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自古逢秋悲寂寥，我言秋日胜春朝。唐. 刘禹锡

摄影：汪红 MD. CASA 华人麻醉医学会

主编： 苗宁
排版： 苗宁
编辑：刘宇燕，张珊，陆晓薇，彭勇刚
校对：刘宇燕，张珊，陆晓薇

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主编之言

Multimodal Analgesia (多模式镇痛)

苗宁 MD

疼痛是组织损伤时不愉快的感觉和情绪反应，对疼痛的感知是一种主观的、有意识的体验。由于疼痛的个体化感受，没有两个人以相同的方式经历疼痛，这增加了疼痛管理的困难性和复杂性。术后患者经受的的急性疼痛更会影响患者的生活质量和术后机能康复。如何更有效、安全地控制疼痛仍是麻醉医生的巨大挑战。

众所周知，传统镇痛治疗主要以阿片类镇痛药物为主, 但其应用会导致一系列不良反应：耐受性，成瘾性，生命体征受损，甚至死亡的报道比比皆是。因此，麻醉医生们都在研究各种方法，并实践如何用药更加有效地镇痛。

现有的镇痛药物包括：阿片类镇痛药，局部麻醉药，非甾体类抗炎药物、NMDA 受体拮抗剂和 α2-肾上腺素受体激动剂等。目前常用的镇痛方法则有硬膜外镇痛，周围神经阻滞, 局部镇痛等。

多模式镇痛是通过联合应用多种不同作用机制的镇痛药物和方法, 在不同时间点和靶点通过影响伤害性信号的产生、传递及调控等过程阻断疼痛发生, 使镇痛效果更加确切并减少单种药物或单种疗法引起的不良反应, 同时可加快患者术后康复。

数月前，方壮霆教授曾生动地描述了多模式镇痛的作用：无可否认，阿片类药物仍是迄今为止最强和最有效的镇痛药物，往往一针见效但副作用也较为明显。非阿片类药物的镇痛药物则依赖于多种药物的综合效应起效。这就像一个篮球大明星面对几个无名小卒。但大明星有时有太多致命的毛病而必须下场时，在场的无名小卒们虽个人技能不高，但可依靠"人海战术"取胜。

目前看来，多模式镇痛做为治疗疼痛的手段日益增进。围术期如果能保证患者的疼痛减轻，病人满意度不减又能少用或不用阿片类药物，由此可能控制 Opioid Crisis 并增加患者围术期的安全性，何乐不为？！

本期专题

A Few Words about Dexmedetomidine

Wei Dong Gao, MD, PhD.

Department of Anesthesiology
Johns Hopkins Medical Center, Baltimore

Dexmedetomidine (DEX) is a very selective α_2-adrenergic receptor (α_2-AR) agonist. In comparison with clonidine, another selective α_2-AR agonist, DEX is about 10 times more selective towards α_2-AR, is more potent, and has shorter distribution (5 min vs. >10 min) and plasma half-life (2-2.5 hr vs. 9-12 hr) (https://en.wikipedia.org/wiki/Dexmedetomidine). DEX was approved by the FDA for sedation and analgesia for intubated patients in the ICU for <24 hours in 1999. However, it was also frequently used for premedication as an adjunct for smooth induction in general anesthesia for other procedures in the operating room. During 2008-2013, DEX was approved for (light) sedation for procedures in non-intubated patients. Since the mid-2000's, when used as an adjunct during general anesthesia, DEX has been shown to maintain hemodynamic stability, enable faster extubation, cause less neurological complications, reduce pain medicine, and facilitate quicker recovery in PACU in various surgeries in small clinical trials. Over the next 10 years, DEX continued to gain its popularity and was used in almost all types of anesthesia for procedures/surgeries from cataract with sedation to open heart surgeries with general anesthesia, in both pediatric and geriatric patients. The administration of DEX varied from intravenous to nerve blocks, from intraperitoneal to intrathecal injections, from intra-articular infiltration to intramuscular injection, and from nasal inhalation to nebulization. Through many clinical studies and trials, DEX is well accepted as a sedative and a non-opioid analgesic with sympathetic suppressing (thus maintaining hemodynamic stability via controlling blood pressure and heart rate) and respiration maintaining properties. Thus, at present, DEX has been used by anesthesiologists all over the world. As DEX's popularity grows, controversies on its clinical effects arise, especially when better-designed, well-conducted, and large scaled clinical trials are being conducted and published. The following is a brief account on these issues.

1. DEX in opioid-sparing and opioid-free anesthesia

Because of its analgesic action, DEX has been employed as an adjunctive agent to reduce opioid use during anesthesia (i.e. opioid-lowering/sparing anesthesia) and postoperative period. Clinical studies (including meta-analysis studies) have shown that intraoperative use (mostly continuous infusion) of DEX was associated with decreased intraoperative consumption of opioid in neurologic, spine, pediatric, laparoscopic, open gynecology surgeries, etc.[1-6] In addition, intraoperative use of DEX has also been shown to reduce opioid consumption in the postoperative period.[1] A recent meta-analysis of 21 randomized trials of intraoperative infusion of DEX showed decreased pain scores during the postop period (i.e. at 2-, 12-, and 24-hr postop) as compared to remifentanil infusion, with less hypotension, shivering and PONV and no differences in heart rate.[7] From these and many other clinical studies, it is clear that

intraoperative us of DEX can reduced (or avoid) opioid during the intra- and post-operative periods (i.e. DEX is effective in opioid lowering/sparing). However, whether this would translate into better outcome is not clear, especially in light of a recent review study in which about 14,000 patients received intraoperative DEX infusion during open heart surgeries.[8] Although they had a lower pain score at discharge, these patients has higher pain score and increased intubation/re-intubation risk at postop.

The role of DEX in opioid-free anesthesia is controversial. Earlier studies showed that intraoperative infusion of DEX was better than remifentanil in pain control with less hypotension, PONV and shivering,[7] but the evidence supporting this claim is moderate since there was large heterogeneity in the maintenance of anesthesia in these patients (i.e. inhalational vs. TIVA). Therefore, there is reluctance (even resistance) to accept that DEX-dependent, opioid-free anesthesia is better. Recently, a French randomized clinical trial compared DEX infusion (opioid-free anesthesia) and remifentanil infusion when anesthesia was maintained by the same regime (infusions of propofol, ketamine, and lidocaine plus inhalational agents and muscle relaxation) involving 314 patient undergoing major/intermediate risk, non-cardiac surgeries.[9] The authors concluded that DEX-dependent, opioid-free anesthesia resulted in great incidence of serious events (hypoxia and bradycardia), delayed extubation, and longer PACU stay. They did find less postop opioid consumption and nausea/vomiting in DEX group. But importantly, the study stopped prematurely due to severe bradycardia reported in several cases in the DEX group. Also, a recent trial in 152 patients for gynecological laparoscopy, DEX-dependent opioid-free anesthesia did not decrease PONV, pain, and opioid consumption.[10] These recent studies indicate that DEX-dependent opioid-free anesthesia may not be safe. In fact, the practice of "opioid-free" anesthesia is currently under scrutiny.[11] "Opioid-free" is not "complication-free" and may, in fact, be harmful. Multimodal anesthesia complicates routine practice and has not been proven to be effective to reduce opioid use and related complications in the postoperative period and beyond.[12] Still, the most effective agent for pain is an opioid in most moderate-severe pain situations.

2. DEX and postoperative delirium and cognitive disorder.

The earlier attempt to address the role of DEX in preventing postop delirium was carried out in patients undergoing for open heart surgeries, in which the sedatives were started in the OR after coming off CPB and continued in ICU for 10-13 hours.[13] This small sample trial (30 patients each in DEX, propofol, midazolam groups, respectively) showed that only 3% developed delirium in DEX group, as opposed to 50% in the other two groups. Another study showed that prophylactic DEX in the ICU decreased incidence of delirium during the first 7 days postop in patients of 65 years old after non-cardiac surgery.[14] A meta-analysis of 18 clinical trials (total 3309 patients) showed that postoperative DEX reduced incidence of delirium without impacting other outcomes (i.e. in hospital mortality, ICU and hospital length of stay, bradycardia and hypotension.[15] But these studies were heterogeneous in timing and dosing of DEX administration, assessment of delirium, patients' age, and lack of power for other outcome measures. More recent studies attempted to control these factors. One study showed that DEX (bolus 1mcg/kg followed by infusion 0.2.-0.7mcg/kg/h during the intraop) decreased delirium at 24h postop as compared to bolus only and saline groups.[16] Other study showed that intraoperative infusion of DEX (0.5 mcg/kg/h) did not reduce incidence of delirium in patients of

≥68 years during the first 5 days postop and postoperative cognitive dysfunction (POCD) at 3 and 6 months. Another more recent clinical trial (30 patients in each group) showed there were no differences in the incidences of delirium (at 48 hours postop) and ICU/hospital length of stay between DEX (bolus after chest closure and infusion in ICU up to 6 hours) and propofol (infusion at chest closure and continued in ICU up to 6 hours).[17] A recent meta-analysis of clinical trials showed that postop DEX did not reduce hospital length of stay and improve outcome after open heart surgery.[18] At present, evidence supporting DEX's role in reducing postop delirium outweighs evidence against it, but no clear conclusion about longer term POCD. Importantly, no definitive studies on its (beneficial) impact on clinical outcome/mortality, which matters the most. This is a bit surprise given that postop delirium negatively affects postop outcome.[19]

3. Perspective

DEX will still be used widely in the practice of anesthesia given its unique action of sedation, analgesia, stress-relieving, and non-respiratory suppressing. However, one should be cautioned about the controversies on its role in opioid-sparing and opioid-free anesthesia. Clearly, DEX could spare / reduce opioid use in a perioperative setting, but we must wait to see if this will translate into better clinical outcomes. More recent evidence suggests opioid-free anesthesia maybe harmful and whether DEX is likely the "culprit" is too early to tell. We will certainly remain vigilant on in-coming clinical evidence.

Overwhelming evidence supports DEX's role in reducing postop delirium in both cardiac and non-cardiac surgeries, particularly when it is administrated during the postop period. There are a few unsettled issues regarding its timing and doses, patient's condition (age, comorbidities), and importantly, its impact on clinical outcomes. Recent two clinical outcome studies in mechanically ventilated patients in ICU showed none superiority for DEX in mortality (at 90 days) and cognitive decline (6 months) as compare with other agents, [20, 21] with one even showing more bradycardia and hypotension in DEX group.[21] It must be point out, however, that these are critically ill, non-surgical patients with severe comorbidities including sepsis (who may be different from surgical patients). We expect more research on DEX's clinical effect in the future, given its action on improving body immune system, reducing inflammation, and decreasing stress.[22]

Based on the clinical evidence, we expect continued incorporation of DEX into enhanced recovery after surgery (ERAS) protocols in major cardiac and non-cardiac surgeries, in outpatient/remote surgeries/procedures, and in ICU. But the use of DEX will be under much more vigilance and scrutiny than before, especially in critically ill patients in the ICU. Moreover, we must be aware that the beneficial effects of DEX could be outweighed by harm in some patients and under certain situations.

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局麻药系统毒性与妇产科神经阻滞

李金蕾 MD, PhD
Department of Anesthesiology
Yale University
New Heaven，Connecticut，USA

椎管内麻醉，尤其是硬膜外麻醉和周围神经阻滞技术是临床麻醉工作中麻醉医生经常选择的麻醉方式之一。随着近几年超声的日渐普及，椎管内麻醉和神经阻滞实施起来也愈加简单安全，易管理，也是基层医院最常考虑的选择，安全性和可靠性也得到了提高。但常言道，麻醉无小事，局麻药的毒性问题，无论是血管毒性反应还是神经毒性反应我们都应加倍重视，提前做好预防措施，并对处理流程烂熟于心。

由于现在超声技术神经阻滞运用的发展，产科神经阻滞时局麻药的毒性还时有发生吗？2018 年一份报告收集了从 1980 至 2000 年由于局麻药中毒导致的麻醉医生被法律诉讼的 110 案例。其中 19 例脑死亡病患中有 7 例是局麻药系统中毒。2015 年一份报告总结 2010 至 2014 年局麻药中毒有 50 几例； 2014-2016 年也有 56 例文献中发表的局麻药系统中毒。中枢神经的毒性占据 12%。FDA 总结了 2012-2016 年间局麻药用后的不良反应。其中 Lidocaine 中毒有 1050 例，Bupivacaine 346 例，Ropivacine 131 例， Exparel 130 例， cocaine 129 例。至 2012 年以来，Exparel 导致了 11 例病患死亡。所以说局麻药，包括使用 Exparel 并非我们想象的那么安全。

产科麻醉时局麻药的中毒率？由于技术的发展，局麻药中毒和死亡率逐年减少，现在大约在 0.013%左右；中枢神经阻滞导致的中毒和死亡率约 0.03%。虽然比例不大，但因涉及母婴两者的安全性而后果严重。除此之外，周围神经阻滞如 TAP 和腰方肌阻滞在产科麻醉中也时有运用。但周围神经阻滞后血药浓度的升高不容忽视。有研究发现 TAP 阻滞后从 40 分钟至 90 小时血药浓度持续升高。如果术前病患使用了中枢神经阻滞，手术完毕前手术医生使用局部浸润麻醉，术后又用了区域外周神经阻滞镇痛，总量局麻药的剂量就应严格计算以防心血管和中枢神经中毒，与手术医生的沟通也十分重要。

局麻药系统中毒性不是老生常谈！超声技术的运用可降低局麻药 80%的中毒率，但是使用超声并且注射器回抽无血并非 100%保证无局麻药中毒危险，有报道称从 2010-2014 年有 67 例病患在超声阻滞下发生局麻药中毒。主要原因是周围神经附近小的静脉，尤其是在超声探头的压力下回抽无血后注射的局麻药可能经由静脉进入血液循环，有时可能针头介于血管内外，局麻药注射后虽可见局部组织的"正常"变化但也有部分局麻药注射进入血管导致中毒。从 1884 年眼科使用 Cocaine 发生局麻药中毒开始，近代使用较新的 Bupivacaine 和 Ropivacaine 仍有中毒案例。迄今为止，尚无一种局麻药无毒性反应。

局麻药中毒性的好发人群？7.5%局麻药中毒发生在"健康年轻孕期"妇女，而大部分发生在高危人群：63%好发于女性病人，45%发生于极端年龄段（<16 岁或>60 岁），尤其是新生儿；37%发生在有合并症的病患：如合并心、肺、肝、肾、神经系统、内分泌或代谢系统病变的病患。这些具有合并症的病患使用局麻药时要注意这些器官的代谢、排泄和潴留作用以及药量对这些器官的影响。

特殊人群对局麻药的敏感性？小于四个月的婴儿其血浓度A-1 酸性糖蛋白（AAG-结合局麻药的急性期蛋白）含量低，计算局麻药剂量时（剂量/kg），相比其他年龄段幼儿至少应少 15%。孕期妇女黄体酮增加神经轴突对局麻药的敏感性而致局麻药的危险性增大。黄体酮增加 Bupivacaine 和 Ropivacaine 对心脏的毒性；动物实验发现雌激素增加心脏毒性；孕妇血液中与 Bupivacaine 结合蛋白明显减少；孕后期心输出量（CO）增加时可进一步增加局麻药的吸收；子宫增大压迫脊髓和硬膜外使之容积变小等。鉴于以上情况，对孕期妇女要相应减少局麻药的用量，既有相同的麻醉效果又可防止局麻药过量。

局麻药的作用与中毒机理：较低浓度的局部麻醉药与电压依赖性 Na+通道结合(Na+通道有许多亚型)，减少 Na+离子通道对动作电位在轴突中的起动作用，使神经传导受阻，产生局麻作用。局麻药浓度增高时，其对离子通道的选择性降低，既抑制 Na^+，也抑制 K^+、Ca^{++}通道以及影响 ATP 的形成等。由此可见，局麻药的中毒反应机制十分复杂。

中枢神经系统（CNS）毒性反应早期以兴奋为主：典型症状如病人口周麻木，耳鸣，烦躁不安，晚期意识丧失或癫痫。近年来的报道发现，早期中枢神经毒性症状减少或未发生，而意识丧失或癫痫发生率增多。

局麻药的心脏毒性：主要为高浓度局麻药对心脏多离子通道和心脏收缩力的抑制所致。从 2015 到 2018 年，心脏骤停的发生率从 7%上升至 22%左右。其严重后果大家不言而喻。

CNS 和心血管系统局麻药中毒的不同之处：1. CNS 中毒的症状和体征较典型，可预测，与局麻药的剂量和血药浓度相关，治疗较容易，预后一般良好，而心血管毒性较难控制和预测，预后较差；2. 心血管/CNS 毒性所需局麻药剂量比例：比例越高局麻药安全性越高；比例越低，心脏毒性越大。Bupivacaine 的比例为 1.6，Lidocaine 为 3.6，说明 Bupivacaine 对心脏的毒性>Lidocaine. 3. CNS 毒性发生时间多半在 10 分钟之内， 但 12 小时后也有发生局麻药中毒的病例，多为局麻药的缓慢吸收所致。

严重 CNS 局麻药中毒的处理：在紧急情况下，为了减少计算时间或计算错误以及尽早静脉推注 20%脂肪乳剂， 如病患体重>70kg, 100ml 脂肪乳剂 2-3 分钟静脉推注 （大量的静脉推注可使脂肪乳剂大量快速结合局麻药），然后持续静脉滴注以持续结合剩余的局麻药量。如是较轻的局麻药毒性反应，如口周麻木或耳鸣，病患需持续观察 2-4 小时可酌情考虑病患出院。

心血管局麻药毒性反应的处理：病患心率增快，血压增高等应观察 4-6 小时才考虑让病患出院。如出现心律失常，心率缓慢和血压降低等，病患应收住院过夜观察。心脏骤停时除了尽早使用 20%脂肪乳剂外，应立即施行心脏复苏术，心脏起搏，体外膜氧合/体外循环，Amiodarone 治疗室性心律失常， Sodium Bicarbonate 使 pH 值>7.25 以上。避免使用其他的局麻药，β受体或钙通道阻滞剂。气道管理预防低氧血症和酸中毒，促进尽快复苏也十分重要。

癫痫的治疗：Benzodiazepine 因其对心脏的抑制最小而为首选，也可使用 Propofol 或 Thiopental 静脉滴注；如癫痫持续，小剂量的 Succinylcholine 可迅速阻止强直性、痉挛性肌肉收缩。

