0.10mg/kg）、中劑量組（0.15mg/kg）和高劑量組（0.20mg/kg）給予單次劑量 remimazolam 後的胃鏡檢查成功率分別是 32%、56%、64%，咪達唑侖組（0.075mg/kg）的成功率是 44%。Remimazolam 組的鎮靜起效時間是 1.5-2.5 分鐘，而咪達唑侖組是 5 分鐘。因為這項研究是給予單次劑量，必要時給予咪達唑侖或丙泊酚以維持鎮靜狀態完成檢查。所有治療組病人鎮靜後的蘇醒都非常迅速，但受單次劑量後選擇的追加藥物的影響。在 remimazolam 和咪達唑侖的安全性上沒有明顯的不同。

結論：這項劑量探索性研究表明在診斷性上消化道內鏡檢查中給予病人單次劑量 remimazolam（0.10-0.20mg/kg）能夠快速鎮靜和快速蘇醒。Remimazolam 的安全性良好，與咪達唑侖相似，保證了這個起效迅速的藥物的進一步發展。

（呂越昌 譯 薛張綱 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.

無針連接元件大量減少了快速輸液時晶體及紅細胞的流速

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

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儘管無針連接元件（NC）被廣泛地用於圍術期，但現代無針連接元件減低輸注液體的速度可能性並未被徹底研究。我們研究了 Level 1 通過不同的靜脈導管輸液的 5 種裝置及無針連接元件在加壓輸注晶體液以及紅細胞時的流速特點。在大於 18 號的導管中，晶體液的速度降低 29% to 85%，在這些導管中，紅細胞輸注流速下降 22% to 76%（ $P < 0.0050$ ）。我們建議臨床實踐者在使用大管徑靜脈導管經行快速輸液時去除無針連接元件。

(吳赤 譯 薛張綱 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.

麻醉操作導致的腸球菌易位的傳播動力學

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

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背景：腸球菌是醫療操作相關感染的第二大病因，該細菌從無害的正常菌群逐步進化為大大增加病人感染率和死亡率的多重耐藥微生物。預防該微生物在醫院內部以及醫院之間蔓延至關重要。本研究主要關注全麻常規操作導致腸球菌易位的傳播動力學。

方法：我們從三大醫療中心內麻醉師經常接觸的腸球菌生存部位（病人鼻咽和腋窩、麻醉師的手、麻醉機限壓閥和調節按鈕）分離腸球菌並按病原種類、短暫接觸以及表型分析（族群分析指數）分別保存，並將麻醉過程中各部位腸球菌的接觸鑒定為可能導致術中細菌傳播的主要事件。然後通過抗生素圓盤內細菌擴散以及細菌對抗生素的敏感性分析來確認傳播事件的發生。最終通過對傳播事件中的接觸分析以確認該事件發生的頻率、方式、起源、傳播部位以及病原菌對抗生素的敏感性。

結果：通過大體形態以及簡單的快速實驗確認麻醉過程中常見細菌儲存部位分離出來的細菌（共 389 例）為腸球菌。進一步通過族群分析參數分析以及短暫接觸鑒定其中 43%（166/389）為可能的術中細菌傳播事件。其中，30%（49/166）通過了抗生素敏感性確認。其中，80%（39/49）為表型 E5 或 E7。在所有兩種表型的細菌中，麻醉師的手均為該細菌的主要來源（E7 96%[72/75];E5 89%[50/56]）以及傳播部位（E7 94%[16/17];E5 89%[19/22]）。

結論：麻醉師的手為麻醉操作過程中導致腸球菌傳播事件的主要細菌來源以及傳播部位。下一步研究方向為提高操作過程中手衛生對術中腸球菌傳播事件的影響。

(郝光偉 譯 薛張綱 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

在靜脈通路中留下的不只是你的指紋：一項關於異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：在麻醉和手術中對靜脈通路中的三通進行操作時可能會導致靜脈管路的污染。在異丙酚這種營養豐富的催眠藥物廣泛應用的情況下，我們提出這樣的假說：異丙酚麻醉增加了靜脈三通管的細菌污染，使用過異丙酚的靜脈三通繼續使用時可能會存在安全隱患。

