# 麻醉与监护论坛

Forum of Anesthesia and Monitoring

中华医学会麻醉学分会
Chinese Society of Anesthesiology

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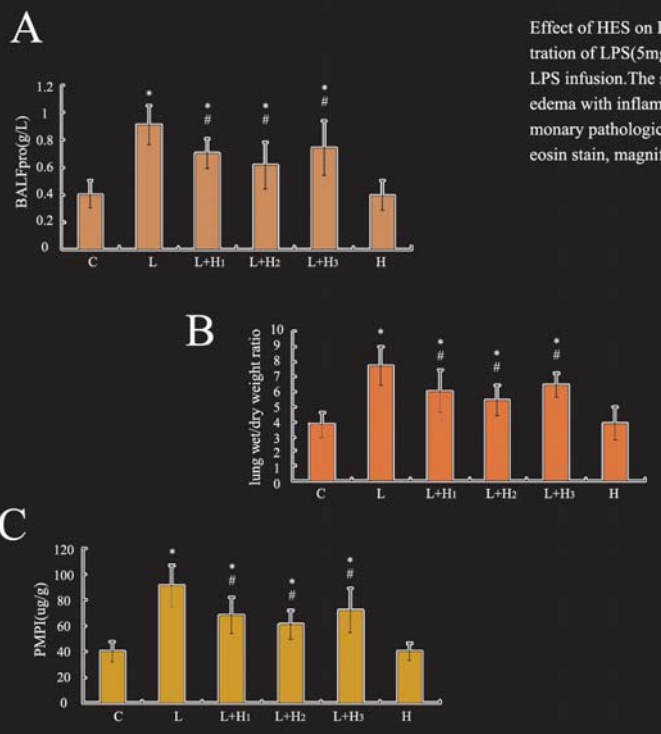
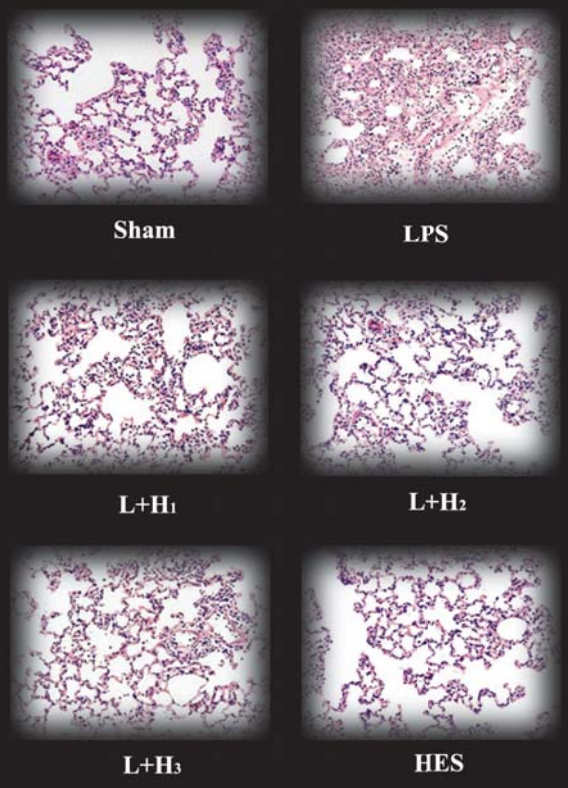



Effect of HES on LPS-induced high pulmonary capillary permeability(values of BALFpro,lung W/D ratio and PMPI) HES at three doses(7.5ml $kg^{-1}$,15ml $kg^{-1}$,30ml $kg^{-1}$)was given i.v. as an infusion 1h before administration of LPS(5mg $kg^{-1}$). BALFpro(A),lung W/D ratio(B)and PMPI(C) were assessed 4h after LPS infusion.Data represent mean ± SD.*P＜0.05 versus Sham group, # P＜0.05 L+H groups versus LPS group.

Effect of HES on LPS-induced lung injury.HES was given i.v. as an infusion 1h before administration of LPS(5mg $kg^{-1}$).Pathologcial results of lung tissue in each group was assessed 4h after LPS infusion.The slices show a normal lung tissue from the Sham group and severe alveolar edema with inflammatory infiltration in the LPS group.Pretreatment with HES mitigated the pulmonary pathological changes in three L+H groups especially in group $L+H_2$.(Hematoxylin and eosin stain, magnification 100)




This study was designed to investigate the effect of HES130/0.4 on lipopolysaccharide (LPS)-induced ALI. Experimental results shows that pretreatment with 6%HES 130/0.4 at the dose of 15ml/kg most significantly mitigated LPS-induced ALI.

*Figure related to "Effects of Hydroxyethyl Starch 130/0.4 Pretreatment on Endotoxin-induced Acute Lung Injury in Rats" by Wei Zhang,Cai Fang et al.,pp.174.*

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# 中华医学会麻醉学分会–发展愿景
# Visions of Chinese Society of Anesthesiology


***Buwei Yu. M.D., Ph.D.***

*Professor and Chairman*
*Department of Anesthesiology*
*Ruijin Hospital, Shanghai Jiaotong University School of Medicine*
*President of Chinese Society of Anesthesiology*