脂肪乳剂是否临床必要？自从 2006 年第一次用脂肪乳剂成功治疗了一位对其他药物无效的年轻局麻药中毒患者以来，脂肪乳剂的运用日益广泛。众所周知，脂肪乳剂非局麻药的特异解毒药，而是非特异性的治疗药。目前认为脂肪乳剂治疗局麻药中毒的作用有两点： 1. 对心脏的作用：脂肪乳剂增加心肌收缩力和外周血管阻力，静脉推注和滴注也增加血管内容量而增加心输出量；2. 脂肪乳剂大量结合血液内的局麻药，血液循环时可大量析出心脏，大脑内的局麻药运送至肾，脂肪和血液已降低重要器官内的局麻药量。2015 年的报道称至少 23%的局麻药中毒患者使用了脂肪乳剂。如果当时未用脂肪乳剂是否会导致更多的局麻药中毒患者失救？我认为产科麻醉中枢神经阻滞时应必备脂肪乳剂以防不时之需。在美国 88%产科麻醉手术室必备脂肪乳剂，95%的产科麻醉 30 分钟内可获得脂肪乳剂。

脂肪乳剂的保质期为 24 个月。常温下保存。使用后两天可测定淀粉酶和脂肪酶以排除胰腺炎的可能性。脂肪乳剂里的脂肪酸可干扰分光广度法测定而可使总血红蛋白和高铁血红蛋白的假性增高。使用时应注意微生物污染，感染风险，炎症反应，肝脾肿大，血栓性静脉炎或脂肪栓塞等，但这些在局麻药严重中毒的救治中退居"二线"考虑。目前人体使用脂肪乳剂的剂量比动物实验中的 D50 致死剂量药少于一个数量级。

脂肪乳剂的使用不仅限于麻醉科，凡是使用局麻药的科室，如门诊手术室，美容科，牙科等局麻药中毒均有所见，脂肪乳剂的必备也十分必要。

局麻药的预防措施：1. 注意高发人群：如产科孕妇等，2. 尽量用最小的局麻药剂量（目前尚无明确的最小安全剂量），3. 超声检测下注射器注射时应多次回抽，3.减少超声探头压力。4. 熟悉局部神经解剖结构和与附近血管的关系。

影响局麻药毒性的因素: 1. 局麻药的剂量大小与其药物本身的作用，毒性以及注射的部位有关。对高危病人一般多选 Ropivacaine，而非 Bupivacaine，就在于后者对心脏的危险性>前者；一旦发生局麻药中毒，Ropivacaine 对脂肪乳剂治疗的有效性也>前者。不同部位注射局麻药其吸收量由高到低依次为：气管插管>肋间神经>骶管>硬膜外神经丛>坐骨/股骨神经>皮下浸润；2. 局麻药（除 Cocaine 外）对血管平滑肌具有双向作用。低浓度下可收缩血管，而较高浓度时可舒张

血管；3. 局麻药可影响线粒体氧化磷酸化的各个环节。所以，对无氧代谢最不耐受的器官，如大脑和心脏所受的不良反应出现最早。

监测和早期诊断：局麻药注射时应注意观察患者的反应：是否有异感、兴奋、嗜睡或神智模糊？注射后应监测病患的心率、血压、心电图至少 30 分至 1 小时，因大多数局麻药中毒在 1 小时内发生，越早诊断并使用脂肪乳剂，病患的成功救治率也越大。神经阻滞时尽量使用小剂量镇静剂以避免掩盖患者的 CNS 或心血管不良反应。局麻药注射前就应算好病患的最大剂量，如果注射常用剂量局麻药无效，首先应排除注射部位错误。

急救措施：我认为一个好的麻醉医生并非是手最巧但一定是对危机准备最完善的那一个！我科常规阻滞设备车内备有：1.常规的气道管理设备；2. 监测仪包括血压，心率，心电图，脉搏氧饱和度，呼气末 CO2，鼻导管常规给氧，3. 监护患者的整个阻滞过程并持续观察 30-60 分钟；4. 应急药物：20%脂肪乳剂（至少 250ml），Atropine，ephedrine，epinephrine（应小剂量使用。主要用于心血管中毒反应如心率减慢，血压降低，外周血管阻力和 CO 减少，心收缩力下降时），norepinephrine，succinylcholine, propofol 和 midazolam 等。5. 建立静脉通路；6. 常规阻滞设备，阻滞针，超声仪，超声凝胶等等。我们现在均已被预先警告局麻药的可能中毒危险，所以必须准备所有设备以备不时之需。

由于局麻药中毒发生率较低，可能由于麻醉医生的小心阻滞预防了局麻药中毒，又或者全麻下用局麻药做区域阻滞，即使出现 CNS 体征，心率快或慢，血压高或低等都会解读为全麻的病人生命体征的反应。但根据文献和 FDA 的报道，目前为止，局麻药的不良反应或中毒反应虽然减少但远远未降至为零。我们的工作仍然是必备抢救物品，计算局麻药剂量，小心监测病人，早期诊断，快速救治。

A Single Syringe Multimodal Non-Opioid 6-2-2 Sedation Method

Zhuang T. Fang, MD, MSPH, FASA, Clinical Professor
David Geffen School of Medicine at UCLA, Department of Anesthesiology and Perioperative Medicine

Monitored anesthesia care (MAC) is broadly used in patients who undergo surgical and diagnostic procedures [1]. However, there is no standardized method of MAC. The ASA closed claims study in 2006 showed, when MAC associated complications occurred, the percentage of permanent brain injury and death was the same as that for general anesthesia, which is about 40% [2]. Over sedation has been identified as a major cause of perioperative patient morbidity and mortality with MAC.

With their powerful analgesic effects, opioids have been used as an important part of the balanced anesthesia technique in treating perioperative pain during GA and MAC for many decades. However, the ongoing opioid crisis in the United States has been worsened by the concurrent Covid-19 pandemic leading to a steady increase in drug overdoses and more than 100,000 deaths in 2021[3]. The economic consequences are enormous with an estimated $80 billion spent yearly in healthcare and treatment, lost productivity, and legal judicial costs 4 anesthesia providers have been under tremendous pressure to reduce perioperative opioid use, as research shows 6% of patients will become chronic opioid users after minor or major surgical procedures.

In the past decade, opioid-sparing and opioid-free anesthesia techniques have been the main strategy and research focus for anesthesia providers battling the opioid epidemic; however, most of the studies focused on general anesthetics (GA) and not on MAC. Unlike GA, in which inhalational agents are an option to provide unconsciousness, immobility, and amnesia, MAC for surgical procedures relies on intravenous agents to provide analgesia, anxiolysis, and desired surgical conditions.

Propofol is the most common anesthetics for MAC in diagnostic procedures, but it is inadequate for surgical procedures because of its lack of analgesia. Dexmedetomidine has been studied extensively in the last two decades, however, its single use in surgical sedation has been limited due to its weak analgesic effect, inadequate sedation, and high incidence of bradycardia and hypotension [4]. Multimodal, or balanced anesthesia, with a combination of propofol, ketamine, dexmedetomidine, or benzodiazepines is a scientifically logical approach for MAC with superior analgesic and sedative effects compared to the use of single agents [5, 6]. Induction is the most challenging phase of MAC, especially in procedures requiring blocks performed before skin preparation and sterilization. However, during induction, it is cumbersome to administer each drug separately, difficult to determine the dose and time interval of administration, and arduous to measure the efficacy and quality of sedation.

In the last 19 years, the single syringe multimodal opioid-based A6-2-2 (alfentanil) and other mixtures (fentanyl, combined alfentanil and fentanyl, etc.) have been routinely used in our institute to provide quality MAC for patients undergoing ophthalmic surgery, comfortably and safely [7, 8]. In the last several years, we also developed a non-opioid KE6-2-2 mixture [9], which contains 6 portions of 10 mg/ml propofol, 2 portions of 10 mg/ml ketamine, and 2 portions of 2

mg/ml etomidate. I am reporting the efficacy of analgesia and sedation, and safety profile with this single syringe multimodal non-opioid KE6-2-2 mixture, focusing on the induction of MAC for ocular blocks.

Preparation of the KE6-2-2 Mixture (Table 1)

The anesthetic KE6-2-2 mixture contained 6 ml of 10 mg/ml propofol, 2 ml of 10 mg/ml ketamine, and 2 ml of 2 mg/ml etomidate, in a volume of 10 ml with a ratio of 6-2-2. The volume was increased to 20 ml or 40 ml depending on surgery length and the patient's need for sedation. The total dose of ketamine was limited to 100 mg and etomidate was limited to 20 mg.

For comparison, I also include the combination of the A6-2-2 mixture which contains 6 ml of 10 mg/ml propofol, 2 ml of 0.5 mg/ml alfentanil, and 2 ml of 10 mg/ml lidocaine. The total dose of alfentanil was limited to 2 mg.

Table 1. Mixture compositions, bolus dose calculation, and administration

6-2-2 mixtures	Component original concentration	Amount of component in mixture	Concentration in 10 mL mixture
KE6-2-2 mixture			
Propofol	10 mg/mL	6 mL	6 mg/mL
Ketamine	10 mg/mL	2 mL	2 mg/mL
Etomidate	2 mg/mL	2 mL	0.4 mg/mL
A6-2-2 mixture			
Propofol	10 mg/mL	6 mL	6 mg/mL
Alfentanil	0.5 mg/mL	2 mL	0.1 mg/mL
Lidocaine, 1%	10 mg/mL	2 mL	2 mg/mL
Standardized bolus dose calculation (for both KE6-2-2 and A6-2-2 mixtures)	**Age <40 years: 1.2 mL/10 kg x ABW or AWFD** **Age 41-60 years: 1.0 mL/10 kg x ABW or AWFD** **Age 61-70 years: 0.8 mL/10 kg x ABW or AWFD** **Age 71-84 years: 0.6 mL/10 kg x ABW or AWFD** **Age >85 years: 0.5 mL/10 kg x ABW or AWFD**		
Dosing weight determination (for bolus dose calculation)	If a patient's BMI <25.0 kg/m^2, the bolus dose of the mixture(s) is calculated based age and Actual Body Weight (**ABW**). If a patient's BMI exceed 25.0 kg/m^2, the bolus dose is calculated based age and Adjusted Weight for Dosing (**AWFD**), using the following calculation with Ideal Body Weight (IBW): **AWFD = IBW + 0.3 (ABW – IBW)**		
Method of bolus dose administration	1.The bolus dose of both mixtures can be administered intravenously by hand push or infusion pump over several seconds. 2. For KE6-2-2 mixture, an additional 10 mg of ketamine (1 ml) is given immediately after the bolus dose (for blocks). 3. When patients reach OAA/S Scale score 3 (responds only after name is called loudly, slurring in speech, marked facial relaxation, and eye glazed and marked ptosis), they are ready for the ocular blocks. 4. After completion of the ocular blocks, verbally stimulate patients to breathe and prevent oxygen desaturation.		

Abbreviations: BMI, body mass index; AWFD, adjusted weight for dosing; OAA/S, Observer's Assessment of Alertness/Sedation Scale

Calculation and Administration of the 6-2-2 Mixture Bolus Dose (Table 1)

The bolus dose for either KE6-2-2 or A6-2-2 mixtures was calculated based on the patient's age and actual body weight (ABW) if BMI <25 kg/m2 or Adjusted Weight for Dosing (AWFD) for BMI > 25 kg/m2. Age criteria was as follows: for patients < 40 yrs., 1.2 ml/10 kg; 41-60 yrs., 1 mL/10 kg; 61-70 yrs., 0.8 mL/10 kg; 71 -84 yrs. 0.6 mL/10 kg; >85 yrs. 0.5 mL/10 kg. The AWFD was calculated using the formula: AWFD = IBW + 30% (Actual weight - IBW) [7], where IBW was ideal body weight. Calculation of the bolus dose was applied to both non-opioid KE6-2-2 or opioid-based A6-2-2 mixtures. The bolus dose was administered by hand push or infusion pump over several seconds.

Patients in group 1 received a single bolus dose without additional supplementation, and patients in group 2 received a bolus dose, immediately followed by an additional 10 mg of ketamine. Patients in group 3 received a bolus dose of A6-2-2 mixture. All patients received supplemental O2 via nasal cannula.

Maintenance of Intraoperative Sedation

Following the initial bolus dose, patients were monitored closely for ventilation, oxygenation, blood pressure and heart rate. When patients regained consciousness, continuous sedation was given by intravenous infusion of the KE6-2-2 mixture at a rate of 12 ml/hr (1 ml/5 min) to 24 ml/hr (2 ml/5 min) to achieve a moderate level (OAA/S= 3) of sedation and ensure patient comfort, while maintaining the ability to follow commands and remain motionless. Alternatively, sedation was maintained with a propofol infusion targeting a moderate level of sedation.

After surgery, all patients entered phase II recovery and were prepared for discharge in the PACU.

Patient Readiness for Ocular Blocks and Quality Sedation Measurement (Table 2)

Table 2. Patient sedation outcomes

Induction outcomes	Group 1 KE6-2-2 wo K10 *n* = 101	Group 2 KE6-2-2 w K10 *n* = 107	Group 3 A6-2-2 w *n* = 104	P-values Group 1 vs 2	P-values Group 2 vs 3
Time to readiness for blocks,[1] seconds	42.8 (12.8)	36.4 (14.8)	51.0 (19.6)	<0.001	<0.001
Starting MAP, mmHg	96.6 (12.5)	95.0 (11.3)	95.9 (12.7)	0.647	0.979
After Bolus MAP, mmHg	96.1 (13.0)	95.6 (10.3)	89.6 (11.7)	0.599	<0.001
Change in MAP	-0.4 (9.4)	0.6 (9.5)	-6.6 (9.6)	0.929	<0.001
Starting HR, BPM	68.7 (9.2)	72.3 (11.1)	68.6 (10.8)	0.036	0.031
After Bolus HR, BPM	69.3 (10.3)	74.0 (12.0)	65.4 (10.6)	0.013	<0.001
Change in HR	0.5 (6.7)	1.7 (7.8)	-3.2 (6.7)	0.411	<0.001
Starting oxygen saturation, %	96.7 (1.6)	96.8 (1.8)	97.0 (1.6)	0.378	0.032
After Bolus Lowest oxygen saturation, %	95.5 (3.1)	95.6 (3.0)	94.5 (4.7)	0.617	0.060
Supplemental O_2 given with induction[2]	101 (100%)	107 (100%)	104 (100%)	<0.001	<0.001
No pain during ocular blocks	87 (87.0%)	105 (98.1%)	102 (98.1%)	<0.001	1.000
No head movement during blocks	91 (90.1%)	107 (100%)	104 (100%)	<0.001	--
No apnea during blocks	99 (98.0%)	106 (99.1%)	103 (99.0%)	0.592	1.000
No oxygen desaturation during blocks	98 (97.0%)	104 (97.2%)	91 (87.5%)	0.763	0.048
No nausea/vomiting during blocks	101 (100%)	107 (100%)	104 (100%)	--	--
No loss of consciousness during blocks	35 (34.7%)	12 (11.2%)	99 (95.2%)	<0.001	<0.001
No chin lift needed for obstruction	99 (98.0%)	105 (98.1%)	102 (98.1%)	1.000	1.000
No mask ventilation	101 (100%)	107 (100%)	104 (100%)	--	--
No intubation	101 (100%)	107 (100%)	104 (100%)	--	--
No recall/awareness of blocks	99 (98.0%)	106 (99.1%)	97 (94.2%)	0.229	0.004
Supplemental O_2 given during surgery,[2]	101 (100%)	107 (100%)	104 (100%)	<0.001	<0.001
No PACU anti-emetic medications needed	98 (98.0%)	98 (91.6%)	101 (97.1%)	0.069	0.203
No PACU analgesic medications needed	84 (83.2%)	87 (81.3%)	95 (91.3%)	0.872	0.085

[1] Patient readiness for blocks determined by the patient reaching a score of 3 on the Observer's Assessment of Alertness/Sedation Scale (OAA/S).

[2] In all groups, supplemental oxygen was automatically given.

Abbreviations: MAP: Mean Arterial Pressure, **mmHg:** Millimeters of mercury, **HR:** Heart Rate, **BPM:** beats per minute, **O_2:** Oxygen, **PACU:** Post-anesthesia Care Unit.

OAA/S score 3 (response only after name is called loudly and/or repeatedly, slurring or prominent slowing in speech, marked facial relaxation with eye glazed and marked ptosis) was the targeted level of moderate sedation and considered as block readiness. In 312 cases, the time

to reach an OAA/S score of 3 was 43 seconds in group 1, 36 seconds in groups 2, versus 51 seconds in group 3 ($p<0.001$). The analgesia efficacy for needle blocks was 87% for group 1 (without 10 mg additional ketamine after bolus), and 98% for group 2 (with 10 mg additional ketamine after bolus), which is similar to group 3, the A6-2-2 group. In group 1, 90% had no head movement during the ocular block, whereas 100% of group 2 and 3 had no head movement. 88% patients in group 3 has no oxygen desaturation during blocks compared to 94 to 97% in all the KE6-2-2 groups. Less than 2% of patients had apnea that required airway intervention in all three groups. Approximately 11% of patients in KE6-2-2 groups 2 had no LOC but 100% had no recall of the block, compared to 95% of patients with no LOC in the A6-2-2 group, with 96% having no recall of the block ($p< 0.001$). In KE6-2-2 group 1, 36% of patients had no LOC with 99% having no recall of the block ($p <0.001$). Figure 2 summarizes the perioperative sedation outcomes.

Discussion:

Analgesia is the most important element of MAC to prevent pain and head movement during ocular blocks (which increases the risk of eye injury [10, 11]), yet MAC without opioids can be challenging. A logical approach for opioid-sparing anesthesia is multimodal and utilizes the additive and synergistic effects from drugs activating different receptors and parts of the central nervous system [12, 13, 14]. This maximizes analgesia from the non-opioid drugs while minimizing adverse effects, leading to decreased need for supplemental opioids.