方法：我們的體外試驗是從當天使用過和未使用過異丙酚的患者的靜脈通路上拆下三通器，並立即作為試驗樣本收集起來。這些三通器在室溫下被分別保存 6, 24, 48 小時。每個時間間隔（6h、24h、48h）我們分別取兩組（使用過異丙酚和未使用過異丙酚）的 50 個樣本進行培養。我們抽取靜脈三通器中死角的殘餘物並將其接種於血平板中進行菌落計數和菌種鑒定來實現細菌的定量培養。

結果：細菌培養陽性率在異丙酚三通組為 17.3% (26/150)而在非異丙酚三通組為 18.6% (28/150)。6 小時點，異丙酚組中：有可見殘留異丙酚的三通的平均細菌計數為 44CFU/ml，無可見殘留異丙酚的三通的平均細菌計數為 41 CFU/mL；在非異丙酚組該值為 37 CFU/mL。異丙酚麻醉後 48 小時，在被污染的三通死角中細菌數增殖 100 倍。無可見殘留異丙酚的三通和非異丙酚組三通比較，無可見殘留異丙酚的三通的細菌計數也存在顯著差異(P = 0.034)。

結論：麻醉過程中特別是異丙酚麻醉中存在靜脈三通細菌污染的隱患。異丙酚麻醉可能增加術後感染的風險，因為細菌會在靜脈三通的死角中繁殖。

(蓋曉冬 譯 薛張綱 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.

應用新技術對手術室內病原菌傳播機制的研究

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

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手術環境中發現的致病菌具有潛在的致感染風險，並可導致一定的致病率和致死率。為了研究手術室內麻醉人員作為帶菌者引起病人感染的機制，我們利用最新的實驗技術在模擬手術室環境內利用高模擬的模擬病人實施了此項研究。

（潘豔 譯 薛張綱 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.

應用呼氣相輔助通氣的方法通過一根小口徑的氣管導管對嚴重低氧血症豬的急救性通氣

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

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背景：抽吸產生的呼氣相輔助通氣（EVA）的方法使得通過一根小口徑的氣管導管進行雙向通氣成爲可能。本研究中我們通過急性低氧血症豬的模型來研究 EVA 在恢復氧和以及通氣的效率。

方法：對六隻體重在 61-76kg 的豬進行麻醉，利用帶套囊的氣管導管進行間斷性正壓通氣。接好監測後，給這些豬置入一根長 75mm，內徑 2mm 的氣管導管。記錄好基礎生命體征後，斷開呼吸機。缺氧 2 分鐘後，通過應用輔助呼氣相通氣的方法進行再氧合並且持續 15 分鐘，這期間氣管導管都是封閉的。本研究中的第二階段，我們將氣管導管半開半閉或者完全開放重複上述實驗過程。實驗中我們即時監測氣道壓力，血流動力學參數及動脈血氣，並進行描述性統計學分析。

結果：在上呼吸道完全或部分梗阻的動物模型中，應用呼氣相輔助通氣的方法能使所有的動物在 20 秒內恢復氧合。在完全梗阻的氣道中，二氧化碳的分壓在 15 分鐘內能保持穩定。在氣道梗阻程度稍輕的情況下，再氧合的時間被延遲。在氣道完全開放的情況下，這一方法的有效性很有限，其中的 2 只豬在 15 分鐘的通氣後動脈氧分壓依然低於 85mmHg，並且二氧化碳分壓上升到 90mmHg。

結論：在嚴重低氧血症豬的模型中，在氣道完全封閉及部分封閉情況下通過輔助呼氣相通氣的方法能使缺氧快速恢復，而在上呼吸道完全開放的情況下，這種方法在恢復氧合和輔助通氣方面就顯得無能爲力。

（王飛 譯 薛張綱 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, PaCO₂ 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 PaO₂ <85 mm Hg even after 15 minutes of ventilation with EVA and a mean PaCO₂ 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.