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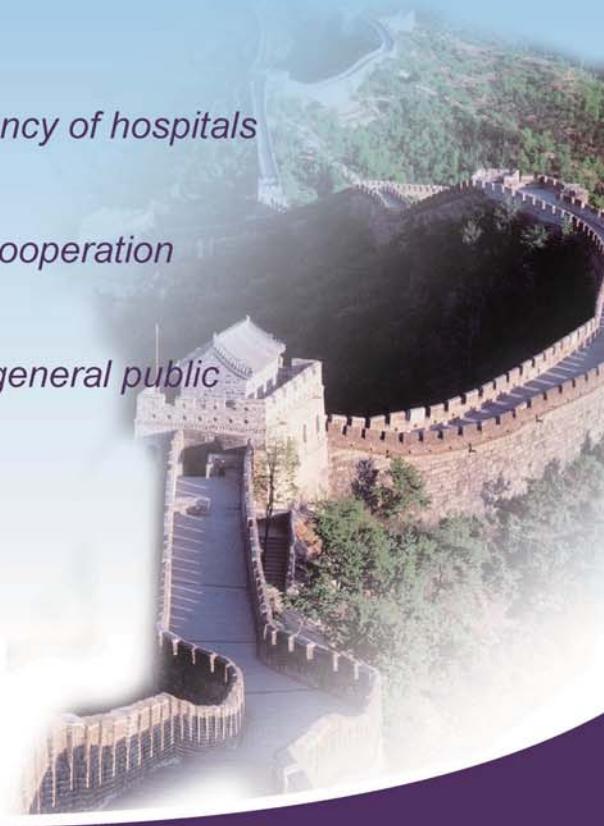

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# 《麻醉与监护论坛》
# AND MONITORING

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【适应症】

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- 蛛网膜下腔麻醉
- 区域阻滞

急性疼痛控制

- 持续硬膜外输注或间歇性单次用药，如术后或阴道分娩镇痛
- 区域阻滞

【用法用量】

| 外科手术麻醉 | 浓度(mg/ml) | 容量(ml) | 总剂量(mg) | 起效时间〔分〕 | 持续时间(小时) |
|---|---|---|---|---|---|
| 腰椎硬膜外给药外科手术 | 7.5 | 15–25 | 113–188 | 10–20 | 3–5 |
| | 10 | 15–20 | 150–200 | 10–20 | 4–6 |
| 腰椎硬膜外给药剖宫产术 | 7.5 | 15–20 | 113–150 | 10–20 | 3–5 |
| 胸椎硬膜外给药为术后镇痛建立阻滞 | 7.5 | 5–15 | 38–113 | 10–20 | n/a |
| 蛛网膜下腔给药外科手术 | 5 | 3–5 | 15–25 | 1–5 | 1–2 |
| 区域阻滞 | 7.5 | 1–30 | 7.5–225 | 1–15 | 2–6 |

| 急性疼痛控制 | 浓度(mg/ml) | 容量(ml) | 总剂量(mg) | 起效时间〔分〕 | 持续时间(小时) |
|---|---|---|---|---|---|
| 腰椎硬膜外给药单次给药量 | 2 | 10–20 | 20–40 | 10–15 | 0.5–1.5 |
| 腰椎硬膜外给药追加剂量(足量) | 2 | 10–15 | 20–30 | n/a | n/a |
| 腰椎硬膜外给药持续滴注 | 2 | 6–14ml/h | 12–28mg/h | n/a | n/a |
| 胸椎硬膜外给药持续滴注 | 2 | 4–8ml/h | 8–16mg/h | n/a | n/a |
| 区域阻滞 | 2 | 1–100 | 2–200 | 1–5 | 2–6 |

【不良反应】

临床试验中报告的大量症状多为阻滞和临床中的生理反应。神经阻滞本身的生理反应在各种局麻药均可能发生，包括硬膜外和蛛网膜下腔麻醉中的低血压和心动过缓，以及穿刺引起的不良事件(如脊髓血肿、椎管穿刺后头痛，脑膜炎及硬膜外脓肿)。

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【注意事项】

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对于有II度或III度房室传导阻滞的患者要谨慎，同时对于老年患者和伴有严重肝病、严重肾功能损害或全身状况不佳的患者，要特别注意。过量或意外注入血管会引起中枢神经系统毒性反应(惊厥、意识障碍)和/或心血管系统毒性反应(心律失常、血压下降、心肌抑制)。

(仅供医药专业人士参考,详细处方资料备索)

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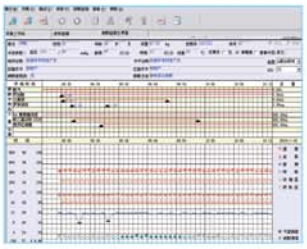



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## Review and CME Lecture



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Eight types of articles are published.

1.Clinical Investigations

2.Laboratory Investigations

3.Review Articles

4.Case Reports/Case Discussion

5.Technical Communications

6.Clinical Experience

7.Letters to the editors

8.Others (including continuing education, subject construction, comprehensive information, etc.)

## Maximum Word Allowance

1.Clinical Investigations: 3000 words ( excluding Abstract)

2.Laboratory Investigations: 3000 words ( excluding Abstract)

3.Review Articles: 4000 words

4.Case Reports/Case Discussion: 800 words

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## Arrangement of Articles

Arrange all articles in the following order.

1.Title page

2.Abstract and Key Words ( not required for all article types )

3.Body Text ( Introduction, Materials and Methods, Results, Discussion )

4.References

5.Tables ( each table should be a separate file )

6.Figures ( each figure should be a separate file) and Figure Legends

## Detailed Information

***Title Page*** ( Page 1). It includes:

1.Title

2.First name and surname of each author with his or her highest academic degree ( M.D., Ph.D., etc. ) and academic rank ( Professor, Associate Professor, etc. )

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2.Book: Barash PG, Cullen BF, Stoelting RK: Clinical Anesthesia, 3rd edition. Philadelphia, Lippincott-Raven, 1997, pp23-4

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***Abbreviations.*** Define all abbreviations except those approved by the International System of Units. Don’t create new abbreviations for drugs, procedures, experimental groups, etc.

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***Statistics.*** Detailed statistical methodology must be reported. Describe randomization procedures. Describe the specific tests used to examine each part of the results: do not simply list a series of tests. Variability should be expressed either as median ± range ( or percentiles ) for nonparametric data or mean ± standard deviation for normally distributed data.

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# *Effects of Hydroxyethyl Starch 130/0.4 Pretreatment on Endotoxin-Induced Acute Lung Injury in Rats*

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Department of Anesthesiology, Affiliated Anhui Provincial Hospital of Anhui Medical University, Hefei 230001, China.