Our non-opioid KE6-2-2 sedation method has several features: 1) the standardized bolus dose is calculated based on the patient's age and weight (Table 3); 2) the bolus dose can be safety administered all at once by hand or infusion pump; 3) an additional ketamine 10 mg after the bolus increases analgesic efficacy from 87% to 98% for ocular blocks; 4) patient readiness for ocular block was 43 seconds without and 36 seconds with the additional 10 mg of ketamine; 5) 98-99% of patients had no apnea and 3-6% had transient oxygen desaturation <90% due to hypoventilation, with 2% of patients requiring brief chin lift but no mask ventilation or intubation; 6) there was no significant change in MAP or HR after bolus; 7) over 80% of patients did not receive opioids for pain postoperatively; and 8) 98-100% of patients had no recall of block even without pre-treatment benzodiazepines. In comparison, patient readiness for ocular blocks with the opioid A6-2-2 mixture was 51 seconds, and analgesic efficacy was 98%. 2% of patients had apnea requiring chin lift and 12% of patients had transient oxygen desaturation due to hypoventilation but recovered quickly. With the exception of KE6-2-2 group 1, all other groups had no head movement during the block. No patient required supplemental sedation during the ocular block. While the non-opioid KE6-2-2 mixture provided comparable analgesia to the opioid-based A6-2-2 mixture, it had faster onset, lower incidence of apnea and hypoxia, and more stable hemodynamics.

Inclusion of etomidate in the KE6-2-2 mixture did not decrease the MAP after the bolus dose (Table 2), suggesting that adrenal suppression is unlikely. PONV incidence was less than 15% even without prophylaxis. Since ketamine could potentially increase HR and BP, it is reasonable to avoid in patients with severe preoperative hypertension (BP 180/90) or tachycardia (HR >100/min) (the opioid-based 6-2-2 mixtures are reasonable alternatives) as well as patients with severe psychiatric disease, especially in those taking multiple medications until future studies prove its safety. Additionally, in this report, no patient received midazolam as pre-

medication and we did not collect data on their psychiatric reaction to the KE6-2-2 mixture. However, from observation, most of the elderly patients' experience was positive (feelings of peace, healing, spirituality, joyful) or neutral (adventures, "psychedelic"). A small group of young patients' experience was negative ("bad dreams") which was improved with midazolam administration intraoperatively. Midazolam pre-treatment seems helpful in preventing such effects.

In conclusion, our single syringe multimodal KE6-2-2 mixture provides quality opioid-free sedation in patients undergoing ophthalmic surgery, which is applicable to other diagnostic and surgical procedures. Its analgesic effect was similar to that of the opioid-based A6-2-2 mixture, but its onset was much quicker, with superior airway and hemodynamic safety profiles.

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Systemic Lidocaine Infusion as Intraoperative Opioid Sparing Technique: Do We Have Evidence?

Evan Huang [1], Andrewston Ting, DO [2]*

1. Carrollwood Day School, Tampa, FL
2. Anesthesiology, HCA Healthcare/USF Morsani College of Medicine GME/Oak Hill Hospital

*Corresponding Author

The opioid crisis has been steadily rising in the past 10 years. Approximately 650,000 opioid prescriptions are dispensed in the United States daily even though opioid use is the leading cause of unintentional death in the United States [1]. Opioid-related deaths have more than quadrupled from 1999 to 2017 and increased by 285% between the time periods of 2002 to 2004, and 2011 to 2014 [2]. Many studies demonstrated that the perioperative period is an important time frame for patients to develop an opioid use disorder (OUD) [3, 4, 5].

OUD development is more likely for patients with a variety of nonmodifiable, psychiatric, psychosocial, and personal history risk factors to develop OUD [6]. It is important that anesthesia providers should consider OUD issues when generating postsurgical pain management plans. Opioids can often target acute postsurgical pain effectively; however, despite their prevalent use, opioids have not been shown to be effective for chronic postsurgical pain.

Enhanced Recovery after Surgery (ERAS) has been widely implemented. Multimodal pain management is the key component of ERAS. Multimodal, opioid sparing analgesia is not a new concept. It has been well known to our perioperative providers for more than 20 years. With the increasing implementation of ERAS and opioid epidemic, opioid sparing analgesia has been more widely adopted perioperatively [7].

It has been reported that perioperative systemic lidocaine infusion has beneficial effects on the bowel function recovery, pain control, narcotic sparing and reduced hospital stay after abdominal surgeries [8, 9, 10]. Therefore, systemic lidocaine infusion has been adapted as a part of ERAS perioperative protocol. However, evidence of systemic lidocaine infusion remained uncertain.

A systematic and meta-analysis study [11] which included 68 trials (4525 randomized participants) to examine effects of systemic lidocaine infusion on postoperative pain control, narcotic consumptions, bowel function recovery, and length of hospital stay.

They examined the effect of IV lidocaine on postoperative pain scores shows a reduction of pain score at 1 to 4 hours (SMD -0.50, 95% confidence interval (CI) -0.72 to -0.28) and 24 hours (SMD -0.14, 95% confidence interval (CI) -0.25 to -0.04), however the effect size lacks clinical relevance. Additionally, at late time points of 48 hours, the effect size is clinically non-relevant (SMD −0.11, 95% CI −0.25 to 0.04). An SMD of 0.11 fewer in pain score corresponds to 0.42 cm to 0.08 cm reduction on the VAS 0 to 10 cm scale. Essentially, the effect of pain reduction is more pronounced in the early time points compared to later time points.

Another category of effect examined by the Cochrane meta-analysis study [11] was the effect on bowel function such as time to first defecation/bowel movement and time to first flatus, as well as postoperative nausea and vomiting at different time points. The study demonstrates a reduced

time to first bowel movements (hrs) (MD -7.92, 95% CI -12.71 to -3.13) and time to first flatus (MD -4.09, 95% CI -6.30 to -1.87). There was no significant effect for lidocaine to shorten the time to first bowel sounds.

The meta-analysis did not find a statistically significant difference between lidocaine infusion and length of hospital stay [11].

Postoperative nausea was found to be reduced in the lidocaine group (RR 0.78, 95% CI 0.67 to 0.91), however, IV lidocaine did not have a meaningful effect over postoperative vomiting (RR 0.83, 95% CI 0.63 to 1.08).

Lastly, the meta-analysis examined intraoperative, postoperative, and overall opioid consumption and found clinically significant reduction in opioid consumption perioperatively. Intraoperative opioid consumption (MEQ, mg) was found to be less in the lidocaine group compared to control (MD -2.14, 95% CI -3.87 to -0.40). Postoperative opioid consumption, PACU (MEQ, mg) was found to be less in the lidocaine group as well compared to control (MD -3.10, 95% CI -3.87 to -2.32), and the overall postoperative opioid consumption (MEQ, mg) was reduced as well (MD -4.52, 95% CI -6.25 to -2.79) [11].

Although aggregate 95% CI showed beneficial effect, the 95% PI crossed the line of identity and demonstrated both beneficial as well as clinical non-relevance for intraoperative opioid consumption and postoperative opioid consumption groups. However, the only definitive benefit was observed in the postoperative opioid consumption, PACU group with a 95% PI below 0, which means there is predicted reduction of postoperative opioid consumption in the PACU with IV lidocaine use [11].

In conclusion, despite reports of IV lidocaine's beneficial effects in the perioperative period and its adoption into ERAS protocols, the heterogeneity of the studies in the aggregate data cast a shadow of uncertainty over the true effect of IV lidocaine. We are uncertain whether IV lidocaine benefits postoperative pain scores, improves gastrointestinal function, reduces postoperative nausea and vomiting, or reduces intraoperative and overall opioid consumption. Thus, more studies are needed before we can make a definitive recommendation.

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The Role of Dexmedetomidine on Immunoregulation in Perioperative Pain Management

Isabelle Yang MD, Jingping Wang MD, Ph.D.

Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School.

Introduction

With growing concerns related to the opioid crisis, multimodal analgesia has been employed increasingly in clinical settings over the last two decades.[1, 2] Multimodal analgesia is a strategy to use multiple drugs that act by different mechanisms along multiple sites of the nociceptive pathway.[3, 4] Effective perioperative analgesia can be achieved via opioid-sparing or even opioid-free analgesia, though it may not always clinically necessary or appropriate.[5, 6]

Common perioperative analgesic agents include opioids as well as non-opioid systemic analgesics such as dexmedetomidine, ketamine, acetaminophen, non-steroidal anti-inflammatory drugs, gabapentinoids, regional anesthesia, and local anesthetics administered intravenously or by infiltration.

Among the potential perioperative analgesics, dexmedetomidine (DEX) has emerged as a common alternative or adjunct to opioids. One unique advantage of DEX over opioids is its beneficial effects on the immune system. Whereas the studied effects of opioids, primarily morphine, have been shown to exhibit predominantly immunosuppressive effects, DEX has been shown to have reduced immunosuppressive effects and even beneficial immunomodulatory effects in pre-clinical studies.[7] These observations raised the possibility that DEX is a superior alternative to opioids in cases where intact immune response to surgical and other stressors is beneficial such as cancer and sepsis.[8]

Several pre-clinical studies have been performed on the effects of DEX on innate immune function. DEX exerts effects on the immune system via several pathways, including directly via alpha-2 adrenergic receptors which are found on many immune cells, indirectly through its sympatholytic effects on the central and peripheral nervous system and the associated changes with increased catecholamines, and indirectly through other cell signaling mechanisms.[8] In general, DEX is thought to preserve innate immunity through preserved natural killer cell function, neutrophil function (chemotaxis, phagocytosis, and production of superoxide radicals), and intact macrophage activation and function but decreased secretion of inflammatory cytokines.[9] However, more research is needed to test these observations in clinical studies.

Immune markers

A meta-analysis conducted by Wang et al in 2019 reviewed sixty-seven studies (including fifty-nine randomized controlled trials (RCTs) and eight cohort studies) with 4842 patients assessed, of which 2454 patients were in DEX groups and 2388 patients were in control (without DEX) groups. Cardiac, abdominal, thoracic, spine, orthopedic, genitourinary, and other cancer surgeries comparing DEX to placebo, propofol, morphine, hydromorphone, fentanyl, and

midazolam were included.[10] It demonstrated that perioperative DEX was associated with decreased release of epinephrine, norepinephrine, cortisol, and glucose; decreased concentrations of IL-6, TNF-a, CRP, and increased concentration of IL-10.[10] Recently published RCTs further supported the notion that DEX has a predominantly anti-inflammatory effect.[11,12] One RCT among patients undergoing posterior lumbar interbody fusion compared the post-operative effects of fentanyl versus fentanyl and DEX on T cell function. It found higher levels of T helper 1 (Th1) cells, which suggested intact cell-mediated immunity, and higher levels of regulatory T (Treg) cells which are known to secrete anti-inflammatory cytokines.[11] Another study comparing intraoperative and postoperative DEX versus placebo on natural killer cell function among uterine cancer patients found increased IFN-γ in the DEX group.[12] These results were surprising as DEX was previously associated with decreased IFN-γ, and authors postulate these unexpected findings may be due to the tumor environment created by invasive cervical carcinoma. Another study among healthy patients undergoing laparoscopic cholecystectomy found a dose-dependent inverse relationship between DEX and CRP, suggesting that its anti-inflammatory effect may be titratable.[13]

Immune Cells

Wang et al. meta-analysis demonstrated that DEX was associated with higher NK cell expression or count.[10] Another RCT study among patients with lung cancer comparing flurbiprofen versus flurbiprofen and DEX found similar results with higher NK cell count in the flurbiprofen and DEX group.[14] Among patients with uterine cancer, no significant difference in NK cell activity was detected.[12] In terms of monocyte function, an RCT study among patients in ASA category 1 or 2 undergoing multilevel spinal fusion found decreased levels of secreted cytokines associated with inflammation and increased levels of secreted cytokines associated with intact immune function in the DEX group, but less is known about DEX's effects on monocyte phagocytosis and antigen presentation.[15] In Wang et al. meta-analysis and other RCTs among patients in ASA category 1 or 2, patients with oral cancer, and patients with colon cancer, use of perioperative DEX was also associated with increased Th1:Th2 ratio and increased CD4+:CD8+ ratio, consistent with intact host ability to launch cell-mediated immune defenses.[10,11,14,16,17] In Lee et al. study among healthy patients undergoing laparoscopic cholecystectomy, investigators found that higher doses of intraoperative DEX were associated with higher IFN-γ/IL-4 ratio (surrogate for Th1:Th2 ratio), and higher IL-17/IL-10 ratio (surrogate for Th17:Treg ratio, which can be interpreted as a marker of immune balance similar to Th1:Th2), suggesting that the immunomodulatory effects may be titratable.[13] DEX may have beneficial immunomodulatory role in offsetting the effect of surgical trauma, which has been associated with a decrease the Th1:Th2 ratio, and that undesired immunomodulatory effects of DEX may be able to be titrated in a dose-dependent manner.[18,19] However, the mechanism behind alpha-2 agonists' effects on immunomodulation of the Th1:Th2 ratio and the Th17:Treg ratio is still unclear.

Wang et al. meta-analysis found that DEX was associated with increased expression of B cells.[10] However, a more recent study found no difference in B lymphocyte count in the DEX group vs control, suggesting that while cellular adaptive immunity is more preserved, there is a smaller or no observed difference in humoral immunity.[16] Further investigation is needed to understand the effect of DEX on adaptive humoral immunity.

Patient Outcomes

Isolating the immunomodulatory effects of DEX on post-operative patient outcomes, rather than attributing the outcomes observed to DEX's other effects such as sympatholysis, analgesia, or anxiolysis remains a challenge in existing studies. In cardiac surgeries, while intraoperative DEX was shown to improve mortality and incidence of cardiac/cerebrovascular events, and delirium, investigators did not observe a statistically significant benefit in reducing sepsis or other post-operative complications.[20–22] The authors reasoned that sepsis was a secondary outcome and the studies may have been inadequately powered to detected a difference.

In non-cardiac surgeries, perioperative DEX use was also associated with fewer adverse cardiac events despite increased intraoperative hypotension and bradycardia.[23] In a non-perioperative randomized control study of sepsis, DEX administration was not associated with improvement in mortality or ventilator-free days.[24]

Cancer

Animal and in vitro studies have demonstrated an association between DEX and tumor progression, possibly through stimulation of alpha-2 receptors on tumor cells.[17, 25–28] In clinical studies, the impact of intraoperative DEX use on recurrence-free survival and overall survival are mixed. Two recent studies, one among adults undergoing lung adenocarcinoma resection and the another among pediatric patients undergoing cytoreductive surgery for peritoneal carcinomatosis, found no significant association between intraoperative DEX exposure and recurrence-specific survival or overall survival.[29,30] In another propensity-matched trial, intraoperative DEX was not associated with recurrence but was associated with overall decrease in survival of patients after non-small cell lung cancer surgery.[31] These results are somewhat surprising as DEX was previously thought to be potentially superior to opioids in cancer patients due to its lack of immunosuppressive effects that were observed in opioids and volatile anesthetics and subsequent tumor progression.[32] Existing studies suggest that dexmedetomidine may not be an optimal multimodal analgesic agent for cancer patients, even if the underlying mechanism is due to different signaling pathways rather than immune suppression.

Conclusion

Dexmedetomidine has an important role in multimodal analgesia due to anti-inflammatory effects and immunomodulatory benefits. Patient and procedure factors, such as inflammatory or oncologic history or dexmedetomidine dosing, must be considered in determining the inclusion of dexmedetomidine in the analgesic plan. Further trials are needed to understand the perioperative effects of dexmedetomidine in diverse clinical situations.

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Into the Weeds: Introduction to the Anesthetic Management for Patients with Chronic Cannabis Use

Brittnee Haynes[1], Sandra Orfgen [2] MD, Andrew Mannes [2] MD

[1] Medical student
[2] Anesthesiologist, Department of Perioperative Medicine, Clinical Center, National Institutes of Health, Bethesda, Bethesda, MD

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Anesthesia, anesthetic management, cannabis, marijuana

Introduction

Cannabis is a plant product that has been used for therapeutic purposes by ancient civilizations, such as China, Egypt, and India [1, 2]. The continued global spread of medicinal cannabis eventually resulted in cannabis being described in the United States Pharmacopoeia in 1850 [2, 3]. Throughout the 1900s, the institution of multiple federal restrictions against cannabis in the United States culminated in the classification of cannabis as a Schedule I drug by the Controlled Substances Act of 1970 [4, 5]. Since the 1996 passage of legislation in California permitting the use of medical cannabis, most state governments have legalized the use of cannabis, whether for recreational use, medicinal use, or both.

With the continued rise of both recreational and medicinal cannabis use, perioperative clinicians are increasingly likely to encounter patients using cannabis. Accordingly, it is important for perioperative providers to have a well-rounded understanding of the additional anesthetic considerations for patients using cannabis, regardless of the legalization status of the drug. Further, the anesthetic management for patients using cannabis is a challenge due to several factors, including multi-system effects of cannabis, variable and unknown compositions of biologically active compounds of cannabis, and conflicting research findings with a lack of high-quality studies due to federal limitations and criminalization of cannabis.

Basics of the Endocannabinoid System

The endocannabinoid system (ECS) is a diffuse neuromodulatory system that plays a major role in homeostasis, such as in cardiovascular, endocrine, pain, neurologic, cognitive, and immune functions [6, 7]. The main endogenous ligands of the ECS are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are cannabinoids synthesized from arachidonic acid, a fatty acid found in the cell membrane [6, 7]. AEA and 2-AG are released in response to overstimulation of post-synaptic neurons, and then bind to cannabinoid receptors to downregulate pre-synaptic excitatory signaling [7].

The cannabinoid receptor type 1 (CB1) is found throughout the central and peripheral nervous systems, such as in the cortex, hippocampus, basal ganglia, amygdala, cerebellum, periaqueductal gray matter, dorsal horn of the spinal cord, and dermal primary sensory nerve endings, with resultant actions in nociception, anxiety, movement, memory, cognition, and emotion. Notably, the lack of CB1 in the brainstem results in the sparing of respiratory effects of cannabinoids, which is an important contrasting point to the depressive respiratory effects of opioids. Further, CB1 are found in multiple other organ systems, like the gastrointestinal, skeletal, and cardiovascular systems, although to a lesser extent than in the nervous system [7].

Another relevant cannabinoid receptor for the perioperative provider is the cannabinoid receptor type 2 (CB2), which has a less well-defined function and is predominately found in the spleen and immune cells, indicating a role in immunomodulation. Interestingly, G protein-coupled receptor 55 (GPR55) is a presumed third cannabinoid receptor with a broad distribution across the central nervous system, peripheral tissues, spleen and lymphocytes, and many cancer cells, thereby indicating potential as a future therapeutic target [8]. Overall, understanding the ECS will assist perioperative providers in determining and predicting the clinical effects of the exogenous cannabinoids found in cannabis.