對於行門診手術的父母和孩子術前準備的基於網路簡明的干預研究（WebTIPS）：形成性評價和隨機對照試驗

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：這項 2 階段的專案的目的是為了對一項新開發的基於網路的簡明干預在父母和兒童術前準備的程式進行形成性評價和初步療效的測試(WebTIPS)。

方法：第 1 階段入組了 13 個接受門診擇期外科手術的 2 - 7 歲兒童和他們的父母，對其進行 WebTIPS 的形成性評價。在定性研究中，家長參與集中研討小組是非常普遍的，而且這是詢問研究參與者對一個產品或概念看法和態度的一個方法。在第 2 階段中，來自兩個醫療中心的 2–7 歲兒童被隨機分配接受 WebTIPS (n = 38)和標準護理(n = 44)。第二階段的主要結果是孩子和家長的術前焦慮。

結果：在第二階段，父母認為 WebTIPS 有效($P < 0.001$)並且易於使用($P < 0.001$)。在第二階段，在進入手術室時($P = 0.02$ ；Cohen $d = 0.59$)和介紹麻醉面罩時(分別為 43.5 ± 21.7 與 57.0 ± 57.0 , $P = 0.01$ ；Cohen $d = 0.63$)，WebTIPS 組的兒童(36.2 ± 14.1)與標準護理組的兒童(46.0 ± 19.0)相比，焦慮程度較低。術前等候區，WebTIPS 組的父母(32.1 ± 7.4)較對照組父母(36.8 ± 7.1)經歷更少的焦慮($P = 0.004$ ；Cohen $d = 0.65$)。

結論：WebTIPS 受到了家長和孩子的廣泛認可，其可減少術前焦慮。

(黃文惠 譯 薛張綱 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 ± 14.1) were less anxious than children in the standard of care group (46.0 ± 19.0) at entrance to the operating room ($P = 0.02$; Cohen $d = 0.59$) and introduction of the anesthesia mask (43.5 ± 21.7 vs 57.0 ± 21.2 , respectively, $P = 0.01$; Cohen $d = 0.63$). Parents in the WebTIPS group (32.1 ± 7.4) also experienced less anxiety compared with parents in the control group (36.8 ± 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.

體外迴圈期間的麻醉管理：一項系統回顧

Anesthetic Management During Cardiopulmonary Bypass: A Systematic Review

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心臟手術期間所必需的體外迴圈目前對於麻醉醫生的特殊挑戰主要在於以下 3 個方面：麻醉、鎮痛和肌松。

在體外迴圈期間特殊的病理生理變化會導致藥代動力學的改變，這一改變則會影響靜脈麻醉藥的血清和組織中的濃度。簡單地說，體外迴圈期間引起藥效學的改變將會影響麻醉效

果。而這些改變所帶來的臨床意義則代表了一種“移動目標”，就像臨床實踐的不斷演變和體外迴圈技術的不斷進步一樣。另外，灌注技術的選擇、修正並維持體外迴圈回路和膜式氧合器。

因此，他們的意義不僅僅是被麻醉醫生所讚賞。這些技術將會對病人的麻醉狀態產生深遠的影響。體外迴圈期間的輸送和維持面臨著獨特的挑戰。在體外迴圈期間。灌注師將直接對麻醉的維持負責，而對於心臟迴圈來說這是一種特殊的狀態。

另外，麻醉深度的監測，包括臨床指征的評估、血流動力學指標、腦電雙頻指數、呼氣末麻醉藥物濃度的監測以及肌張力的監測等在體外迴圈期間都將是缺失的、不可信的、甚至直接被這種特殊的病理生理學因素所影響。在心臟手術期間，這些監測不足所帶來的困難將會大大增加術中知曉的發生率。

更複雜的是，醫療器械的規格缺少具體的臨床指南以及國際政策的不斷變化將會增加醫療機構內甚至是國家之間更多的複雜醫療糾紛並引入新的實踐變化。

因此我們對文獻進行了一些列系統的調查來確定體外迴圈期間的麻醉操作是否有證可循，從而發現了文獻中存在的差異，這一調查為我們今後的研究提供了指導，並且探索了不斷發展的手術操作、灌注技術以及國際政策對於體外迴圈期間麻醉、鎮痛和肌松所帶來的影響。

（王慧娟 譯，李士通 審校）

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.