## Abstract

***Background***: **Acute lung injury(ALI) has a high death rate reaching up to 30~40%,because of acute respiratory failure.Experimental evidence has documented the protective effect of hydroxyethyl starch(HES) 200/0.5 on ALI.HES130/0.4 is a novel preparation of colloid with the narrow molecular weight distribution.This study was designed to investigate the effect of HES130/0.4 on lipopolysaccharide(LPS)-induced ALI.**

***Materials and Methods*: Adult male Sprague-Dawley(SD) rats were randomly divided into six groups(12 rats/group): (a) Sham(saline 30ml/kg); (b) LPS alone(5mg/kg);(c,d and e) LPS(5mg/kg) plus HES (7.5ml/kg, 15ml/kg, 30ml/kg); and (f)HES alone (30ml/kg). HES130/0.4 was infused 1h before administration of LPS.Arterial blood gas,inflammation-related factors,pulmonary capillary permeability,pulmonary neutrophils infiltration and pathological examination were measured 4h after infusing LPS.**

***Results*: We demonstrated that administration LPS could provoke severe injury in lung,characterized by $PaO_2/FiO_2 \leqq 300mmHg$.Pretreatment with HES at three different doses of 7.5ml/kg, 15ml/kg, 30ml/kg respectively increased $PaO_2$ ,while reduced pulmonary neutrophils infiltration, pulmonary capillary permeability and inflammatory factors.The changes of pathology were consistent with the results above,which attenuated lung injury,whereas,administration HES alone had no influence.**

***Conclusions*: Pretreatment with 6%HES 130/0.4 at the dose of 15ml/kg most significantly mitigated LPS-induced ALI. The resultant effect might be that HES could downregulate expression of imflammatory factor,block aggregation of PMNs in lung ,reduce generation of oxygen free radicals and lower microvascluar permeability.**

***Key Words*: hydroxyethyl starch;sepsis;acute lung injury; capillary permeability;inflammatory factors**

***Corresponding Author*: Cai Fang, E-mail:doctor_fc@yahoo.com.cn**

## Introduction

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are common clinical syndromes that affect both medical and surgical patients. These two conditions are often progressive, characterized by distinct stages with different clinical, histopathologic, and radiographic manifestations. The acute or exudative phase, in which the death rate reach up to 30~40%,is manifested by the rapid onset of respiratory failure in patients with the risk factor for the aboved two conditions. Pathologic changes include diffuse alveolar damage, accompanied by neutrophils, macrophages, erythrocytes and hyaline membranes, and protein-rich edema fluid in the alveolar spaces.[1]

Hydroxyethyl starch (HES) is the most common artificial colloid in clinical use for volume replacement to maintain or improve tissue perfusion in patients with sepsis, trauma, shock, or surgical stress today. [2]Recently, experimental evidences have suggested a beneficial effect of 6% hydroxyethyl starch 200/0.5 in reducing interstitial edema due to systemic inflammatory response through various mechanisms: fluid reabsorption in the interstitium, downregulation of inflammatory mediators sustained by suppression of NF-kappa B activation, and sealing of the microcirculatory endothelial lesions ,which seems to reduce the extravascular leak of fluids and inflammatory cells.[4,5,6,7]A novel HES preparation (HES 130/0.4, 6%) has been developed showing the narrowest molecular weight

distribution of all HES specifications. It has an average molecular weight ($M_w$) of 130 kDa, a degree of substitution of 0.4, and a C2/C6 ratio of 9.[3,8] Due to its beneficially pharmacochemical properties, this new preparation used in the present study is unlikely to accumulate in plasma and tissue.

The purpose of this study is to characterize the expression level of molecular factors involved in neutrophil recruitment and sepsis in order to investigate the effect of 6%hydroxyethyl starch 130/0.4 pretreatment on ALI. We here describe the effects of hydroxyethyl starch 130/0.4 in the pretreatment of ALI induced by intravenous lipopolysaccharide(LPS) injection through measuring artery blood gas, degree of lung inflammatory response, neutrophils infiltration in lung, variables of pulmonary microvascular permeability and lung histopatholotic alterations.

## Materials and Methods

***Animals.*** Adult male Sprague-Dawley rats(220~250g body weight) were obtained from Animal Center of Anhui Medical University, Hefei, China and kept in accordance with the Institutional Animal Care Committee's guidelines.The rats were housed in an approved facility and maintained in a 12-h light/dark cycle with water and food available ad libitum before surgery.The rats were randomly assigned to six groups(12 rats/group): (a) sham (saline 30ml/kg); (b) LPS alone(5mg/kg);(c,d and e) LPS(5mg/kg,5mg/kg,5mg/kg), plus HES (7.5ml/kg, 15ml/kg, 30ml/kg); and (f)HES alone (30ml/kg). The HES(hydroxyethyl starch,medium molecular weight,low degree of substitution;HAES-steril 130/0.4,6%,Fresenius Kabi,Bad Homberg,Germany)was infused,beginning at time 0,with a rate of 0.2ml/min.Endotoxin-induced acute lung injury in rats was performed by using LPS as described previously,with minor modifications,[4] Briefly,LPS(5mg/kg,i.v.lipopolysaccharide, Escherichia coli O55:B5,sigma chemical Co,USA)was administrated over 20 seconds immediately after time 1hour. In the control and HES alone group,0.9% saline vehicle(3ml/kg,i.v.)was given instead of LPS at time 0.In the control and LPS group,30ml/kg saline was infused beginning at the same time with the same rate instead of HES.All procedures were approved by the ethics committee of Anhui Medical University.