Exogenous Cannabinoids

The three major species of cannabis plants are *Cannabis satvia, Cannabis indica,* and *Cannabis ruderalis*. Hundreds of organic compounds, such as terpenes, flavonoids, and cannabinoids, have been identified and extracted from cannabis plants. These exogenous cannabinoids bind to CB receptors, thereby exerting their effects through the ECS. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied and relevant cannabinoids with regards to perioperative cares.

THC, the main psychoactive cannabinoid, is a partial agonist at CB1 and CB2 [9]. In contrast, CBD, a non-psychoactive cannabinoid, is primarily a negative allosteric modulator at CB1 and CB2, though it has also been described as an antagonist at CB1 and inverse agonist at CB2 [10, 11]. CBD may moderate some effects of THC, most commonly resulting in a reduction in the acute effects of THC, which plays a valuable role while gathering information from patients regarding the THC/CBD ratio or content of the cannabis product [12].

Furthermore, these exogenous cannabinoids, especially CBD, act at a variety of other receptors within the nervous system, including some which may impact anesthetic management of patients using cannabis. The actions of cannabinoids at opioid, N-methyl-D-aspartate (NMDA), and γ-aminobutyric acid (GABA) receptors are significant to perioperative providers due to the close association of cannabinoid signaling with each of these receptor pathways [13].

For instance, cannabinoid and opioid receptors are found within the same cells and CNS neurons, and they mediate common intracellular signaling mechanisms. Cannabinoids also act at kappa and delta opioid receptors to increase endogenous opioid synthesis and release [13].

Similarly, as the NR1 subunit of the NMDA receptor is closely coupled to CB1 receptors, NMDA activation stimulates the release of endocannabinoids, resulting in a negative feedback mechanism to reduce the number of NMDA receptors. Moreover, as compared to endogenous cannabinoids, exogenous cannabinoids are thought to be more potent inhibitors of NMDA

receptors, thereby resulting in a greater inhibitory effect that leads to neural dysfunction and NMDA hypofunction [13].

Lastly, in certain brain regions like the hypothalamus, hippocampus, and cortex, GABA and CB1 receptors have overlapping localizations, are found in the same cells, and share a common signaling pathway. Due to these close linkages, cannabinoid activation of CB1 inhibits both the release and synaptic uptake of GABA, while also allosterically modulating GABA receptors [13].

Relevant pharmacokinetics

The pharmacokinetics of cannabinoids are difficult to determine due to the variable absorption, metabolism, and elimination of cannabinoids, which is dependent upon multiple factors, such as THC/CBD concentration of the product, route of administration, body fat percentage of the patient, and acute versus chronic use [11, 13, 14, 15].

For instance, according to the World Health Organization, a typical cannabis cigarette contains approximately 500-1000 mg of cannabis [16]. If the THC/CBD percentage of the cannabis is known, then the dosage can be calculated: THC/CBD dose equals the THC/CBD percentage multiplied by the milligrams of cannabis. However, the actual amount delivered depends on factors such as the smoking technique and inspiratory effort [14]. Further, the clinical effects vary based on quantity consumed and chronicity of use. This simple example illustrates the resultant complexities in clinical management of patients using cannabis as well as the challenges faced by researchers.

Nevertheless, the known pharmacokinetics of THC and CBD may guide perioperative providers. Cannabinoids are metabolized via the cytochrome P450 system in the liver, resulting in numerous active metabolites as well as potential interactions with drugs that are also metabolized via this mechanism [13]. Elimination of cannabinoids occurs through urine, bile, and feces [13]. An important consideration is the hepatobiliary recycling which may prolong the half-life of cannabinoids [13]. The plasma half-life of cannabinoids is 20-30 hours with a tissue half-life of up to 30 days [9]. The prolonged tissue half-life is due to the high liposolubility of cannabinoids, resulting in their accumulation in adipose tissue. Therefore, consideration of factors that may contribute to a prolonged half-life or drug interactions are relevant to the perioperative provider.

Screening & Weaning

Routine preoperative screening for current or past use of cannabis is recommended for every patient [17]. Since cannabis use may be stigmatized, it is imperative to remain non-judgmental while encouraging patients to disclose information that is paramount to optimal anesthetic care.

Due, in part, to the pharmacokinetic variability previously discussed, it is difficult to define significant cannabis consumption. Ladha et al. provides perioperative recommendations based on current literature and the experiences from an expert panel [17]. The recommendations are based on significant cannabis consumption, defined by the following: 1) greater than 1.5 g/day of inhaled cannabis, or 2) greater than 300 mg/day of CBD oil, or 3) greater than 20 mg/day of THC oil, or 4) consumption of a cannabis product more than 2-3 times per day with an unknown CBD or THC content [17].

If a patient uses either recreational or medicinal cannabis, additional information to gather may include duration of use, daily intake amount and frequency, method of consumption, use of "Spice" or "K2", time of last consumption, adverse effects of cannabis use or withdrawal, and time to onset of withdrawal. The composition of the cannabis product (i.e., THC/CBD ratio or content) is also useful information that may be found on the license or product label, however recreational users may not have access to this information due to the heterogeneity of cannabis products and varied product legality.

Consider screening for cannabis use disorder (CUD) if a patient reports using recreational cannabis greater than once per day or medicinal cannabis more than prescribed. There are several validated screening tools, such as the revised CUD identification test, which a brief 8-item screening assessment with 91% sensitivity and 90% specificity [17, 18]. Consideration of a referral to addiction medicine or psychiatry may then be warranted [17].

Moreover, in patients who meet the inclusion criteria for significant cannabis consumption, consider cessation or weaning of cannabis use if there are more than seven days prior to the surgery. The target for pre-operative cannabis use should be less than the inclusion criteria for significant cannabis consumption, with an even lower goal depending on sufficient time before surgery, level of patient motivation, and therapeutic use of the cannabis regimen. If the patient consumes greater than 2-3 times the inclusion criteria doses, consider pain medicine, addiction medicine, or psychiatry review of a plan for weaning or cessation. Under these conditions, Ladha et al. states that weaning or cessation of cannabis use is safe with possible benefit and may decrease adverse outcomes [17].

Although Ladha et al. had no consensus for patients using cannabis within 1-6 days prior to surgery, the authors recommended to continue cannabis use within 24 hours of surgery because weaning or cessation may increase the risk of cannabis withdrawal syndrome and possibly exacerbate associated underlying medical conditions, such as anxiety or chronic pain [17]. However, this recommendation varies amongst the current literature. For instance, Echeverria-Villalobos et al. recommends avoiding general and regional anesthesia for elective surgeries for at least 72 hours from last cannabis exposure due to the adipose accumulation of cannabinoids that may be associated with sustained tachycardia as well as the increased risk for acute myocardial infarction, which will be discussed below [19].

Cardiovascular effects

Cannabis has multiple effects on the cardiovascular system, which are mainly mediated by CB1 stimulation [7]. However, the end result of the cardiovascular effects of cannabis is a complex determination that depends on the THC/CBD ratio, chronic versus acute consumption, dose, route of administration, and time since last consumption [15, 19]. For instance, acute THC consumption stimulates sympathetics and inhibits parasympathetics resulting in a dose-dependent increase in heart rate, myocardial oxygen demand, and blood pressure, while CBD not only moderates the adverse effects of THC but may also reduce heart rate and blood pressure [12, 13, 15, 19]. However, with chronic cannabis use, patients may develop tolerance to the sympathetic effects, like tachycardia [11, 19]. Therefore, perioperative providers should be prepared for either positive or negative effects on the cardiovascular system due to the potential for a mixed clinical scenario depending on multiple factors of cannabis use habits.

In addition to the autonomic actions of cannabis use on the cardiovascular system, another consideration is that THC is associated with endothelial dysfunction and oxidative stress, which contributes to the increased risk of myocardial infarction in cannabis users [7]. One study demonstrated an almost five-fold increased risk within the first hour after smoking, which has been demonstrated by additional studies, including a recent nationwide inpatient sample illustrating that chronic cannabis consumption is associated with a meaningful increase in the risk of postoperative myocardial infarction [20, 21]. Cannabis use has also been associated with malignant arrhythmias, sudden-onset atrial fibrillation, coronary spasm, sudden death, cerebral hypoperfusion, and stroke [19]. Therefore, cumulative evidence suggests that a preoperative EKG and echocardiogram may be valuable components to perioperative cardiovascular monitoring [15].

Respiratory effects

There is little evidence of respiratory system effects of cannabis when administered by routes other than smoking or vaping, and the effects of cannabis consumption via these inhaled routes are similar to those of tobacco smoking. Inhaled routes of cannabis administration facilitate the entry of high concentrations of cannabinoids and non-cannabinoid chemicals into the airway and lungs, which then quickly enter the bloodstream, like those associated with tobacco smoking. These chemicals can act as bronchial irritants, like tobacco cigarette smoke, causing airway hyperactivity, edema, obstruction, chronic cough, bronchitis, emphysema, and bronchospasm [11, 13, 15, 19]. There is also concern that cannabis may be more irritating to the airways due to burning at a higher temperature than tobacco [19, 22, 23]. Further, certain characteristics of cannabis smoking, such as the technique and inspiratory effort previously mentioned, may result in greater carboxyhemoglobin levels and tar retention in the airways [24]. More specifically, prolonged or deep inhalation, shorter butts, and higher combustion temperatures may result in these respiratory effects that could complicate perioperative cares [19]. Due to these parallels between tobacco and cannabis smoking, perioperative providers may also consider an ASA classification 2 for current cannabis smokers.

In addition, the dangers of vaping is evident by the U.S. Food and Drug Administration (FDA) warning about vaping THC oil, which was due to a multitude of reports of severe pulmonary disease development, termed e-cigarette or vaping-use associated lung injury (EVALI) [25]. Inhalational exposure to these chemicals can result in extensive airspace opacification seen as a centrilobular nodular pattern that resembles pneumonia and has been described as a “tree-in-bloom” sign on imaging [26]. Therefore, any patient presenting in the perioperative period with new-onset respiratory disease and a history of vaping THC should be evaluated with concern for EVALI and other potential respiratory issues [13].

Cannabis smoking has also been associated with postoperative airway obstruction, such as pharyngeal and uvular edema [27-29]. Accordingly, it is recommended to postpone surgery when the patient has smoked cannabis shortly before an elective surgery, which is congruent with the recommendation to avoid elective surgery for at least 72 hours after cannabis use due to the cardiovascular effects described above [19]. Nevertheless, perioperative providers may consider the administration of steroids in order to reduce the risk of airway obstruction due to edema or inflammation, however it would be prudent to remain mindful of the increased risk for myocardial infarction within one hour of cannabis use.

Induction & Maintenance

Multiple studies have described an increased requirement of several anesthetic medications in patients with chronic cannabis use. The relevant mechanisms of action shared by perioperative medications and cannabinoids are through opioid, GABA, and NMDA receptors, thereby resulting in a potential for drug interactions.

A 2009 prospective, small sample size, human study found that chronic cannabis use increased the propofol dose required for induction when inserting a laryngeal mask [30]. More recently, a retrospective cohort study with 250 patients determined that regular cannabis use had a significant effect on the amount of sedation required, with cannabis users requiring 14% more fentanyl, 19.6% more midazolam, and 220.5% more propofol for the duration of the endoscopic procedure [31].

For inhaled anesthetics, a retrospective study demonstrated an increased delivery of intraoperative inhaled anesthetic among preoperative cannabis users, which may be due to increased tolerance [32]. This finding of a significantly greater sevoflurane requirement in cannabis users is consistent with other studies that demonstrated a link between cannabis use and a higher tolerance of inhaled anesthetics, such as isoflurane [33-34].

Therefore, anesthesia providers should be prepared to administer increased dosages of induction and maintenance anesthetic agents in patients with chronic cannabis use. These patients may also benefit from more rigorous monitoring as the interpretation of heart rate and blood pressure as factors in the determination of anesthetic depth may be complicated by the cardiovascular effects of cannabis [15].

PONV, acute pain, and withdrawal

Three postoperative considerations for chronic cannabis users include postoperative nausea and vomiting (PONV), acute pain, and cannabis withdrawal syndrome.

Chemotherapy-induced nausea and vomiting is an accepted indication for medicinal cannabis depending on state legislature, however studies have shown not shown cannabis to be useful in the prevention of PONV [35-37]. Cannabis use can even result in severe refractory cyclic nausea and vomiting, termed cannabis hyperemesis syndrome. In a retrospective analysis, daily cannabis users were found to have an increased risk of PONV, however another study found no difference in the rate of PONV among chronic cannabis users and cannabis naïve patients [38-39]. Ladha et al. found limited evidence in support of additional PONV prophylaxis for cannabis users, though the authors ultimately determined that the potential benefit outweighed the risks and stated that additional PONV prophylaxis is unlikely to result in harm [17].

Chronic pain is another accepted indication for medicinal cannabis depending on state legislature because cannabinoid effects on CB2 receptors in the dorsal horn have been shown to cause a reduction in inflammation and the modulation of pain [7]. However, cannabis has not been demonstrated to be useful in the acute, postoperative pain setting. Due to the close linkage between the cannabinoid and opioid systems, chronic cannabis use may result in difficulties in postoperative management of pain. The literature describing postoperative pain in cannabis users yields mixed results. Multiple studies indicated greater pain and opioid requirements, while

others report no difference or even less pain and opioid use in cannabis patients [40-46]. Ladha et al. states that it is appropriate to consider that postoperative analgesic requirements may be higher for patient who consume a significant amount of cannabis due to those multiple studies demonstrating greater levels of postoperative pain in cannabis users [17]. Moreover, it is important to remain cognizant of other causes of increased postoperative pain as well as the potential role of cannabis withdrawal, particularly if the cannabis is used for pain or anxiolytic indications [17]. Thus, a referral to an acute pain service may be beneficial for certain patients.

Although cannabis withdrawal syndrome (CWS) is not severe and does not have a high risk of severe adverse outcomes in most patients, CWS may contribute to morbidity in the postoperative period [17, 47]. There may be an increased prevalence and severity of withdrawal symptoms based on certain variables, including cannabis potency, daily cannabis use, female gender, and comorbid psychiatric disorders or polysubstance use [19, 47]. Notably, CWS is unlikely to occur in patients consuming 300 mg/day or less of smoked CBD-dominant cannabis and in patients that are also opioid-dependent [17, 19]. CWS onset generally occurs within 1-2 days, peaks within 2-6 days, and dissipates within 2-4 weeks [47]. However, the high liposolubility and consequent adipose accumulation may impact this general timeframe and severity of symptoms.

To avoid CWS, providers may instruct patients to continue with cannabis use until surgery, however this may conflict with the potential for adverse effects of cannabis on anesthesia. If CWS is suspected, perioperative providers may assess patients with the 19-item Cannabis Withdrawal Scale, or other withdrawal scales, and should refer to a psychiatry service as appropriate [17, 48]. Another approach to avoiding CWS is to consider continued administration of cannabis oil or edible cannabis while hospitalized. The consensus reached by Ladha et al. states that the continuation of cannabis oils and edibles may be appropriate on a general post-surgical ward, but no consensus was reached for ICUs, high-dependency units, or step-down units; this recommendation should be kept in concordance with evidence-based care, institutional regulations, and current legislation and, moreover, does not apply to inhaled cannabis [17]. Similar to the current regulations regarding tobacco smoking in hospitals, cannabis smoking or vaping is never appropriate in a hospital setting.

Conclusion

With the continued rise of recreational and medicinal cannabis use, the anesthetic management for chronic cannabis users requires additional investigation to address the questions and limitations posed by the current body of literature. Herein, we reviewed the basic physiologic and pharmacologic principles of the endocannabinoid system and exogenous cannabinoids that are relevant to perioperative providers, and then discussed considerations and recommendations for the anesthetic management of chronic cannabis users. Each patient should be screened for recreational or medicinal cannabis use, with additional information gathering about cannabis consumption as appropriate. The importance of adequate preoperative information gathering cannot be overstated because the information regarding frequency, amount, potency, route of administration, THC/CBD content, adverse effects, and withdrawal may be valuable during the anesthetic management, particularly with respect to cardiorespiratory effects, induction and maintenance of anesthesia, and certain postoperative cares. Amongst the literature, the major research limitations included the variable and unknown composition of the biologically active compounds of cannabis products, the federal legislation and criminalization

of cannabis which contrasts most state legislation, and a lack of high-quality human studies to guide perioperative decision-making.