曲馬多及其代謝產物 M1 會選擇性的抑制瞬態電壓感受器陽離子通道受體 1 (TRPV1) 的活性，而不是暫態受體電位香草酸受體 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：暫態受體電位香草酸受體 1 (TRPV1) 和瞬態電壓感受器陽離子通道受體 1 (TRPA1) 都在感覺神經元處表達，他們是負責感受傷害性刺激的多形態非選擇性陽離子通道。最近的報導指出這些通道在炎性、神經病理性以及癌性疼痛中有非常重要的影響，從而在鎮痛藥的藥理學目標的研究方面起到了積極的作用。曲馬多是在臨床實踐中使用的一種有效的鎮痛藥。據研究，曲馬多和它的代謝產物 M1 和 μ 阿片受體結合從而抑制單胺類受體在中樞神經系統的再攝取，從而啟動下行抑制系統。然而，曲馬多在疼痛控制方面的作用機制目前尚未研究清楚。TRPV1 和 TRPA1 也許是曲馬多的作用靶點，但是目前沒有被廣泛研究。

方法：我們通過運用鈣離子成像檢測和全細胞膜片鉗記錄的方法研究了曲馬多和它的代謝產物 M1 對於人胚胎性腎 293 細胞是否以及如何表達暫態受體電位香草酸受體 1 (hTRPV1) 和瞬態電壓感受器陽離子通道受體 1 (hTRPA1)。

結果：分別與辣椒素組（一種 TRPV1 激動劑）和異硫氰酸烯丙酯組（一種 TRPA1 激動劑）相比，曲馬多和它的代謝產物 M1 在人胚胎性腎 293 細胞中表達 hTRPV1 和 hTRPA1 的同時本身並不增加細胞內鈣離子濃度。而且，在辣椒素的作用下，人胚胎性腎 293 細胞表達的 hTRPV1，經過曲馬多或它的代謝產物 M1 預處理 5 分鐘後，也不會影響細胞內鈣離子濃度的增加。反過來，在異硫氰酸烯丙酯的預處理後，曲馬多和它的代謝產物 M1 在人胚胎性腎 293 細胞表達 hTRPA1 的同時，則明顯抑制了細胞內鈣離子濃度的增加。另外，膜片鉗的研究發現，在異硫氰酸烯丙酯的作用下，曲馬多和它的代謝產物 M1 則降低了細胞的內向電流。

結論：這些資料表明了曲馬多和它的代謝產物 M1 會選擇性的抑制 hTRPA1 的作用，而對 hTRPV1 無影響，而且 hTRPA1 在鎮痛藥的化合物中起到了重要的作用。

（王慧娟譯，李士通審校）

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 μ -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 Ca^{2+} imaging assay and whole-cell patch-clamp recording.

RESULTS: Tramadol and M1 (0.01–10 μM) alone did not increase in intracellular 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 μM) and M1 (1–10 μM) 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 μM) 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-細菌病原體的傳播動力學研究

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

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背景：革蘭氏陰性菌是感染及社區傳播流行病原體健康護理的主要關注對象。我們的主要目的是描述麻醉工作環境（AWE）中常見 G-細菌的傳播動力學。並研究這些傳播事件與術後 30 天護理相關感染（HCALs）之間的關係。