***Experimental protocol.*** Tail veins of the rats were catheterized in order to administer different doses of HES 130/0.4,saline and LPS. The rats were anesthetized with 1% sodium pentobarbital in saline(25mg/kg,intraperitoneally,Sigma Chemical Co,St Louis,MO,USA) at 4h post-LPS challenge for $PaO_2$ and $PaCO_2$.If $PaO_2/FiO_2 \leqq 300$mmHg,it was considered that ALI model in the rats were succeeded in the experiment.Each anesthetized rat was treated with an endotracheal tube through a tracheostomey.6 rats in each group were used for pulmonary microvascular permeability index(PMPI),infusing Evans blue(Sigma co,USA).Another 6 rats in each group were used for tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-10(IL-10), maleic dialdehyde(MDA) and superoxide dismutase (SOD).The lungs were collected at 4hour post-LPS challenge for protein content of bronchoalveolar lavage fluid(BALF),wet/dry weight ratio(W/D),myeloperoxidase(MPO) analysis and pathological analyzer frozen in liquid nitrogen,and stored at -80℃.

***Arterial gas analyses.*** In all groups of anaesthetized animals at 4hourr after administrating LPS, arterial gas analyses were performed by a method with an automatic instrument (i-STAT Blood Gas Analyzer,Abbott co,USA) via femoral artery.

***Pulmonary microvascular permeability index(PMPI).*** PMPI was determined with Evans blue dye extravasation method that was described by Tian et al.[4] As briefly, 6 rats in each group were injected with 1%Evans blue(1ml/kg,Sigma co)via the jugular vein.After 15min rats were executed and their lung tissues were harvested,which were weighed and incubated with 4ml formamide at 37℃ for 24h.The dye was extracted from lung and came to the solution,which was determined with spectrophotometer at 620 nm.The total amount of Evans blue was calculated by means of the standard calibration curve and expressed as ug/mg of lung tissue.

***Plasma inflammation factor and MDA,SOD measurements.*** The blood was collected form remaining 6 rats in each group via the jugular vein and stored at -70℃ after centrifugation.

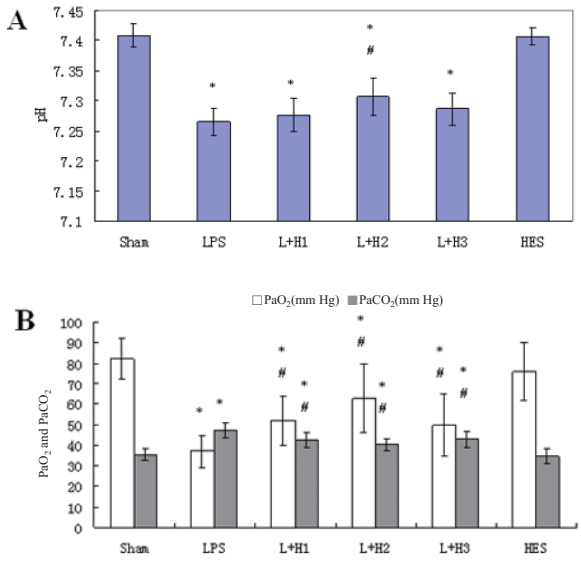


**Figure1. Effect of HES on Arterial blood gas(values of pH(A) and $PaO_2$ ,$PaCO_2$ (B)in blood).HES at three doses(7.5ml $kg^{-1}$,15ml $kg^{-1}$,30ml $kg^{-1}$)was given i.v. as an infusion 1h before administration of LPS(5mg $kg^{-1}$). pH(A) and $PaO_2$ ,$PaCO_2$ (B) were assessed 4h after LPS infusion. Data represent mean ± SD.*P＜0.05 versus Sham group, # P ＜0.05 L+H groups versus LPS group.**

Plasma TNF-α,IL-1β,IL-10 concentration were measured by enzyme-linked immunosorbance assays(ELISA)(rat TNF-α,IL-1β,IL-10 test kits, R&B co,USA) according to the specific manufacturer's instructions.MDA and SOD were quantified by the thiobarbituric acid method and the xanthine oxidase method,respectively.

***The protein content of bronchoalveolar lavage fluid(BALFpro),Lung wet/dry weight ratio and MPO assay.*** Animals were excised and their lungs were obtained immediately.Left lungs were used to lavage with normal saline at 4℃,2ml per each,totally 3 times. The bronchoalveolar lavage fluid(BALF) was collected to measured for the protein content with the methods of coomassie brilliant blue dye.Right upper lungs were weighted after excision then were measured drying weight after stoving to constant weight at 80℃ for 24h.The lung wet/dry weight ratio(W/D) was calculated.

***Pathological examination.*** Histologic sections of the right subtus lungs were stained with hematoxylin and eosin(HE) methods and examined by light microscopy for the pathological changes.

***Statistical analysis.*** Data were analyzed with a commercially available statistics software package(SPSS for windows10.0). After confirming normal distribution, the results were presented as mean ± SEM and one-factor analysis of variance(ANOVA) was used to detect differences between groups.After confirming skewed distribution, the results were presented as median ± inter-quartile range and Kruskal-Wallis test was used to compare groups