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CASA 线上会议

肺动脉高压的麻醉管理

苗宁 MD

CASA 的线上"肺动脉高压的麻醉管理"于 9/17/2022 19:30 在 Zoom 上举行。大家针对麻醉医生如何在临床上更好地管理肺动脉高压患者而展开热烈的讨论。

此次研讨会由德州 Baylor Medical Center Texas Heart Institute 的潘伟教授主持。University of Louisville 的黄佳鹏教授（CASA 前会长）邀请到北京安贞医院麻醉科赵丽云教授分享妊娠期肺动脉高压孕妇的术中管理病例的分析，还邀请到 Ohio State University 产科麻醉主任，ICAA 候任院长夏云教授参加讨论。对肺动脉高压有深入研究的来自 Texas Heart 潘伟、Johns Hopkins 高卫东、首都医科大学卢家凯教授将点评并回答与会会员们的各种问题。

潘教授开篇介绍了肺高压的治疗进展：30 几年前仅有钙通道阻滞剂用于治疗肺动脉高压，而今至少有 14 种不同作用机理、治疗途径和疗效的药物用之于肺动脉高压的治疗。

赵丽云教授详尽地介绍安贞医院十几年来妊娠合并心脏病住院患者的人数仍旧居高不下，其原因有孕妇年龄增加以及外院转诊等。她这次主要向与会者报告了一例 Eisenmenger 综合征孕产妇剖宫产的麻醉管理 。

Eisenmenger 综合征是一组因先天性心脏解剖缺损，导致心、肺内血液循环异常，未经手术矫正而逐渐发展至肺动脉高压的后果。房、室间隔缺损，动脉导管未闭等先天性心脏病，可由原来的左向右分流，由于进行性肺动脉高压发展至器质性肺动脉阻塞性病变，出现右向左分流，皮肤粘膜从无青紫发展至有紫绀时，既称为 Eisenmenger 综合征。该病症以进行性的肺小动脉阻力增高为特征，伴有肺血管扩张试验阴性的低氧血症，可以引起右心室功能衰竭并最终导致患者死亡。在临床上，此时患者表现为呼吸困难、紫绀、活动耐量下降、浮肿、眩晕、晕厥、咳血、杵状指、心律失常并可合并脑血管事件的发生，最终导致患者的生活质量下降，生存时间减少。相关研究与临床报告均表明，Eisenmenger 综合征对于孕妇和胎儿均有着非常不利的影响。

赵教授引用大量国内外研究资料论述妊娠合并肺高压及 Eisenmenger 综合征对孕产妇的危险性（下图示）：

安贞医院 ANZHEN HOSPITAL

Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC)

Jolien Roos-Hesselink ✉, Lucia Baris, Mark Johnson, Julie De Backer, Catherine Otto, Ariane Marelli, Guillaume Jondeau, Werner Budts, Jasmine Grewal, Karen Sliwa, ... Show more

European Heart Journal, ehz136, https://doi.org/10.1093/eurheartj/ehz136
Published: 25 March 2019 **Article history ▼**

欧洲心脏病协会2007–2015年前瞻性注册研究

53个国家—138个中心—5739名孕妇，平均年龄29. 5岁

ESC GUIDELINES

CHD With High Risk and Extremely High Risk for Pregnancy

Significantly Increased Risk Of Maternal Mortality or Severe Morbidity (mWHO Class III) (Cardiac Event Rate 12%-27%)	Extremely High Risk Of Maternal Mortality or Severe Morbidity (mWHO Class IV)* (Cardiac Event Rate 40%-100%)
Unrepaired cyanotic heart disease	PAH
Moderate LV impairment (EF 30%-45%)	Severe LV impairment (EF <30% or NYHA Class III-IV)
Systemic RV with good or mildly decreased ventricular function	Systemic RV with moderate or severely decreased ventricular function
Fontan circulation. If the patient is otherwise well and the cardiac condition uncomplicated	Fontan with any complication
Severe asymptomatic AS	Severe symptomatic AS
Moderate mitral stenosis	Severe mitral stenosis
Moderate aortic dilatation (40-45 mm in Marfan syndrome or other HTAD; 45-50 mm in BAV; 20-25 mm/m^2 in Turner syndrome)	Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD; >50 mm in BAV; >25 mm/m^2 in Turner syndrome)
Mechanical valve	Severe (re-)coarctation

Abbreviations: AS, aortic stenosis; ASI, aortic size index; BAV, bicuspid aortic valve; CHD congenital heart defect; EF, ejection fraction; HTAD, heritable thoracic aortic disease; LV, left ventricle/ventricular; mWHO, modified World Health Organization; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; RV, right ventricle/ventricular; ToF, tetralogy of Fallot.

* Pregnancy should definitely be avoided in women with these conditions.Modified from Baumgartner H et al, 2020 ESC Guidelines for the management of adult congenital heart disease. European Heart J. 2020;42:563-645.[3]

Journal of Cardiothoracic and Vascular Anesthesia 36 (2022) 2738--2757

Pregnancy contraindication

Box 1
High maternal risk, WHO class IV, pregnancy contraindicated

Eisenmenger syndrome

Transposition of the great arteries, systemic RV with moderate dysfunction and/or severe tricuspid regurgitation

Univentricular heart with or without Fontan palliation and any of the following:
- Decreased ventricular function
- Moderate to severe atrioventricular valve regurgitation
- Cyanosis
- Protein-losing enteropathy

Ehlers-Danlos type IV (high risk aortic dissection)

Coarctation of the aorta, repaired or unrepaired, with significant obstruction

Turner syndrome with dilated aorta (>27 mm/m^2)

Current or prior type B aortic dissection

Heart failure of any cause with functional class III or IV

Abbreviation: RV, right ventricle.

赵教授介绍一例安贞医院收治的重度肺高压妊娠产妇的麻醉处理措施

Case

- 产妇，32岁，65kg,停经33周
- 自觉胸闷憋气两月余,近20天间断咳嗽，咯血一次，夜间不能平卧
- 既往史：18年前当地医院诊断为“先天性心脏病-室间隔缺损”，未治疗
- 无晕厥病史

心脏超声

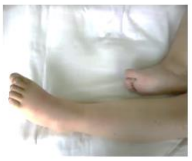
- 室间隔缺损（膜周部，双向分流）,肺动脉高压（极重度）SPAP:131mmHg.三尖瓣重度反流,心功能减退（LVEF45%），右心扩大 .永存左上腔

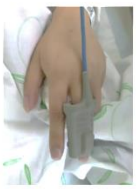
ECG：窦速，完全性右束支传导阻滞，S-T改变

X-Ray
肺血多，肺动脉段突出，心影大，胸腔积液

体格检查

- 端坐呼吸，发绀，杵状指，双下肢重度水肿
- 生命体征:
  - BP147/82mmHg, HR 106bpm
  - SpO2 85%(吸氧)





实验室检查阳性结果

血气分析（吸氧）
pCO_2 27mmHg,PO_2 47mmHg,SpO_2 85%。。。。

血常规-----血小板28.0 ×10^9/L,HGB:166.0g/L,
溶血---血红蛋白尿
尿蛋白300mg/L
低蛋白血症

BNP:1247pg/ml

入院诊断

- 1 宫内孕33⁺周
- 2 艾森曼格综合征
- 3 妊高症，,子痫前期，部分HELLP综合征?（血小板减少、溶血）
- 4 心衰，心功能IV级

多学科会诊(MDT)

产科：

- 患者心衰严重，原则上应抗心衰治疗，但合并HELLP综合征，需要尽快终止妊娠
- 围术期随时会发生猝死
- 胎儿娩出后采用压迫腹部缓慢剥离胎盘的方式，防止回心血量突然增加导致急性心衰，
- *与麻醉密切配合！*

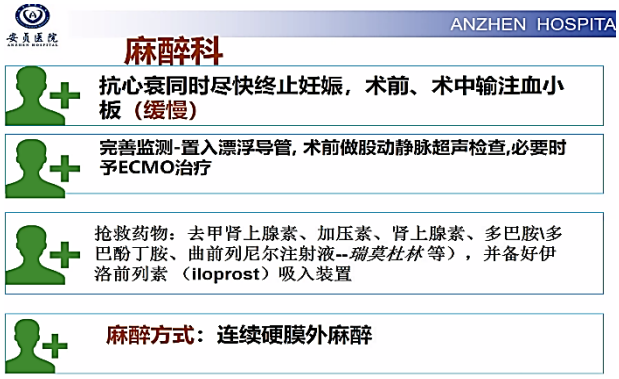
多学科会诊(MDT)

心内科

- 患者心衰严重，咳血、原则上应抗心衰治疗
- 降肺动脉高压治疗---磷酸二酯酶5抑制剂西地那非，间断吸入伊洛前列素及持续吸氧
- 强心利尿---呋塞米首选，限制液体，告知病人侧卧姿势防止仰卧位低血压

入院后治疗约36h后手术

- 患者半卧位吸氧入手术室，呼吸急促
- 面罩吸氧：PO_2 51 mmHg, SO_2 88 %
- 建立外周液路，*缓慢*输液
- 桡动脉血压125/76 mmHg，并在局部麻醉下右颈内静脉置入三腔中心静脉导管，同时放置Swan-Ganz导管
- 备好急救药品



麻醉实施及手术过程

- 中心静脉管连接：

去甲肾上腺素[去甲肾上腺素0.06mg×体重（kg）/50ml]，加压素（24u/50ml）

肺动脉导管端连接多巴酚丁胺[多巴酚丁胺0.03mg×体重（kg）/50ml]、曲前列尼尔[0.03μg×体重（kg）/50ml]

备吸入药物伊洛前列腺素

麻醉实施及手术过程

术前复查血小板：73.0 ×10^9/L，凝血功能正常

- 硬膜外麻醉：L_{1-2}间隙
- 平面T_6-S_4
- 血管活性药物硬膜外给药前启动：

去甲肾上腺素0.05-0.1ug/kg/min+加压素2-3U/h

多巴酚丁胺2ug/kg/min+瑞莫杜林1ng/kg/min

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麻醉实施及手术过程

- 取出胎儿前双下肢驱血带充气，压力稍高于血压
- 胎儿娩出后头高位（减少回心血量）
- 剖出胎儿后产科予腹部手法加压，待产妇情况稳定*缓慢*娩出胎盘（间隔5min以上）

胎儿娩出胎盘剥离后血压下降\体肺压力持平或倒置（产妇情况恶化多发生在此刻）

- 麻醉平面进一步扩散?
- 羊水过敏样反应?
- 回心血量增加右心功能不全?

- 羊水清亮，胎儿头位娩出顺利，阿氏评分7-8-9分
- 胎儿娩出后，*加大血管收缩药剂量，同时吸入万他维（5U/10ml）*及氧气，缓慢剥离胎盘
- 产妇主诉憋气-----头高位，娩出胎儿后给予5ug舒芬太尼

液体管理

- 入量
  - 血小板：1u（缓慢）
  - 术毕复查血小板计数：82.0 ×10⁹/L
  - 乳酸钠林格氏液： 100ml
- 出量
  - 出血：300ml
  - 尿量：100ml

术毕状况

血管活性药物

去甲肾上腺素 0.1ug/kg/min+加压素6U/h

多巴酚丁胺3ug/kg/min+瑞莫杜林1ng/kg/min

SBP(mmHg)	SPAP(mmHg)	SaO2 (%)
133/75（97）	126/90（106）	85（吸氧）

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术后	SBP(mmHg)	SPAP(mmHg)	SaO2 (%)
第1天	120~140	110~120	79~85
第2天	110~125	100~120	78~88
第3天	120~130	115~125	78~89
第4天	130~135	120~130	86
(转出ICU)			

- 用药情况：
  - 多巴酚丁胺、 去甲肾上腺素\加压素
  - 万他维
  - 西地那非（口服）

术后ICU情况

- 血管活性应用同前
- 吸氧， 依洛前列腺素间断吸入
- 口服西地那非
- 谨慎利尿/出入平衡

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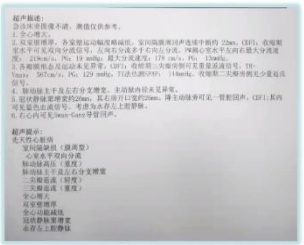
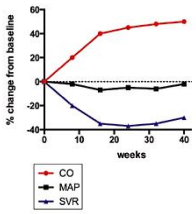
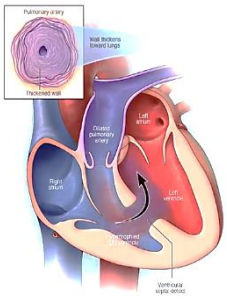
- ICU 4天后转入普通病房



- 10天后出院，随访良好
- 继续肺高压药物治疗

一、终止妊娠时期？？





<<共识>>

- ◆重度特发肺动脉高压、艾森曼格综合征患者--禁止妊娠
- ◆孕12周前发现尽早终止
- ◆孕28周以前胎儿出生后存活率极低，对出现心衰及血氧饱和度低下者(任何一种情况)，予强心、利尿等纠正心衰，应以产妇为主，控制病情并及时行剖宫取胎术
- ◆**重度肺动脉高压若合并B型钠酸肽（BNP）增高、双下肢水肿、胸腔积液、无法平卧等右心功能不全者，围产期死亡率大大增加**
- ◆**本例产妇均存在**

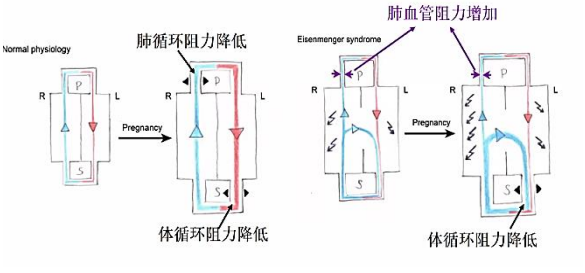
咳血、重度紫绀、贫血、血小板减少、就诊晚等

三、PAC放置？

- □ 超声心动图测定的肺动脉压是估测
- □ PAC更准确，并且可经PAC通路输入扩肺血管药，还可监测左右心功能
- □ PAC并不能改善肺动脉高压孕产妇的生存率，且确有肺动脉破裂、肺动脉血栓形成等PAC相关的并发症风险
- □ 难以到位者放右室

□ ***PAC为监测手段 非治疗手段***

Eisenmenger综合征&孕产妇



<<共识>>

- ◆妊娠晚期至孕32周后新生儿成活率明显提高，对治疗均未能奏效的严重心衰，特别是危及孕妇生命时，可边控制心力衰竭边紧急剖宫产
- ◆若血压尚可，首先进行降低肺动脉压力的治疗，间断吸入伊洛前列素及持续吸氧
- ◆强心利尿限制液体，左侧卧姿防止仰卧位低血压

本例

艾森曼格(Eisenmenger)综合征

\+

HELLP综合征

↓

充分权衡各种风险，术前输注血小板，采用硬膜外麻醉，避免全麻对重度肺动脉高压的冲击

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四、肺动脉高压 ---围术期管理原则

- □ **避免血压下降**
  (维持基础血压)
- □ **降低右心前后负荷**
- □ **防止心脏过度做功**

→

- ◆**防治低血压，适当强心**
  - **去甲肾上腺素**
  - **多巴酚丁胺（重症）**
  - **血管加压素（重症）**
- ◆**控制容量**
- ◆**降肺压（重症）**
  - **瑞莫杜林（静脉）**
  - **前列环素（吸入）**
- ◆**防止缺氧酸中毒**

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血管活性药物应用

- 肺动脉压力超过主动脉压力或二者持平，椎管内麻醉给药前泵注升压药（去甲肾上腺素和/或加压素）+降低肺血管阻力药（曲前列尼尔注射液）+吸入氧气+适当强心（多巴酚丁胺）防止血压下降治疗，术中酌情吸入万他维
- 若主动脉压力超过肺动脉压，泵注少量升压药物（去甲肾上腺素和/或加压素）+吸氧，同时进行硬膜外注药
- 术中根据血流动力学变化及时进行灵活调整

避免增加心室每搏功

- 针对右心血管活性药物的应用

适度的右室心排量及每搏功（RVSW）

$$RVSWI=(MPAP-CVP)\times SV \times 0.0136$$

$$PVR = 80 \times (mPAP - PAOP) / CO$$

$$MPAP=PVR \times CO/80+PAOP$$

容量管理理

- 容量不足与过荷均降低CO
- 围术期控制液体摄入，遵循量出为入或负平衡原则，尤其防止胎儿娩出后回心血量骤增
- 术前测定基础中性静脉压/肺毛细血管楔压作为参考

五.缩宫素？？

- 缩宫素直接扩血管，可造成严重低血压，甚至心跳骤停
- 胎儿娩出和缩宫素同时应用，使子宫突然缩小，回心血量骤增，对心脏病孕妇极易诱发心衰
- 我院对特发肺动脉高压（中-重度）、Eisenmenger综合征，催产素为禁忌
- 缩宫素心血管副作用剂量相关，以<5U/次缓慢静注，或一定剂量稀释后静脉点滴，对血流动力学影响较轻
- 左右室流出道梗阻患者？？？

TABLE 2 Issues That Should Be Taken Into Consideration Regarding Pregnancy in Women With Eisenmenger Syndrome

Indication	Pregnancy in women with ES is very high risk (mWHO IV) Women with ES should be counselled strongly against pregnancy
Contraception	High-dose estrogen therapy should be avoided because of the risk of thromboembolism Consider double contraception with male/female barrier devices plus slow-release subcutaneous progestin implants, Mirena coil, or male/female sterilization
Termination	Ideally conducted before the 10th week of gestation
Counselling when transition from pediatrics (ideally) or prepregnancy	Essential to inform patients and their families about maternal and fetal risks
Pregnancy management	
Care in expert centers	Need for a multidisciplinary team A detailed delivery plan, including the optimal mode and timing of delivery should be agreed by the pregnancy heart team
Avoid dehydration	Dehydration leads to hypovolemia, reduction of right ventricular filling pressure, reduction in pulmonary perfusion, hypoxemia, and fetal distress
Optimize targeted PAH therapy	ERAs are contraindicated during pregnancy Prostanoids and PDE-5 inhibitors (monotherapy or combination therapy) reduce hypoxemia and right to left shunting and improve maternal outcomes Inhaled nitric oxide may be used in the peripartum
Mode of delivery	Caesarean section and vaginal delivery are both valid options Individualized approach in expert centers
Anesthesia	Regional anesthesia is usually preferred over general anesthesia Anesthesia could result in significant systemic vasodilatation with worsening of right to left shunting, which must be actively corrected
Limit the duration of labor/epidural anesthesia	Uterine contraction causes autotransfusion, which may increase cardiac output by 25% and thus unbalance the delicate ES hemodynamic status increasing the risk of acute decompensation
Avoid emergency delivery, if possible	Plan an elective delivery with the necessary cardiological and anesthetic support Supplemental oxygen seldom increases the systemic saturation but may have a pulmonary vasodilation effect The use of oxytocin must be carefully considered, as if may have significant deleterious effects
Prevent or actively manage common causes of death in the peripartum period Hypovolemia (mainly after delivery) Thromboembolism Preeclampsia Massive hemoptysis Subarachnoid hemorrhage Intractable right ventricular failure	The indication for anticoagulation, even in prophylactic dose, must be carefully considered based on the individual patient (pregnancy is associated with an 8-fold increase of thrombosis, which is even higher in the peripartum) taking also into consideration the hemorrhagic risk of the particular patient Diuretic therapy must be considered with caution on an individualized basis as well

ERAs = endothelin receptor antagonists; ES = Eisenmenger syndrome; PDE-5 = phosphodiesterase type 5; mWHO IV = maternal World Heart Organization IV.

Eisenmenger Syndrome .JACC,2022:79（12）:1183 – 1198

- mWHOIV
- 尽可能10W前终止
- 告知猝死风险
- 多学科
- 尽可能进行术前准备如强心利尿，但注意脱水
- 主张靶向治疗
- C-S终止妊娠（不主张急症）
- 区域阻滞优于全麻
- 避免低血压
- 缩宫素恶化病情

赵教授的发言完毕后，大家踊跃提问：

1. 围产期 Eisenmenger 综合征的死亡率?