方法：從三個主要的學術醫療中心的 AWE（病人鼻咽部和腋部，麻醉實施者手部，麻醉機的可調式限壓閥和代理撥號？）得到 G-細菌的分離株，並通過對細菌病原體吧、類型，事件關係，及表型分析定義可能書中細菌感染事件。前 5 中常見事件採用抗生素紙片擴散敏感性試驗來確定流行病學相關傳播事件。流行病學相關傳播事件中，同病例及病例間傳播的相互作用採用多因素回歸分析比例二項檢驗統計學分析進行研究。研究包括納入及未納入在一個給定研究單位下同一菌屬的重複感染（所觀察的每個手術室的第一個及第二個病例）來檢驗統計學依賴的潛在影響。傳播的菌株通過凝膠電泳進行比較區別術後 30 天 HCLs 致病細菌。

結果：最常見的 5 中 G-菌屬包括，不動桿菌，假單胞菌，短波單胞菌，腸桿菌屬，和莫拉菌，共占可能感染事件的 81%(767/945)。通過抗生素藥敏試驗檢驗，22%的可能感染事件被為流行病學相關性並有待進一步傳播動力學研究。20 例涉及同病例及病例間傳播，其中 19%與流行病學相關。作為流行病學相關傳染源，麻醉實施者的手部比對病人或環境污染存在更低的傳染可能性。暴露於 HALs 及存在術中 G-暴露的病人中，同病例及病例間的傳播發生率相同。凝膠電泳發現 8%（2/23）的 G-與感染致病微生物相連。術後 30 天護理相關感染中，發現病人及麻醉實施者的手部為傳染來源，病例間傳播事件中環境是載體。

結論：病例間及同病例間的 G-細菌傳播經常發生，通過脈衝凝膠電泳可以術後 30 天感染相關。污染環境及病人皮膚表面比麻醉實施者手部更容易成為細菌感染源。

（王慧娟譯，李士通審校）

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.

雙層手套，一個減少手術室污染的簡單策略評估的隨機對照試驗

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

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背景：對於病人和醫護人員，口腔菌群失調，血源性病原體和細菌污染造成感染的直接風險，。我們採用新驗證的技術在模擬手術室環境中，研究是否使用 2 層手套，並在氣管插管後立即脫去外層手套可減少這種風險。

方法：41 位麻醉住院醫師（培訓 2-4 年）被納入研究（包括個人及團體模擬）。進入模擬手術室後，住院醫師行麻醉誘導及氣管插管（定時約 6 分鐘），他們並不知研究設計。22 個模擬試驗中，11 位住院醫師在氣管插管時佩戴單層手套，11 位佩戴雙層手套並在插管完成後立即脫去外層。在類比實驗開始前，我們在模型的嘴唇及口腔塗抹螢光標記的膠體替代病原體。實驗後，觀察者手持紫外線燈檢查手術環境的 40 處，來確認替代病原體是否轉移到病人或病人所處環境中。佩戴雙層手套的住院醫師在護士的引導下於完成氣管插管後立即脫去外層手套，40 個潛在病原體傳播地點確定並分級。

結果：兩組的污染率存在臨床及統計學顯著差異。單層手套組污染處數量為 20.3 ± 1.4 (mean \pm SE); 雙層手套組污染處數量為 5.0 ± 0.7 ($P < 0.001$)。

結論：當麻醉師佩戴兩層手套進行誘導及插管，並與完成插管後立即脫去外層手套，可顯著減少手術環境的污染。

（許紅嬌 譯，李士通 審校）

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 ± 1.4 (mean \pm SE); the number of contaminated sites when residents wore double gloves was 5.0 ± 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.