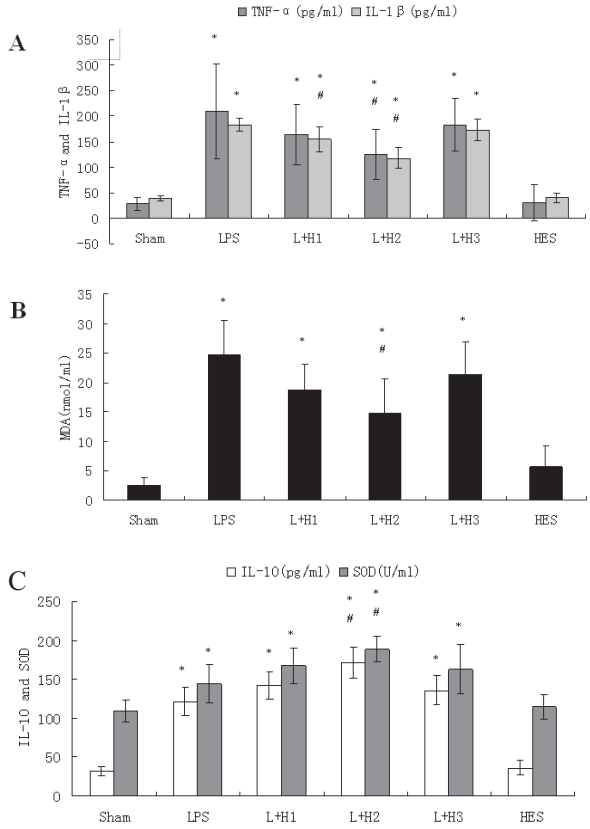


**Figure2. Effect of HES on LPS-induced systematic inflammation(values of TNF-α,IL-1β,MDA, IL-10 and SOD in serum).HES at three doses(7.5ml $kg^{-1}$,15ml $kg^{-1}$,30ml $kg^{-1}$) was given i.v. as an infusion 1h before administration of LPS(5mg $kg^{-1}$). Serum level of TNF-α,IL-1β(A),MDA (B) and IL-10,SOD(C) were assessed 4h after LPS infusion.Data represent mean ± SD.*P＜0.05 versus Sham group, # P＜0.05 L+H groups versus LPS group.**

where appropriate. P values less than 0.05 were regards as statistically significant.

## Results

***Effect of HES on Arterial blood gas.*** The basal pH,$PaO_2$ and $PaCO_2$ were 7.409±0.019, 82±10mmHg, 35.6±2.8mmHg respectively. Infusion of LPS caused a significant decrease in pH,$PaO_2$ and $PaCO_2$ (7.265±0.023, 37±8mmHg, 47.0±3.5mmHg,respectively, P＜0.05 vs.Sham group) and $PaO_2/FiO_2$≦300mmHg. Otherwise, HES at dose of 7.5ml/kg, 15ml/kg, 30ml/kg intravenous increased LPS-induced reduction of pH,$PaO_2$ and $PaCO_2$ and administration of HES at 15ml/kg was optimal one in the three doses(Figure1).Infusion HES alone did not cause any significant changes of pH,$PaO_2$ and $PaCO_2$ up to the dose of 30ml/kg(7.407±0.014, 76±14mmHg, 34.6±3.8mmHg,respectively,P>0.05 vs. Sham group).(Figure 1)

***Effect of HES on LPS-induced systematic inflammation.*** Compared to group C, serum level of TNF-α ,IL-1β ,IL-10,MDA and SOD were higher in groups L, L+$H_1$, L+$H_2$,and L+$H_3$ ,implying systemic inflammation as a resulte from LPS administration. TNF-α ,IL-1β and MDA were lower and IL-10, SOD were higher in group L+$H_2$ compared to group L. No significant difference was found between groups Sham and HES (P>0.05).(Figure 2)

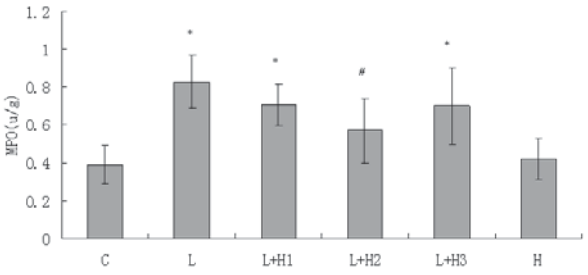


**Figure3. Effect of HES on LPS-induced neutrophils infiltration of the lung as assessed by MPO activity. HES at three doses(7.5ml $kg^{-1}$,15ml $kg^{-1}$,30ml $kg^{-1}$)was given i.v. as an infusion 1h before administration of LPS(5mg $kg^{-1}$). MPO activity in lung were assessed 4h after LPS infusion.Data represent mean ± SD.*P＜0.05 versus Sham group, # P＜0.05 L+H groups versus LPS group.**

***Effect of HES on LPS-induced neutrophils infiltration.*** As shown in fig 3,the lung levels of MPO,reflecting granulocyte infiltration,dramatically increased 4h after LPS injection compared to sham group(from sham 0.39±0.10 to 0.83±0.14u/g).the MPO response in the HES group was similar to the sham group (0.42±0.11 vs 0.39±0.10u/g) .while in three L+H groups the increase of MPO activity were attenuated significantly in response to LPS groups,especially in group L+$H_2$(0.57±0.17u/g, P＜0.05 vs. LPS and Sham groups,respectively).

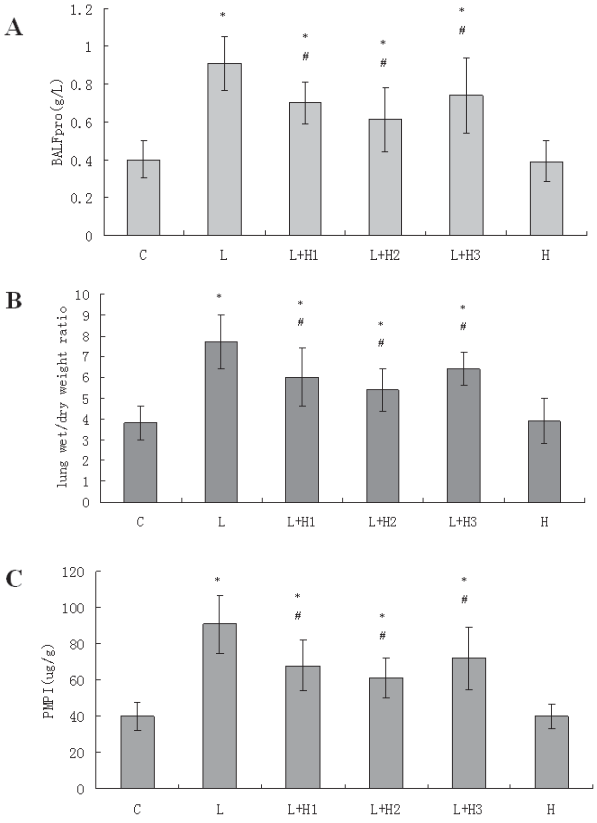


**Figure4. Effect of HES on LPS-induced high pulmonary capillary permeability(values of BALFpro,lung W/D ratio and PMPI) HES at three doses(7.5ml $kg^{-1}$,15ml $kg^{-1}$,30ml $kg^{-1}$)was given i.v. as an infusion 1h before administration of LPS(5mg $kg^{-1}$). BALFpro(A),lung W/D ratio(B)and PMPI(C) were assessed 4h after LPS infusion.Data represent mean ± SD.*P＜0.05 versus Sham group, # P＜0.05 L+H groups versus LPS group.**