潘伟教授点评：根据 WHO 发布的统计数据大概为 40%；北美 20%左右；中国国内死亡率大概 10%；而安贞医院的统计为 6.4%，优于国内外的统计数据。这得利于安贞医院妇产科医生的产前保健，充分与患者沟通其危害性，随访，定时产检；麻醉科医生和其他多学科医生的科室紧密合作，认真精细地观察患者病情进展，药物治疗，重要体征检查；麻醉和手术方案的制订，实施以及面临的可能危险性的预防和处理措施富有经验所致。另外 Eisenmenger 病人，因有高凝倾向，围产期应慎用 TXA。

夏云教授分享美国的患 Eisenmenger 综合征孕产妇的管理经验。

- 他非常认同赵教授关于围术期对这些病患的各种诊治措施。

- 在美国肺动脉高压的孕产妇中，特发性肺动脉高压约占 60%，合并心脏病或心瓣膜病的肺动脉高压各占 10-20%，合并心衰的肺动脉高压的孕产妇约占 6-7%

- 在俄亥俄州立大学，患有心脏病和肺动脉高压的高危孕产妇一般在妊娠早期就已经进入一个名为 COACH 的专门监测高危心肺疾病孕产妇医学团队的视野。这个多学科团队包括：高危产科、麻醉科、新生儿科和心脏科的专职医生，必要时也邀请呼吸科、血液科和神经等其他专科的医生参与讨论和会诊，每月一次。

- 产前为孕产妇或待孕的妇女提供咨询，应告知 PAH 风险，还包括遗传咨询和妊娠及围产期 PAH 治疗。一般情况下，肺动脉高压（PH），特别是肺小动脉高压（PAH）的患者，应建议避免怀孕，并提供适应 PAH 患者 的避孕方法。针对 PAH 患者，早期及时的综合治疗方案非常重要。

- 所有怀孕的重症 PAH 患者都应制定终止妊娠的计划，尤其是妊娠早期（<12 weeks) 或有右心衰竭恶化的患者。如果患者想继续妊娠，应优化和加强 PAH 治疗以提高成功的机率。剖宫产是首选的分娩方式，建议使用硬膜外或小剂量腰硬联合麻醉，而不是全身麻醉。建立预防和治疗血管迷走性晕厥 Vaso-vagal syncope 的预案。PAH 孕产妇需要抗凝治疗，预防肺动脉栓塞，因此需要合理安排抗凝药物的桥接和椎管内麻醉的时机。

- 麻醉管理和监测非常重要，对 PAH 孕产妇进行标准监护的同时，应考虑 A-line, CVC，较少使用 PAC。避免可能导致 PA 血管收缩和 RV 功能恶化的情况：缺氧、高碳酸血症、低温和酸中毒，积极纠正心律失常。

- 择期手术可以给医护人员提供充足的时间做好准备工作。手术前硬膜外早期置管，常用 0.5% Ropivacaine 相对小剂量，多次注射，缓慢达到手术需要麻醉平面可防止突然血压下降而使症状加重恶化。麻醉平面达不到手术需要的麻醉平面，绝不实施手术，以防止镇痛不足而致的交感神经兴奋。血压降低时可用 Phenylephrine 或 norepinephrine IV 推注或点滴，必要时，准备好其他血管活性药物。

- 产后早期，血容量改变，严重 PAH 产妇可能会出现血流动力学不稳定，导致心肺功能衰竭和/或猝死，分娩和产后第一周是特别的危险期，大多数 PAH 孕产妇死亡发生在分娩后第一个月。高危 PAH 患者分娩后的头几天应在重症监护室进行监测。

赵教授阐述她们对于患 Eisenmenger 综合征的产妇多用硬膜外阻滞麻醉，Lidocaine 3ml 作为试验量，维持量为利罗合剂（1%利多卡因+0.5%罗哌卡因混合液）10ml。这样做的优点是麻醉起效较迅速，防止因麻醉平面不够而至交感神经兴奋，加重肺高压的临床症状；她们使用 norepinephrine IV 推注或点滴 （此药虽可增加血压但减慢心率）。安贞医院对轻-中度肺高压产妇多为自然分娩，而对患 Eisenmenger 综合征的产妇用剖宫产娩出胎儿以免恶化肺动脉高压。

2. 胎盘娩出后，大多数患者血压突然下降的原因？

夏教授认为可能的原因有出血量增加、心脏前负荷减少、腹腔压力下降以及缩宫素导致的血管扩张作用。

3. Eisenmenger 患者分娩后为何头高位？

卢家凯教授认为这是一种简单、有效措施以减少右心室的负荷量，避免恶化肺动脉高压。

4. 肺动脉高压产妇分娩后，是否肺动脉高压的临床症状好转？预后？

高、卢、夏和潘教授都认为全世界关于这方面的研究尚显不足；大多患者出院后未发现明显临床症状好转；药物可缓解轻-中度肺高压的恶化；Eisenmenger 综合征的患者可能需要将来的心肺联合移植术以根治其严重肺高压。

在美国行医的妇产科郑勤田医生表述了他的看法。他认为 Eisenmenger 妊娠病人需产科医生和心脏科医生共同产检。他认为：

- 心脏病不是剖宫产的手术指征；
- 自然分娩时可用抬头吸引术将胎儿顺利娩出；
- 胎盘娩出后，应用 IV Pitocin 而非子宫肌注射 Pitocin。因为子宫肌注射的 Pitocin 还是要通过血液吸收再作用于其受体而发挥作用。

卢家凯教授点评：他们开展妊娠动物肺高压模型用以研究终止妊娠 PAH 病情恶化的机制。他认为 PAH 患者的肺血管内皮增殖、舒张能力下降，妊娠可一定程度降低肺血管阻力，但终止妊娠后的雌孕激素水平的急剧下降, 会使肺血管阻力、肺动脉压力以及右心室后负荷呈显著增加趋势，对于严重 PAH 患者，此变化有诱发肺高压危象风险。这也是为什么重症 PAH 患者终止妊娠后的一周内， 在 ICU 内 PAP 有增高趋势，病情加重、严重心血管事件发生率更高的原因所在。

高卫东教授工作的医院对即将分娩的 Eisenmenger 综合征的产妇：

- 一般由 5 个团队医生共同协同工作： 妇科，高危产科，新生儿科，心脏科和麻醉科。
- 治疗肺高压孕产妇时首先明确病因是毛细血管前或是毛细血管后肺高压。毛细血管后肺高压多半由左心室功能不全导致肺静脉压增高；毛细血管前肺高压由各种原因导致的肺血管阻力增加所致，厘清不同原因导致的肺高压对症用药治疗十分重要。
- 剖宫产多为全麻，OR 和 ECMO 随时待命使用。他认为产前一定要详尽了解病史，身体检查；Echo 诊断为肺高压重症。
- 他指出维持右冠脉灌注量取决于右心室收缩压高低，而左冠脉 2/3 灌注量取决于左室舒张期的长短。如长期右心功能下降导致肺血管的永久受损，肺高压将无可逆转。
- Vasopressin 主要作用于外周血管而升高血压，但使用时应注意其对肾功能的影响。

卢教授认为使用 ECMO 救治 PAH 孕产妇难度较大，救治成功率低于非妊娠患者，可能原因是由围生期病理生理状态下发生肺高压危象的特殊性决定的。因此，此类患者围生期安全的重点之一就是在各个处理环节预防肺高压危象发生。

5. 曹会长提问：Eisenmenger 综合征患者是否可使用 Tranexamic Acid （TXA）以及最新治疗肺高压的药物?

潘教授指出：1990 年以前，仅有钙通道阻滞剂治疗肺高压；现在已有 14 种不同药物已被 FDA 批准临床使用。常用的有 Nitric oxide （NO）吸入；Prostaglandin (前列环素类药物) 用于吸入、IV 点滴、口服和皮下注射等途径；Phosphodiesterase 类抑制剂，如 Milrinone 因增加细胞内 cAMP 可扩张肺动脉，用于高阻力右心衰。但应注意大剂量时可致血压下降 。遇到严重肺高压患者一定多团队介入，管理和多学科合作；如果患者右心室功能不良或衰竭则应慎用β阻滞剂。

潘教授并指出当这类患者有出血倾向时常用 TXA， 因其能竞争性抑制纤维蛋白的赖氨酸与纤溶酶结合，从而抑制纤维蛋白凝块的裂解，产生止血作用，临床主要用于纤维蛋白溶解亢进所致的各种出血。

卢教授认为：临床上对肺动脉高压患者的首要考虑原则就是要以孕产妇的安全为主。尽管很多肺高压患者临床处理中并未发生严重不良事件，但妊娠合并心脏病 mWHO 分级在四级的患者

应尽早终止妊娠，这是决定此类患者终止妊娠时机的最重要原则之一。重症肺高压孕妇在妊娠28-32 周的病情发展十分迅速，越晚终止妊娠，对孕妇安全的威胁越大。

卢、夏两教授均认为在重症肺高压孕妇终止妊娠处理中，对于缩宫素，麦角新碱和欣母沛的使用，一定要特别谨慎。对于重症 PAH 患者，两个宫缩药物都有明显增加肺血管阻力、诱发肺高压危象风险。特别提出缩宫素的快速扩张体循环血管、降血压、增加肺血管阻力作用，是诱发肺高压危象的重要常见原因，应禁用。

因为时间关系，潘教授和曹会长对今天的讨论做了以下小结：

- 感谢赵、卢两教授今天的病例报告和分析，他们围术期的准备，病患评估和术中的处理措施及时，周到和安全。
- 对于肺高压孕产妇的医疗，应采用多学科的协作。
- 紧急状态下可使用 ECMO 设备以救助病患的生命。
- 安贞医院的 Eisenmenger 综合征产妇的死亡率 6.4%具世界先进水平。
- 感谢高、夏、彭教授以及曹会长的点评与分享。

曹会长感谢所有教授今天的付出，也感谢前会长-黄佳鹏教授召集这次会议以及潘伟教授今天的主持。她请国内外的麻醉医生多多分享自己的麻醉经验和教训，她认为有些国内麻醉医生的麻醉处理措施优于国外。今年 ASA 麻醉年会上胡灵群教授有关于《无痛分娩中国行》的报告，CASA 届时也会有相应活动，请大家踊跃参加。

最后，曹会长一并衷心感谢所有人对我们 CASA 的一贯支持！

转载文章

第十篇 妊娠合并心脏病患者接受剖宫产围麻醉期病例分析

第二十二章 妊娠合并艾森门格综合征患者接受剖宫产麻醉管理

林多茂，赵丽云, 教授

引言：妊娠合并肺动脉高压是妊娠合并心脏病中死亡率最高的类型，妊娠合并艾森门格综合征更是妊娠禁忌，一旦妊娠应及时终止。妊娠合并艾森门格综合征产妇就诊晚，往往已经合并心力衰竭，围产期处理极为棘手,猝死率高，围产期血流动力学目标管理原则及细节问题尤其重要，需要多学科参与诊治，麻醉管理更是重中之重。

一、病例概要

（一）病史

患者，女，26 岁，57kg。主因“停经 32 周，心慌、憋气，无法平卧 2 周”入院。患者出生后发现先天性心脏病，房间隔缺损，自幼无心慌、憋气等不适。停经 18 周出现咯血，超声心动检查结果：先天性心脏病，房间隔缺损，心房水平双向分流，肺动脉高压（重度），三尖瓣反流（中度），艾森门格综合征。紧急组织全院专家会诊，一致建议立即终止妊娠，但患者拒绝。孕 29 周时因活动后心慌、憋喘再次入院，超声心动图显示肺动脉收缩压（SPAP）为 112mmHg，三尖瓣重度反流，指脉搏氧饱和度（SpO2）87%（吸氧后）。因告知立即手术中止妊娠并不能保证胎儿存活，心力衰竭纠正好转后患者及家属强烈要求出院并签字。32 周时患者心慌、憋气加重并且呈端坐状态再次入院。

（二）术前检查结果和体征

查体：神清，重病容，坐位，呼吸急促，发绀，杵状指（趾）。血压 121/82mmHg，心率 106 次/min，呼吸 36 分/min，SpO2 85%（吸氧下）。

辅助检查：

心电图（ECG）示：窦性心动过速，右心室肥厚，完全性右束支传导阻滞，ST-T 改变。

心脏超声心电图示：先天性心脏病，房间隔缺损，艾森门格综合征，肺动脉高压（重度），TI 法估测肺动脉压 155mmHg，右心左心房增大，三尖瓣反流（重度），心包少量积液（图 22-1）。

胸部 X 线：肺动脉高压，肺动脉段显著突出，两肺血增多，肺血管呈树根状增厚，右心房室增大（图 22-2）。腹部 B 超：肝淤血，腹腔内积液。术前血气结果：pH：7.46，PCO2：27mmHg，Pa02：47mmHg，SO2：85%，Hb：17.1g/dl，Lac：1.0mmol/L，Mg2+：0.56mmol/L，Ca2+：1.25mmol/L，K+：3.96mmol/L。BNP：784pg/mL，NT-proBNP：2685pg/mL。

入院诊断：孕 32 周，合并艾森门格综合征，心功能Ⅳ级。

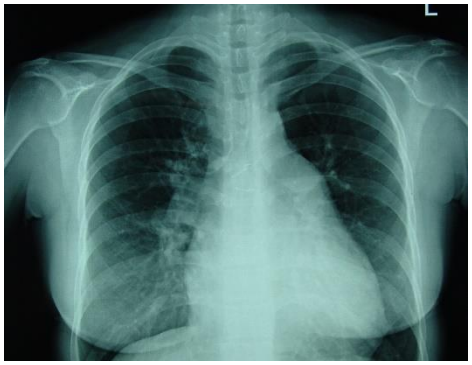
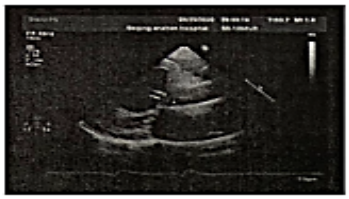
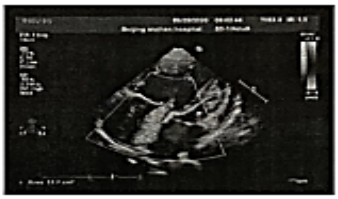


图 22-2 患者术前 X 线





主动脉根部		27	mm	室	厚度	10	mm	左心收缩功能			左心舒张功能			
升主动脉内径		25	mm	间	运动幅度	8	mm	射血分数	67	%	E 波最大流速	88	cm/s	
二尖瓣	瓣口面积		cm^2	隔	与左室后壁向运动			缩短分数	36	%	A 波最大流速	117	cm/s	
	瓣环径		mm		舒末内径	35	mm				E/A			
	压力减半时间		ms	左室	收末内径	22	mm	主动脉最大流速	90	cm/s				
肺动脉	主干径	45	mm		后壁厚度	8	mm	左室流出道流速		cm/s	肺动脉最大流速	105	cm/s	
	右肺动脉径	36	mm		后壁运动幅度	11	mm	压力阶差						
	左肺动脉径	25	mm	右室	前后径	46	mm	收缩期			舒张期			
左房	47		mm		流出道	45	mm	取样部位	流速	cm/s	取样部位	流速		cm/s
右房	51×64		mm		前壁厚度		mm		压差	mmHg		压差		mmHg

超声描述：

1.左心房、右心房增大，左心室内径正常。

2.四腔切面心房房间隔中部连续中断约 33mm,断端距二尖瓣约 12mm,心房顶部残缘约 3mm；大动脉短轴切面房间隔中部连续中断约 34mm,距主动脉根部约 3.7mm,心房顶部残缘约 0mm；剑下切面显示不清。CDFI：心房水平可见双向分流信号。

3.心室室壁厚度及运动幅度正常。心室室间隔连续完整，肺动脉与降主动脉间未见异常通道。

4.各瓣膜形态及运动未见异常，CDFI：收缩期三尖瓣心房侧见大量反流信号，反流束面积 11.7cm^2，TRVmax：603cm/s，PG：145mmHg，TI 法估测 SPAP：155mmHg。收缩期二尖瓣心房侧见少-中量反流信号沿后叶走行，反流面积 3.7cm^2。

5.主动脉弓、降部显示欠清。肺动脉主干及分支增宽。肺静脉汇入左心房。

6.心包腔内可探及少量液性暗区，左心室侧壁积液深 9mm。

超声提示：

先天性心脏病

房间隔缺损（II 孔型）

心房水平双向分流

肺动脉高压（重度）

三尖瓣反流（重度）

二尖瓣反流（轻-中度）

肺动脉主干及分支增宽

左心房、右心房增大

心包积液（少量）

图 22-1 患者超声心动图

二、患者围手术期主要风险

产妇合并艾森门格综合征，孕 32 周胎儿存活的可能性增加，继续妊娠产妇随时会有发生肺高压危象甚至危及生命，经全院多学科讨论，决定积极控制心力衰竭的同时尽快进行剖宫产终止妊娠。围手术期风险如下：

1.患者多次劝说终止妊娠无果，现心力衰竭严重，围手术期任何刺激均可导致病情恶化及猝死。

2.术前积极纠正心力衰竭的同时，需要口服药物进行降低肺动脉高压的治疗，但降低肺动脉高压治疗的同时会降低体循环压力，并且术前仰卧位低血压引起的血压降低也可使体肺循环压力倒置，出现病情恶化。

3.拟选择连续硬膜外阻滞，硬膜外麻醉导致的低血压同样增加患者出现意外的风险。尽可能避免全身麻醉，但若椎管内麻醉效果不佳需要改为全身麻醉，或出现意外需要紧急气管插管对该类患者影响大，可因插管刺激及正压通气诱发肺高压危象，或术后难以脱离呼吸机。

4.房间隔缺损导致的艾森门格综合征，左心室发育差，对容量的耐受性极差，术中胎儿胎盘娩出后回心血量突然增加会导致肺高压危象、急性右心衰竭和全心衰竭危及生命。

5.分娩和产后第一周为该类产妇最脆弱的时间段，产后回心血量的增加导致容量负荷过重加重心力衰竭，特别手术过程中血流动力学不稳定或有右心衰竭的患者。

6.该类患者高凝状态，围手术期还会出现血栓栓塞并发症。

综上，本例患者围手术期可能发生的风险包括：肺动脉高压危象，急性右心衰竭、全心衰竭、恶性心律失常，心脏停搏，猝死；重要脏器栓塞梗死；咯血、肺部感染；胎儿宫内缺氧、胎死宫内。

因此术前向家属交代患者随时猝死可能，并交代可能需要紧急使用体外膜氧合（ECMO）进行抢救。

三、麻醉及术中管理

（一）麻醉前

患者半卧位吸氧入手术室，神清合作，面罩吸氧血气结果：PO2：50.7mmHg, SpO2：88.7%。连接五导联心电图，半卧位在局部麻醉下行有创动脉压穿刺置管,血压 125/76mmHg，并在局部麻醉下行右颈内静脉穿刺置入四腔中心静脉导管，测定中心静脉压 8cmH2O。同时放置