專為孩子和父母定制的門診手術前準備網路版的運行操作（網路貼士）

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

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背景：由於費用控制的強制，目前的門診手術前準備程式無法應用于大多數孩子與父母。最近網上流行了一種教孩子和父母術前準備的好方法。在這篇文章中，我們主要講述網路版門診手術前準備的運行操作（網路小貼士）。

程式運行：一個多學科工作組認為基於網路的干預首先是由輸入，矩陣，輸出三大模組組成。接下來，輸入的各種變數的內容，矩陣的邏輯及輸出的內容是發展的。輸出產品有一個大人模組和一個小孩模組，詳見 <http://surgerywebtips.com/about.php>。小孩模組使用的準備策略是資訊提供，建模，玩耍和應對技能訓練。貼士的大人模組提供的策略是資訊提供，應對技能訓練，放鬆及分散注意力技能。著名的動畫和網頁設計公司開發出一種安全的連網產品基於上述描述。

結論：在這篇文章中我們講述了術前準備程式網路版的原理與操作步驟，父母和孩子在手術前後可多次這個程式網站。在 *Anesthesia & Analgesia* 雜誌上有後續文章對此有標準化的評估及網路版術前準備的初步效果。

（許紅嬌 譯，李士通 審校）

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 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.

EN3427：一種新型陽離子氨基苄型長效局部麻醉藥的性能

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藥物提供了相對簡單的局部麻醉，在某些情況下是合適的，甚至是有優勢的，但藥物作用時間不足將影響其臨床情況的使用。我們試圖找出新的局部麻醉劑的分子，具體論證了一種長效藥物發現計畫，在傷害感受器感覺傳入表示暫態受體電位（TRP）通道的優先激動。我們測試的假設是基於相對浸透膜局部麻醉藥分子可以持久的麻醉效果，假如神經元的訪問是由 TRP 通道的啟動。當前的工作描述了從發現，鉛分子體內研究 en3427，到建立一些齧齒類動物疼痛模型。

方法：雄性 SD 大鼠，採用急性機械手爪夾 2 模型誘發和針刺誘發疼痛的表現。對傷害性刺激的行為反應進行了評估，在基線，任何藥物干預前、後在不同的時間點，一個單一的神經周圍或皮下注射 en3427 單獨或聯合利多卡因。縮爪閾值或皮膚 trunci 反射進行量化，和前藥後的值進行方差分析，然後 Dunnett 多範圍檢驗進行統計學分析。

結果：注射利多卡因（2%）產生的爪子拯救誘發疼痛，是從基線到 1 小時的時間點差異顯著（ $P = 0.0081$ Dunnett 多重調整後），在同一模型中，產生一個持久的疼痛，疼痛閾值顯著高於基線到 18 小時時間點（Dunnett 多重調整後的 $P = 0.0002$ ）；en3427 的組合（0.2%）和利多卡因（2%）產生更持久的鎮痛，疼痛閾值顯著高於基線通過 24 小時時間點（Dunnett 多重調整 $P = 0.0073$ ）。用針刺的方法得到了相似的結果。單次皮下注射利多卡因（2%）產生了完整的感覺喪失皮膚針刺通過 0.5 小時，但靈敏度閾值是沒有什麼不同的基線的 1 小時的時間點，一個類似的 en3427 單獨注射（0.2%）產生的一種感覺喪失

失，明顯不同於基線通過的 8 小時時間點（Dunnett 多重調整後的 $P = 0.0045$ ），和利多卡因的組合（2%）加 en3427（0.2%）的出現進一步增強鎮痛持續時間，雖然這是顯著不同的從基線只能通過 10 小時時間點（Dunnett 多重調整 $P = 0.0048$ ）。鎮痛效果與劑量呈正相關；採用聯合注射的方法，我們發現，增加在 en3427 劑量與一個固定的 2%利多卡因 LED 大幅延長鎮痛和增加劑量的利多卡因聯合固定劑量的 en3427（0.2%）LED 只有小幅增加作用時間。

結論：目前的研究表明，一種新的分子實體，en3427 生有效的和持久的對齧齒類動物疼痛模型的鎮痛。與利多卡因相比，en3427 鎮痛效果明顯持久。結果相對於利多卡因 TRP 通道的啟動，該藥物可能介導和促進神經元的交流而產生隨後的誘捕持續時間延長療效相關。

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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.