***Effect of HES on LPS-induced high pulmonary capillary permeability.*** Compared to group Sham,BALFpro,Lung W/D ratio and PCPI were higher in groups LPS,L+$H_1$, L+$H_2$,and L+$H_3$,4h after LPS injection.while in three HES+LPS groups the increase of pulmonary capillary permeability was attenuated in response to LPS ,especially in group L+$H_2$(BALFpro 0.61±0.20 g/L,Lung W/D ratio 5.4±1.0 and PCPI 61±11 ug/g , $P<0.05$ vs. LPS and Sham groups,respectively).There was no difference in pulmonary capillary permeability between HES and Sham groups($P>0.05$).(Figure 4)

***Pathological examination.*** Figure 5 shows the results of the pulmonary tissues pathology assessed 4h after LPS infusion in each group. In contrast to the Sham group,thickening of interalveolar membranes(interstitial edema),impairment of alveoli,and infiltration of leukocytes were observed after LPS injection.These effects of LPS were antagonized by HES treatment to a great extent .

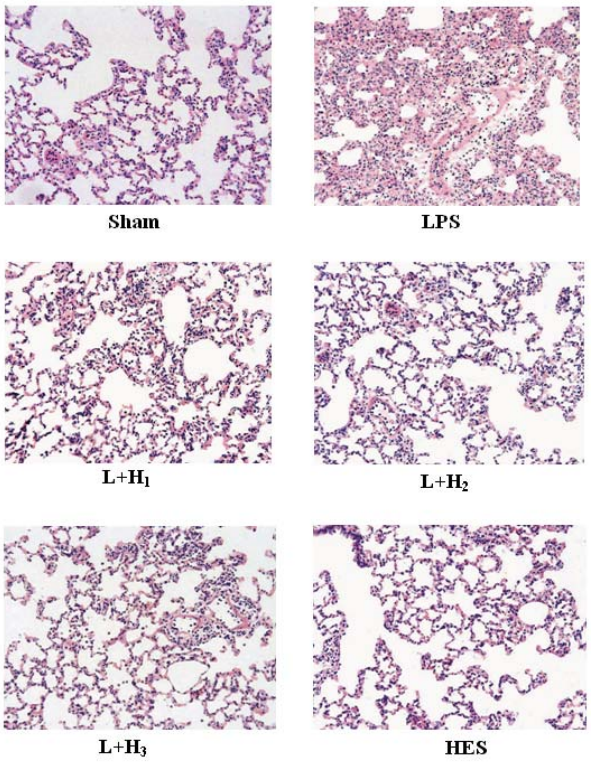


**Figure 5 Effect of HES on LPS-induced lung injury. HES was given i.v. as an infusion 1h before administration of LPS(5mg $kg^{-1}$).Pathologcial results of lung tissue in each group was assessed 4h after LPS infusion.The slices show a normal lung tissue from the Sham group and severe alveolar edema with inflammatory infiltration in the LPS group. Pretreatment with HES mitigated the pulmonary pathological changes in three L+H groups especially in group L+$H_2$. (Hematoxylin and eosin stain, magnification 100)**

## Discussion

Severe hypoxemia was the main character of ALI, the pathological changes of which were the high vascular permeability and pulmonary edema induced by non-microvascular endothelial cells injury. The ALI model of rats had been established by LPS at 5mg/kg intravenously in this study and $PaO_2/FiO_2 \leqq 300$mmHg was thought to be one of the crucial standards described previously.[9] According to the result especially the blood gas ,the rats with ALI were successfully rescued in our study.

ALI participated by pyrogen cells(most of mononuclear cells/macrophages) produce proinflammatory factors (including TNF-α ,IL-1,interferon(IFN),IL-6),which causes pyrogen effect in the body and the quantitative change of polymorphonuclear neutrophils(PMNs),provokes various acute phase reactive proteins and destroys pulmonary tissues in the end. TNF-α ,as one of initial critical proinflammatory factors, causes the systematic inflammation through the cooperation with IL-1,which has a amplified effect in the process of inflammation,as called immuno-inflammatory waterfall effect.[10]The elevation of IL-10,as one of endogenous antagonists of TNF-α ,restrains the production of proinflammatory factors and their biologic activity.[11]In this study,the values of TNF-α ,IL-1β had a significant decrease in the 3 groups of LPS+HES, particularly in LPS+$HES_2$ group(HES 15ml/kg).At the same time, the value of IL-10 increased significantly in LPS+$HES_2$ group, implying the protective mechanism of HES ,in part, restrained proinflammatory factors.

Within cellular signaling pathway, NF-κB is one of the critical transcription factors and plays an important role in the physiological or pathological processes of immunity, inflammation and stress response. The main function of NF-κB in these processes is to promote gene expression of diverse cytokines through binding to the definite sites in

DNA molecule after entering into the nucleus, and causing inflammation. Many articles have presented the protective effect of HES on LPS-related ALI by reducing the expression of NF-κB.[12,13,14]The decrease of TNF-α,IL-1β in three groups of LPS+HES may be caused by downregulation of NF-κB expression induced by HES.