Swan-Ganz 导管，肺动脉压力为 122/64mmHg。中心静脉管连接去甲肾上腺素[0.03mgX 体重（kg）/50ml]，肺动脉导管端连接多巴酚丁胺[0.03mgX 体重（kg）/50ml]、曲前列尼尔注射液（瑞莫杜林）[0.03μgX 体重（kg）/50ml]待用。双下肢膝关节以上置驱血带备用。

（二）麻醉实施

于 L1～L2 间隙穿刺行连硬外麻醉，头侧置管，2%利多卡因 3ml 作为试验剂量，5 分钟后追加 1%利多卡因与 0.5%罗哌卡因合剂 10ml，血流动力学稳定再次追加合剂 5ml。同时泵注去甲肾上腺素 0.05μg/(kg/min)、多巴酚丁胺 2μg/(kg/min)、瑞莫杜林 1ng/(kg/min)。

（三）术中管理

麻醉平面确定后双侧大腿中上 1/3 扎止血带待充气，并备好吸入伊洛前列素雾化吸入装置（5μg 伊洛前列素/10ml 生理盐水），严格控制输液速度，10 分钟后测试阻滞平面 T6～S4，血流动力学无明显变化手术开始。术中羊水清亮，胎儿头位娩出顺利，Apgar 评分 5-6-7 分，新生儿反应差，呼吸弱，予以气管插管辅助呼吸后转入新生儿病房。胎儿娩出后即刻置产妇头高位控制回心血量，静脉缓慢给予舒芬太尼 5μg，产科医师压迫下腹部约 8 分钟后娩出胎盘，胎盘娩出后血压有下降趋势，并出现体肺动脉压力倒置，立即行双下肢止血带充气，压力 130mmHg（稍高于主动脉压力），并增加去甲肾上腺素剂量至 0.08～0.1μg/(kg/min)，加用垂体后叶素 5U/h，加大多巴酚丁胺剂量至 5μg/(kg/min)，并吸入伊洛前列素，血压及肺动脉压力均增高趋势，氧饱和度 79%。待循环稳定后缓慢将双下肢止血带放气（每次每侧释放 50mmHg 的压力）。术中子宫收缩好，胎盘胎膜娩出完整,未使用缩宫素。术毕血流动力学状态基本稳定，血压 131/65mmHg，肺动脉压力 136/68mmHg，SpO280%（吸氧）。血气分析同术前, 吸氧状态及监测下安返监护室。

术程总入液量为 350ml，尿量 250ml，出血 200ml。

术中管理详见麻醉记录单（图 22-3）。

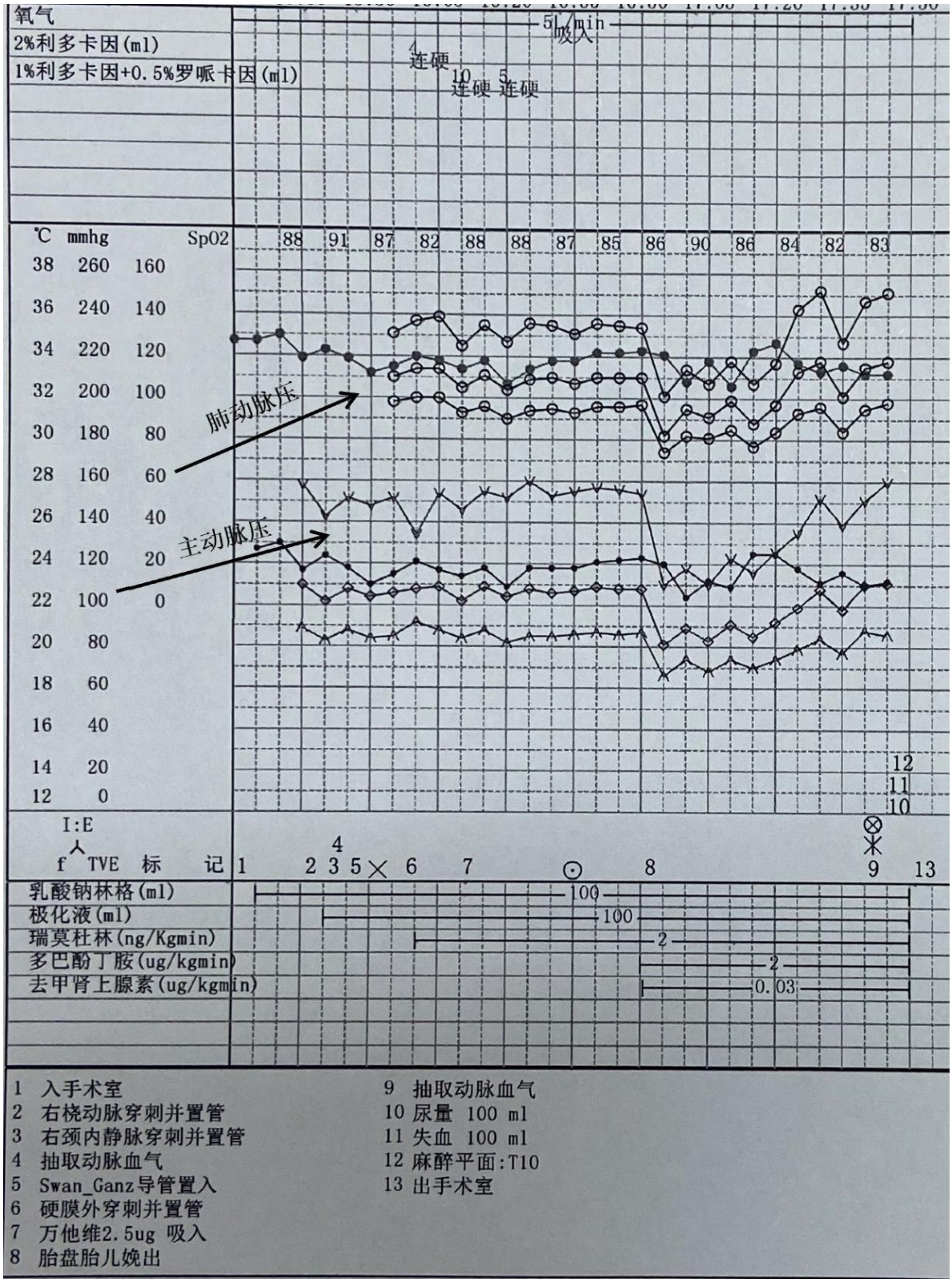


图 22-3 患者麻醉记录单

四、术后管理及转归

患者入监护室情况稳定，床旁胸片显示同术前，Swan-Ganz 导管位置正确（图 22-4），治疗同前，继续间断吸入伊洛前列素（5μg/d）。术后第 2 天出现血氧饱和度下降，最低时为 76%（双通道吸氧），心率增快 130 次/min 左右，体肺压力倒置，增加去甲肾上腺素剂量达 0.15μg/ (kg/min)，积极纠正酸中毒，利尿，镇静镇痛，并口服万艾可、地高辛，病情逐渐稳定，即刻床旁超声估测肺动脉压力 144mmHg。术后第 3 天病情逐渐好转，逐渐减量血管活性药物，确定无产科活动性出血后应用小剂量低分子量肝素抗凝。术后第 5 天循环稳定，血气值基本满意，少量去甲肾上腺素、多巴酚丁胺维持血压。第 6 天嘱患者屏气状态下拔除 Swan-Ganz 导管（防止反常气栓），返回普通病房。

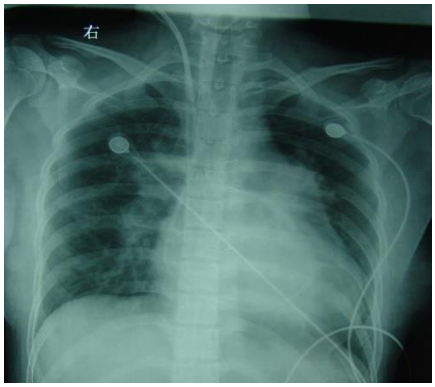


图 22-4 术毕 ICU 床旁胸片及 Swan-Ganz 位置图

五、妊娠合并艾森门格综合征患者接受剖宫产围麻醉期管理要点

妊娠合并艾森门格综合征是对整体医院管理团队的考验，每一个环节的管理至关重要，总结如下：

（一）术前准备

术前吸纯氧可提高氧分压解除肺血管痉挛，降低肺血管阻力。无产科急症术前应首先积极抗心力衰竭治疗（强心、利尿）。无低血压者口服降低肺动脉压力的药物（西地那非）。维护血气电解质平衡，防止酸中毒使肺血管收缩，防止利尿期间低钾、低镁等发生。安抚情绪。术前尽可能降低心力衰竭指标如脑钠肽（BNP）或脑钠肽前体 N 末端片段（NT-proBNP）水平。

若术前存在以下状态，提示病情极其严重：

1. BNP>300pg/mL、NT-proBNP>1400pg/mL。
2. 右心房压>14mmHg，CI<2.0L/（min · m2），SvO2<60%。
3. 右心房面积>26cm2，三尖瓣环收缩期位移<1.5cm，并有心包积液。

4. 有心力衰竭症状、晕厥及 6 分钟步行试验<165m。

（二）术中管理原则

防止低血压、避免肺血管阻力进一步增高为该类患者管理的核心。预防麻醉后外周血管阻力明显降低和心脏功能抑制；预防胎儿娩出后子宫收缩及下腔静脉梗阻解除导致的静脉回流增加，导致的产妇血容量迅速增加，胎儿娩出后置产妇头高位，同时胎儿娩出前控制容量输入，量出为入或负平衡。及时纠正酸中毒。

（三）合理选择血管活性药物

由于硬膜外麻醉不可避免导致的外周血管阻力下降，因此几乎所有患者均需要使用血管收缩药物来维持血压。目前多使用去甲肾上腺素和/或血管升压素，但需要注意二者对肺血管阻力的影响。酌情持续泵注曲前列尼尔注射液以及吸入伊洛前列素扩张肺动脉，降低肺血管阻力，降低右心后负荷。但要注意曲前列尼尔及伊洛前列素均可降低外周血管阻力导致低血压，注意输注及吸入剂量的控制。正性肌力药多选择多巴酚丁胺，心力衰竭严重时加用肾上腺素。

（四）术中监测

此类患者的监测包括心电图（ECG）、有创动脉压（ABP）、指脉搏血氧饱和度(SpO2)、中性静脉压（CVP）及 Swan-Ganz 导管。Swan-Ganz 导管可实时监测肺动脉压力，同时经 Swan-Ganz 导管可直接输入扩张肺血管的药物，利于围手术期及时进行血流动力学指标的调控，但如果置入困难或诱发心律失常严重，建议放弃 Swan-Ganz 导管放置，同时不建议测定肺动脉楔压。

此外，因该类患者多选择椎管内麻醉，无法进行 TEE 监测，经胸超声监测（TTE）的应用具有重要意义。其可直视心脏收缩功能，辅助判断容量状态，及时发现肺高压危象前驱症状，建议采用。

特别注意，若患者是由于动脉导管未闭导致的艾森门格综合征，因存在差异性发绀，术前需要同时监测双上肢及下肢动脉压及血氧饱和度，以判断病情严重程度。术中监测上肢血压和氧饱和度的同时，需监测下肢血压及氧饱和度。

（五）产科医师配合

手术时产科医师需要控制好胎儿及胎盘娩出的时间和速度，防止回心血量骤增使病情恶化。胎儿娩出后压迫下腹部防止回心血量骤增，待血流动力学平稳后缓慢娩出胎盘，并采用子宫按摩等促进宫缩，禁忌使用缩宫素。若有严重宫缩乏力，总量要控制在 5U 以下，并且需要经静脉缓慢滴注，发现异常立即停止应用，避免宫体直接注射缩宫素。

（六）产妇情况恶化的应急处理方案

产妇情况恶化多发生在胎盘娩出后，一方面由于胎儿胎盘娩出后回心血量增加导致心脏负荷加重，另一方面可能由于少量羊水入血导致的肺血管收缩反应或全身过敏样反应，患者多表现为憋气，主肺动脉压力倒置，氧饱和度下降等。一旦发生多需要紧急吸入伊洛前列素、加大升压药物剂量并双下肢驱血带充气，若效果不佳，多需紧急气管插管，小潮气量高频率通气，同时吸入一氧化氮，并使用血管收缩药物、正性肌力药物、扩张肺血管药物维持血流动力学平稳。如果情况继续恶化，需要紧急体外膜氧合（ECMO）维持，此时患者往往预后较差。

（七）术后管理

术后监护室需要精准管理，缓慢撤退血管活性药，避免容量负荷过重，特别是在产后最初 72 小时之内，可针对性使用利尿剂。如果患者出现血压下降、混合静脉氧饱和度下降、右心房压力上升等均提示患者病情恶化，需要及时调整血管活性药。需要注意，产妇术后由于血容量增加会持续到产后 24 周，因此有必要对孕妇进行数月的监测以提高生存率。术后尽快恢复口服降肺压治疗

六、相关知识延伸

（一）艾森门格综合征（Eisenmenger syndrome）

艾森门格综合征是一组先天性心脏病发展的后果。房、室间隔缺损、动脉导管未闭等先天性心脏病，可由原来的左向右分流，由于进行性肺动脉高压（pulmonary artery hypertension，PAH）发展至器质性肺动脉病变，出现双向或反向分流，伴有肺血管扩张试验阴性的低氧血症。临床表现为呼吸困难、发绀、活动耐量下降等，即称为艾森门格综合征。艾森门格综合症最早在 1897 年被描述，Wood 在 1958 年重新定义。对于没有或已经失去手术适应证的艾森门格综合征患者，如果强行手术治疗，只会加重患者肺动脉高压的进展，术后早期会出现右心功能和全心衰竭，缩短患者寿命。因此对于此类患者，强调通过采用降低肺动脉压力的靶向药物治疗，以达到延缓肺动脉高压进展、改善症状、延长寿命的目的。

临床中特别注意，先天性心脏病动脉导管未闭的患者，连续性左向右分流，使大量血液流向肺循环而形成肺动脉高压，当肺动脉压力超过主动脉压时，左向右分流明显减少或停止，产生肺动脉血流逆向分流入降主动脉，出现差异性发绀，左上肢有轻度青紫，右上肢正常，下半身青紫，呈现双下肢紫绀重于双上肢，左上肢重于右上肢，即差异性发绀（differential cyanosis）。动脉导管未闭大都单独存在，但有 10%的病例合并其他心脏畸形,如主动脉缩窄、室间隔缺损、肺动脉狭窄。

（二）肺动脉高压分类

表 22-1 第五届世界肺动脉高压论坛推荐的肺动脉高压分类

分类	致病因素
1．动脉型肺动脉高压	
(1)特发性肺动脉高压	
(2)遗传性肺动脉高压	
(3)药物和毒物相关性肺动脉高压	
(4)疾病相关性肺动脉高压	结缔组织病；人类免疫缺陷病毒感染；门静脉高压；先天性心脏病；血吸虫病
2．左心疾病相关肺动脉高压	左心室收缩功能不全；左心室舒张功能不全心脏瓣膜病；先天性 / 获得性左心流入道 / 流出道梗阻
3．慢性缺氧性疾病相关肺动脉高压	慢性阻塞性肺疾病；间质性肺疾病；其他限制性或阻塞性肺疾病；呼吸睡眠暂停；肺泡低通气疾病；慢性高原病；先天性膈疝；支气管肺发育不良
4．慢性血栓栓塞性肺动脉高压	
5．由多种未知因素导致的肺动脉高压	

正常人静息状态下的平均肺动脉压为(14±3)mmHg，正常上限为 20mmHg，静息状态下右心导管测定的平均肺动脉压≥25mmHg，即定义为肺动脉高压（PH）。2013 年法国尼斯肺动脉高压会议上对肺动脉高压的分类进行了更新，分为五类，如表 22-1。

临床中妊娠合并肺动脉高压，多以先天性心脏病导致的肺动脉高压为主，这类患者大部分是先天性心脏病未纠正仍存在解剖分流导致肺动脉高压，而小部分是解剖分流已纠正但仍存留肺动脉高压。此外，还有较小比例的妊娠合并肺动脉高压的病例是特发性肺动脉高压、左心疾病相关肺动脉高压。值得注意的是，临床中解剖分流已纠正的先天性心脏病病例和特发性肺动脉高压病例的麻醉处理更为棘手，因心腔间无分流，一旦出现肺血管阻力增高，更容易出现肺高压危象。因此这两类肺动脉高压患者的围产期管理需要更加精细，谨慎使用缩血管药物，防止肺血管阻力增加。

（三）妊娠对肺动脉压力的影响

正常妊娠后产妇的耗氧量、血容量、心排血量、肺血容量等均增加，外周血管阻力下降。孕前左向右分流的心脏病随着妊娠的进展及血容量的增加，大量左向右分流致肺循环血流量增加，使肺动脉高压逐渐加重并加快出现双相分流或右向左分流的进程。孕妇合并肺动脉高压代偿高血容量的能力比正常人显著下降，易于发生急性右心衰竭和全心衰竭。

（四）肺动脉高压危象及防治

肺动脉高压危象是指肺动脉压力急剧增高，达到或超过主动脉压力水平，导致严重的低血压及低氧血症的严重综合征，即肺动脉高压、缺氧、心力衰竭。常见于两周内肺循环阻力尚未下降的新生儿、术前双向分流并发重度肺动脉高压者或特发性肺动脉高压患者。任何微小刺激（如缺氧、酸中毒、气管吸引等）均可诱发急性肺动脉高压危象的发生。其病理生理特点是肺小动脉痉挛引起肺小动脉前充血, 压力增高, 右心的血液不能顺利通过肺循环进入左心系统, 从而引起左心系统缺血, 低血压。

肺动脉高压危象小发作时,除肺动脉压升高外,其他表现不明显,易被忽视。肺动脉高压危象急性发作时表现为血压急剧下降, 血氧饱和度降低, 肺动脉压和右心室压上升，甚至猝死。为避免围手术期发生肺高压危象，要遵循一定的管理原则，具体措施如下：