The mechanism of capillary permeability syndrome in the processes of injury, shock, ischemic reperfusion or spesis is PMN aggregation and adhesion to endotheliocyte.[15]Activated PMNs that increase the permeability of capillary in lung released a great quantity of reactive oxygen species and proteinases which induced tissue injury.In ALI, PMNs aggregation in lung play a critical role in increasing capillary permeability.[16]MPO is the specific enzyme in PMNs and the quantity of the MPO in lung determines the extent of PMN aggregation. SOD , a scavenger of hyperoxide radical anion($O_2$•), protected pulmonary histiocyte in ALI. MDA, the oxidative product of cellular membrane, could reflect the damage of cellular membrane. In this study, the content of MPO in lung increased, PMNs aggregated in interstitium and the serum level of MDA increased in contrast to decreased SOD 4h after injecting LPS. Taken above, PMNs aggregation and subsequently increasing oxidative free radicals induced damage and high permeability of pulmonary capillary ,which cascadely result in ALI finally. Administration of HES could decrease the heightened levels of MPO, MDA in serum and raise the activity of SOD. Pathological examination was consistent with the results. Interestingly, group LPS+$HES_2$ had the best result, indicating administration 6%HES 130/0.4 at the dose of 15ml/kg restrained PMNs aggregation and activation, reduced the generation of oxygen free radicals, mitigated membrane lipid peroxidation and reduced pulmonary injury to the most significant degree among these 3 groups finally.

PMPI,BALFpro and W/D increased 4h after infusing LPS,impling high pulmonary capillary permeability. Pretreatment with 6%HES 130/0.4 refrained the heightening of PMPI,BALFpro,W/D,which reduced capillary permeability and pulmonary injury.On one hand,HES,a giant molecule,might have the potential to block capillary endothelial cell gaps.On the other hand,HES,which reduced expression of L-selection in PMNs,[17]could restrain adhesion between PMNs and vascular endothelicytes.

In the study, it was designed that in the three groups pretreating with HES at low,medium and high dose respectively,however,it was found that the protective effect of HES on ALI was non-dose-dependent. Tian[5]et al noted that the activity of NF-κB reduced while using HES at a high dose. Activity of NF-κB might be regulated by several kinds of pathways of mitogen-activated protein kinases. HES could activate different mitogen-activated protein kinases under different doses, which could explain the effect of HES on ALI .Deeply researches should be done for clarifing the mechanism of HES.

In conclusion, pretreatment with 6%HES 130/0.4 at the dose of 15ml/kg most significantly mitigated LPS-induced ALI. The resultant effect might be that HES could downregulate expression of imflammatory factor,block aggregation of PMNs in pulmonary,reduce generation of oxygen free radicals and lower microvascluar permeability.

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## 摘要

目的：观察神经病理性痛模型大鼠损伤侧损伤和邻近未损伤背根神经节神经元高电压激活钙电流的变化，以探讨两组神经元钙电流在大鼠神经病理性痛发病过程中的潜在作用。方法：采用SD雄性大鼠，以左侧L5脊神经结扎离断术建立神经病理性痛模型。酶消化法急性分离模型组损伤侧L5(SNL–L5组)、L4(SNL–L4组)以及正常对照组L5、L4背根神经节神经元(C组)，采用全细胞膜片钳技术记录神经元高电压激活钙电流。结果：SNL–L5组与SNL–L4组峰值钙流密度均较C组降低（P<0.05），且SNL–L5组的峰值钙电流密度亦低于SNL–L4组（P<0.05）。与C组和SNL–L4组相比，SNL–L5组钙电流半数激活电压向超级化方向移动（P<0.05），其N型钙电流比例上升(P<0.05)。三组钙电流稳态失活曲线均无显著性差异（P>0.05）。结论：神经病理性痛模型大鼠损伤背根神经节神经元高电压激活钙电流密度降低，电流激活曲线向超级化方向移动，N型$Ca^{2+}$电流比例升高，提示损伤背根神经节神经元高电压激活钙电流可能在诱发神经病理性痛的过程中起主导作用。

关键词：钙通道；神经痛；神经节，脊；神经元

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# 神经病理性痛大鼠背根神经节神经元高电压激活钙电流的变化

# Changes of High-Voltage-Activated Calcium Current in Dorsal Root Ganglion Neurons Isolated From Neuropathic Pain Rats

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## Abstract

**Objective**：We investigate the changes of high-voltage-actived (HVA) current in axotomized and neighboring intact dorsal root ganglion (DRG) neurons in a rat model of spinal nerve ligation (SNL) and the underlying contribution.

**Methods**：Pathogen-free male SD rats（weight ,180~220mg）aged 4-6 weeks were used in this study. The animals were anesthetized with intraperitoneal pentobarbital sodium 50 mg/kg. L5 spinal nerve was ligated between DRG and sciatic nerve and cut distal to the ligature. The animals were decapitated on the 14th postoperative day. L5 and L4 DRGs were respectively isolated and the neurons in the ganglion were enzymatically dissociated. The control group of rats were not accepted the surgery. The lumbar DRG neurons of this group were gained with the same method.The HVA-$Ca^{2+}$ current was recorded using whole cell patch clamp technique.

**Results**：Peak calcium current density was significantly diminished in the SNL-L5 and SNL-L4groups compared with that in the control group（P<0.05）. Compared with the SNL-L4group, the SNL-L5 group also markedly reduced peak current density (P<0.05). Half-activation value ($V_{a1/2}$) was also significantly lower in the SNL-L5 group versus in the control and SNL-L4 groups（P<0.05）. The N-type relative contribution to the total HVA-$Ca^{2+}$ current markedly elevated in the SNL-L5 group compared with that in the control and SNL-L4 groups（P<0.05）. There was no significant difference in steady-state inactivation curves among the three groups(P>0.05).

**Conclusion**：In neuropathic pain rats , the HVA-$Ca^{2+}$ cuurent of the injured DRG neurons may play a key role in inducing neuropathic pain.