1. 吸纯氧提高血氧分压解除肺血管痉挛，降低肺血管阻力。

2. 若采用全身麻醉或抢救性插管，要采用肺保护性通气策略，因潮气量对肺血管阻力（PVR）的影响呈 U 字形改变（图 22-5），过低或过高的潮气量均致 PVR 增加，同时避免吸痰刺激呛咳。患者处于功能余气量时段的肺血管阻力最低。慎用 PEEP。

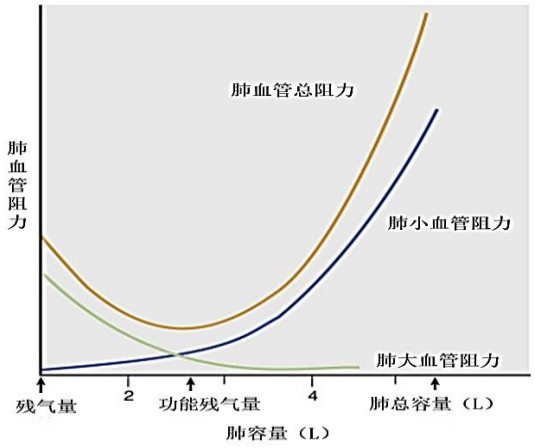


图 22-5 潮气量对肺血管阻力的影响 3.合理选择血管活性药物，防止体循环阻力降低及血压下降。注意血管活性药要采用能发挥作用的最低剂量，缩血管药同时增加肺动脉压力，需要精细调节。注意降低肺动脉高压治疗的同时导致的外周血管阻力降低，需要注意速度及剂量。

4. 容量治疗量出为入甚至负平衡。

5. 出现肺高压危象经上述积极治疗仍未奏效，可考虑体外膜氧合治疗暂缓病情（见后）。

（五）艾森门格综合征孕妇剖宫产时机的选择

1. 艾森门格综合征患者原则上禁止妊娠，若孕 12 周前发现应尽早终止。

2. 坚决继续妊娠的患者，应加强肺动脉高压相关治疗，以改善预后（见后）。

3. 孕 28 周以前胎儿出生后存活率极低，对于出现心力衰竭、重度肺动脉高压及血氧饱和度低下者 (任何一种情况)，予强心、利尿等纠正心力衰竭后，应以产妇为主，控制病情后及时终止妊娠，行剖宫取胎术，可提高孕妇存活率。

4. 妊娠晚期至孕 32 周后新生儿成活率明显提高，对难以控制的严重心力衰竭，特别是危及孕妇生命或估计胎儿能够成活时，可积极治疗，尽量降低心功能恶化程度，剖宫产结束分娩。

（六）体外膜氧合

体外膜氧合（extracorporeal membrane oxygenation，ECMO）通过将静脉血由合适插管引出体外，氧合和排出二氧化碳后泵回体内而替代心肺功能,是缓解严重心肺功能不全的有效方法。其作用是通过体外循环，对一些因心脏和肺病变导致的呼吸或循环衰竭患者进行有效支持，使心肺得以充分休息，为心肺功能的恢复赢得宝贵时间。当心肺功能逐渐恢复能承担全身的呼吸与循环功能时，再逐渐撤离 ECMO。ECMO 虽可改善低氧，降低肺动脉压力，减少血管活性药物应用剂量，促进心脏功能的恢复，但 ECMO 不能治愈严重肺动脉高压导致的肺血管不可逆的病变。因此要严格掌握其应用指征，提高 ECMO 救治的成功率 (见第十一篇第四十三章)。

（七）麻醉方式的选择

目前国内外专家多倾向于椎管内麻醉。安贞医院的经验是在没有椎管内麻醉禁忌者均选择椎管内麻醉，术程精细管理，合理应用血管活性药多会安全度过手术关。为避免血流动力学的波动，重度肺动脉高压者避免采用蛛网膜下腔阻滞方式。如需要全身麻醉，应尽可能避免全麻气管插管及拔管导致的血流动力学变化，尤其避免吸痰刺激，选择深麻醉下拔除气管导管。

（八）孕产妇围手术期降低肺血管阻力的方法

孕期肺动脉高压新疗法的出现对于提高产妇生存率极其重要，但特别注意降低肺血管阻力原则上不应大幅度降低主动脉血压，治疗前若产妇血压偏低，降肺压治疗需要格外慎重，并且密切监护，根据既往史、体格检查、影像学（超声心动图）和实验室测试评价及时调整用药。

1. 前列腺素类 按世界卫生组织功能分类 (FC) 第IV类或有严重右心功能损害的产妇，建议使用肠外前列腺素类药物。国外目前应用最多的是静脉注射应用依前列醇(共识)。曲前列尼尔（瑞莫杜林）是一个新型稳定的前列环素类似物，可舒张肺血管，抑制血小板聚集及平滑肌细胞增生，半衰期较长，改善肺动脉高压患者心功能及降低死亡率，可在术前、术中及术后通过皮下、静脉持续应用。安贞医院对于重度肺动脉高压产妇多应用此药。也可采用吸入伊洛前列素。

2. 磷酸二酯酶 5 抑制剂 磷酸二酯酶 5 抑制剂可用于有正常右心室功能的产妇，多用西地那非，注意需要密切随访，安贞医院多采用此类药物。

3. 钙通道阻滞剂 无右心衰竭且肺血管舒张反应阳性的产妇，可采用钙通道阻滞剂治疗。

4. 一氧化氮 气管插管者可吸入低浓度一氧化氮扩张肺动脉，但需要专用的特殊装置，并且有撤离后肺高压反跳现象。

5. 正性肌力药 围手术期正性肌力药物可考虑使用多巴酚丁胺及米力农降低肺血管阻力，严重心功能不全考虑应用肾上腺素。

（九）肺动脉高压产妇围产期抗凝治疗

特发性肺动脉高压（IPAH）、低氧性肺动脉高压（HPAH）和先天性心脏病导致的肺动脉高压如艾森门格综合征、慢性血栓栓塞性肺动脉高压（CTEPH）的患者，均需要考虑抗凝治疗，通常使用低分子量肝素接受长期抗凝治疗。所有 PAH 患者围产期均推荐预防性应用肝素，分娩时低分子量肝素可以切换到普通肝素，以方便麻醉选择。华法林由于致畸作用为妊娠期禁忌。新的口服抗凝血剂(例如达比加群酯、利伐沙班、阿哌沙班) 在 PAH 患者中的使用无系统性研究，不建议使用。

（十）肺动脉高压孕产妇血管迷走反射性晕厥

迷走反射和晕厥均可造成重度肺高压产妇致命性的心排量下降，导致猝死。

血管迷走反射性晕厥的特点是血液流向大脑和/或血容量分布的变化引起了突发性的低血压及心率过缓及不齐。由于肺动脉高压孕产妇代偿能力有限，一旦出现病情凶险。诱因包括血管舒张、静脉回流减少(例如蛛网膜下腔阻滞、子宫颈操作和导致疼痛和/或焦虑的任何程序的干预)。一旦发生，需要进行迅速和有针对性的干预如变换体位、提高血压和心率及对症处理。需要强调的是，此类产妇可能存在对处理措施不敏感或血流动力学迅速恶化的可能，因此应以预防为主。

（十一）缩宫素对肺动脉压力的影响

缩宫素是治疗产科宫缩乏力的首选，其加强子宫收缩、迅速关闭子宫肌层创面的血窦、阻断血流的效果确切，但缩宫素有其固有的副作用，通过直接（包括反射）作用或间接作用可导致产妇显著短暂的低血压、心动过速和/或心律失常，缩宫素还有直接抑制心脏收缩力及导致冠脉痉挛的作用。对于心肺功能较差的产妇无相应的代偿性反应，尤其对于肺动脉高压者，往往会导致体肺压力倒置，出现肺高压危象。同时胎儿的娩出和缩宫素的应用，子宫血窦内的血液回流至体循环，回心血量骤然增加，右心难以承受前负荷的突然增加，会即刻出现右心衰竭。

缩宫素的心血管副作用同剂量相关，目前研究认为，以<5U/次缓慢滴注，或以一定剂量稀释后静脉滴注，对血流动力学影响较轻。

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2022 ASA 年会

CASA 部分成员的科研，教学成果汇报

1. **彭勇刚 教授和住院医生**

   Poster:
   - Management of patient with prolonged brain hypo-perfusion in setting of type 1 aortic rupture
   - Protamine reaction in a patient undergoing trans-catheter aortic valve replacement
   - Blood transfusion is an independent risk factor for delayed discharge for COVID patients after lung transplantation
   - Effects of right ventricular function on ECMO duration and hospital stay after lung transplantation due to sars-cov 2 related end stage lung disease

   彭教授被选入多个 ASA committees in 2022

   - ASA committee member on transplant anesthesia
   - Committee member ASA's abstract review subcommittee on clinical circulation
   - ASA Committee member on scientific and educational exhibition

2. **Jeff L Xu, MD, FASA. Chief, Division of regional anesthesia & acute pain management**
   Westchester Medical Center/NY Medical College

   Speaker:
   Session PN 240. Novel Techniques in pain management for spine surgery

3. **Xiaowei Lu, Ning Miao, Andrew Mannes, MD**
   Department of Perioperative Medicine, Clinical Center, National Institute of Health

   Poster: Von Willebrand disease patient with high bleeding risk for combined hepatectomy and nephrectomy

4. **黄建宏 教授**

   Poster:
   - Patients with previous blood transfusions received more blood transfusion during curative cancer surgery
   - Complications of blood transfusion in curative cancer surgery: a prospective observation study
   - Anesthesia consideration for a patient with incidentally diagnosed anomalous origin of right coronary artery originating from pulmonary trunk (ARCAPA): A case study

5. 汪红 教授

   Faculty: Faculty of ASA diagnostic POC_US workshop

6. 李金蕾 教授

   - **Speaker:** Updates on ambulatory TJA
   - **Speaker**: How to minimize iatrogenic nerve injury by anesthesiologists

7. 胡灵群 教授

   - **Presenter:** FAER Medical Student and resident Symposium
   - **Presenter:** SOAP Research network Symposium
   - **Presenter:** Maternal and Neonatal outcome in Morbidity parturient for elective cesarean delivery at term under spinal anesthesia
   - **Keynote speaker:** Chinese American Society of Anesthesiology Annual Meeting.

8. 方壮霆 教授

   Poster：

   - Room air intravenous sedation is possible with a single syringe multimodal non-opioid 6-2-2 sedation method
   - Non-opioid multimodal single syringe mixture for ASA physical status class 4 patients undergoing ocular block and ophthalmic surgery

9. **Ning Miao, Xiaowei Lu, Kevin Driscoll, Andrew Mannes, MD**

   Department of Perioperative Medicine, Clinical Center, National Institute of Health

   Poster: Fatal Venous Air Embolism and Cardiac Arrest during Hepatectomy

由于收集不齐，肯定漏掉一些 CASA 同行们在 ASA 年会上的科研成果展示, 在此一并致歉!

麻醉教授 99 华诞

做麻醉届枝繁叶茂不老的常青树

邵新立　苗宁　钱晖　魏华锋

今年 10 月是一个特别欢喜与值得纪念的日子，我们将为金士翱教授隆重庆祝 99 岁华诞。

因为疫情的缘故，我们在海外的学生不能亲自前往祝贺，留下不少遗憾，但我们的心中充满了对金教授的感激与敬意，以此文向我们的老师表达深深的思念与祝福。

金教授是中国麻醉学的创始人之一，为新中国麻醉学事业的发展奉献了毕生的精力。早在上世纪 50 年代，金教授与中国外科学鼻祖裘法祖教授等一道从上海同济大学迁往武汉同济医学院，在裘教授的建议下成立了麻醉科，并成为第一任科主任。彼时麻醉科还是非常单薄的科室，麻醉的意义尚未得到广大患者的认识与重视，麻醉医生的地位也远远落后于其他学科。就是在这样艰苦的条件下，金教授不畏困难，不惧挫折，从零开始，逐渐培养起一批吃苦耐劳、立志奉献于麻醉事业的专科医生。在金教授高尚医德、精湛医术与虚怀若谷人格魅力的感召与带领下，同济医学院麻醉科成为了中国麻醉学人才培养的重要摇篮，获得了教育部最早一批硕士、博士学位的授予点以及中国与世界发达国家麻醉学科交流合作的平台，在中国麻醉届建立起了举足轻重的前沿地位。回首往昔，追古抚今，我们清楚地看到，正是在金教授这样一批具有高尚情操与无私奉献精神的老一辈的医学家的指引与带领下，中国麻醉学的发展从无到有，从弱到强，逐步缩短了与世界先进国家的差距，在短短的数十年时间里取得了长足的进步与发展。作为老师的学生，我们受益于他老人家的谆谆教诲，感念于他对我们无微不至的关心与爱护，发扬光大老师的殷切寄托与厚望，成为学科发展的亲历人与见证者，心中充满了无限的感激与敬仰。

自 2005 年到迄今的十余年时间里，我们海外的学生曾数次回国看望老师与拜访科室，每一次教授都亲自接待，热情欢迎，在古朴典雅的小屋里与我们畅谈，从国家大事、家庭生活到细微小事，教授嘘寒问暖、关心备至，让我们在外漂泊的游子们感到仿佛回到了温暖的家中，无拘无束，轻松愉快。教授就像慈爱的长辈，对学生们的关爱与真情，点点滴滴，举手投足之间尽显，让人无比动容。另外一个非常令人惊讶的情景是教授的思维清晰，谈吐优雅，并且声音宏亮，中气充沛，让人难以置信教授已是 90 多岁的高龄。记得 2019 年末前去专程拜访教授，在武汉家中受到教授的热情接待，长谈数小时，教授毫无倦意，亲自搬出数十年收集收藏的摘要、手稿、照片等一一讲述给我，尤其谈到他在上世纪八十年代初前往德国杜塞多夫大学附属医院麻醉科进行访问学习的经历，教授以深厚的语言交流能力与娴熟的学术专业知识深深打动了德国大学医院的教授们，令他们刮目相看这位来自中国武汉的麻醉医生，在教授学习结束后主动提出希望建立起两家医院麻醉科的长期合作，并且愿意资助前来访问交流的中国医生，这几乎是中国麻醉届在恢

复改革开放后最早的国际合作项目之一，在随后的多年里发挥了人才培养的重要作用。另外，在上世纪九十年代，教授继续开拓国际交流的渠道并与日本麻醉学届建立起了深入的合作关系，连续多年举办“中日中青年麻醉学术会议”，为年轻麻醉医生的成长创造了良好的条件。1998 年当我站在福冈市会议大厅，远眺中华大地，心潮澎湃，没有教授这样的甘为人梯并为中国麻醉学科的发展殚精竭虑、奉献一生，又何来我们学生的成长与发展？在谈到这些往事时教授从来没有任何居功自傲与炫耀的成分，他娓娓而言，平淡朴实，铅华无尘，对所有的人物、时间、地点、事项都记得清清楚楚，明明白白 ，令人仿佛在品尝一瓶陈年的老酒，看似平常，却意犹深刻，回味无穷。

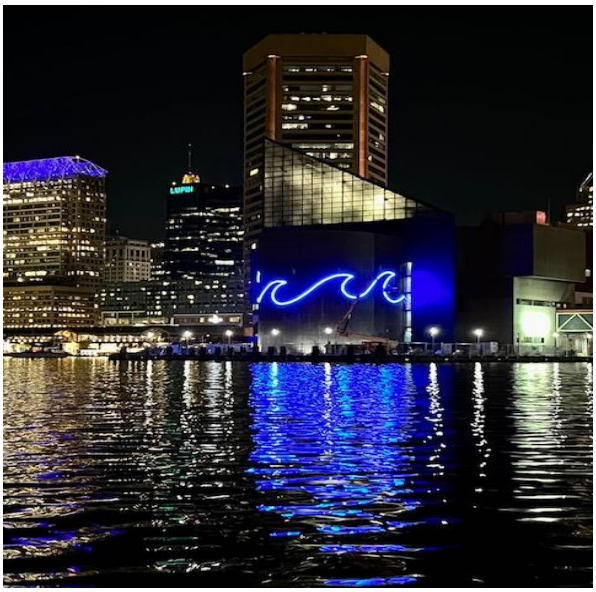
唐代韩愈曾说“师者，所以传道授业解惑也”。金教授就是这样一位忠厚的长者，慈祥和蔼、平易近人，学富五车，倾心指导帮助学生成长，一生淡泊名利，品德高尚，医德感人，实为我们最好的人生楷模。我们今天在万里之遥，谨以这样的方式，祝贺我们的老师 99 岁生日快乐，健康长寿！

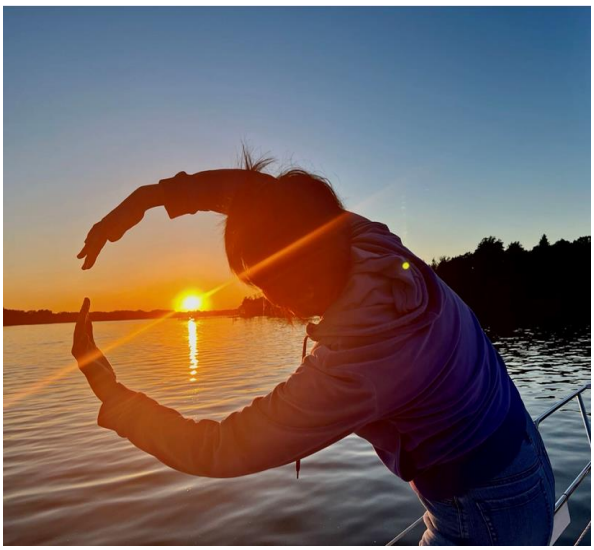
愿老师像泰山之巅的常青树，永远翠绿，永远具有强大的生命力，永远指引我们前行的道路！

碧云天，黄叶地，秋色连波，波上寒烟翠。
山映斜阳天接水，芳草无情，更在斜阳外。　　宋. 范仲淹
摄影:　鸟人　　摄影群

麻醉医生的退休生活

陶青， MD





航海后在巴尔的摩港停靠， 欣赏美丽的夜景，安排船上一周的生活必须。勇敢尝试并锻炼了胆量和意志。




清晨，初升的旭日，平静的海湾，银色的月亮，蔚蓝色的天空。咖啡，甜点，美丽的大自然，令人流连忘返。与海岸警备队的两位检查船只的帅哥们合影。

百啭千声随意移，山花红紫树高低。
始知锁向金笼听，不及林间自在啼。　　宋. 欧阳修

摄影：汪红 MD.　　CASA 华人麻醉医学会

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