**Key Words**：Calcium channels；Neuralgia；Ganglia,spinal；Neurons

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神经病理性痛是临床上常见的顽固性疼痛的综合症，其发病机制复杂，目前尚未完全阐明。在发病过程中，背根神经节(dorsal root ganglion,DRG)神经元所表达的高电压激活（high-voltage-actived，HVA)$Ca^{2+}$通道对神经元敏化的形成和维持起关键作用[1]。目前认为，脊神经结扎离断(spinal nerve tight ligation,SNL)模型中至少有两组神经元产生异位放电：损伤及邻近未损伤传入神经元。二者均被假设能诱发和维持神经病理性痛，然而关于两组神经元在发病过程中的作用及地位问题一直存有争议[2]。本研究运用全细胞膜片钳技术，以正常大鼠腰段DRG神经元为对照，观察SNL大鼠损伤及邻近未损伤DRG神经元HVA-$Ca^{2+}$电流的变化，对比研究两组神经元HVA-$Ca^{2+}$电流是否或如何参与神经

病理性痛的发生。

## 一、材料与方法

### 1. 模型制备与鉴定

健康清洁级SD雄性大鼠，年龄4～6周，体重180～220g，由南京军区南京总医院实验动物中心提供。根据Kim的方法建立大鼠左侧L5脊神经结扎离断模型[3]：腹腔注射戊巴比妥钠50mg/kg深麻醉后，在腰椎上方做皮肤切口，暴露并咬断左侧L6脊椎横突，用5-0医用丝线在靠脊柱侧结扎L5脊神经，并在远端剪断，然后逐层缝合肌肉和皮肤。于术后3，7和14天，进行后肢机械刺激回缩反应测定。机械刺激产生快速回缩为正常反应，而出现持续2s以上的抬足、甩足或舔足敏化反应特征行为时为阳性反应。每天重复测试5次，间隔3分钟，选取在3天测试中，伤害足平均阳性反应率超过20%而对侧足反应正常的SNL大鼠用于实验。

### 2. 神经元急性分离

参照Gold的方法进行DRG细胞的急性分离[4]：术后14天时，腹腔注射戊巴比妥钠50mg/kg深麻醉后，将SNL大鼠断头处死，迅速提取腰段脊柱，放入预先充好氧气的冰冻DMEM培养液（DMEM 13.4g/L，$NaHCO_3$ 3.7g/L，pH值7.2）中，分离出损伤侧L4和L5DRG，将其放入装有I型胶原蛋白酶（2mg/1ml）和I型胰蛋白酶（1.2mg/1ml）的玻璃试管中，将玻璃试管放入恒温（定温至36.5℃）水浴箱中，并通入含5%$CO_2$/95%$O_2$的混合气体。孵育25min后，用细胞外液（mmol/L：TEA-Cl 145、$MgCl_2$0.8、$CaCl_2$5、HEPES 20、D-glucose 10，Trisbase调pH值至7.3）清洗5-6遍以终止酶的消化。用吹打管吹打神经节，将制成的细胞悬液滴入35mm培养皿中，细胞自然贴壁2～3h后开始膜片钳实验。每次实验均在细胞分离后8h内完成，所有实验均在室温（22～25℃）下进行。

### 3. 实验分组

选取胞膜清晰、折光性好，表面光洁的中等大小（30～40μm）的神经节细胞进行实验，共分为三组：正常对照组（C组），SNL大鼠L5DRG组（SNL-L5组）和SNL大鼠L4DRG组（SNL-L4组）。SNL-L5组为结扎离断的L5脊神经的DRG细胞，SNL-L4组为邻近L5脊神经的L4脊神经DRG细胞。C组大鼠不进行手术，用同样方法获取其腰段DRG细胞作为对照。

### 4. $Ca^{2+}$电流记录

采用EPC-9膜片钳放大器（HEKA公司，德国）进行全细胞$Ca^{2+}$电流记录，电刺激脉冲方案和电流的记录由pulse+pulsefit程序控制完成。记录用微电极尖端直径为1～2μm，充灌电极内液（mmol/L：CsCl135，MgCl22，EGTA11，$CaCl_2$ 1，HEPES20，Mg-ATP5，Li-GTP0.4，Trisbase调pH至7.3）入液后电极阻抗为2-6MΩ。细胞破膜以及电流记录过程中的慢电容、串联电阻、系统电阻、电容电流和漏电流均自动补偿。实验过程中，选取串联电阻＜20MΩ且电流稳定的数据为有效数据。形成全细胞模式以后，在步阶电压的刺激下，得到一内向电流，此前我们的研究已证实，此内向电流即为HVA-$Ca^{2+}$电流[5]。破膜后稳定10min，给予不同的刺激方案记录$Ca^{2+}$电流。

### 5. 观察指标

(1)激活曲线：膜钳制电位为-90mV，施加一组-70mV～+40mV，以10mV递增，时程为80ms的指令电压记录激活电流，激活曲线由Boltzmann方程G/Gmax=1/{1+exp[($V_{a1/2}$-Vm)/Ka]}进行拟合，G为电导，G=I/(Vm-Vr)，I为电流，Vm为指令电压，Vr为反转电位，$V_{a1/2}$为半数激活电压，Ka为激活斜率因子；(2)电流-电压（I-V）曲线：采用激活刺激方案记录不同去极化电压的$Ca^{2+}$电流，以电流密度（电流值和细胞容积的比值）为指标作I-V曲线；(3)失活曲线：膜钳制电位为-90mV，给予-90mV刺激10ms，随后施加一组-70mV～+20mV，以10mV递增，时程为500ms的指令电压，然后给予-10mV，时程为80ms的命令电压记录失活电流。稳态失活曲线由Boltzmann方程I/Imax=1/{1+exp[(V-$V_{i1/2}$)/Ki]}进行拟合，I为电流，V为预刺激电压，$V_{i1/2}$为半数失活电压，Ki为失活斜率因子；(4)神经元各亚型HVA-$Ca^{2+}$电流比例变化：膜钳制电位-90mv，对DRG神经元先施以-10mv（或0mv），时程80ms的刺激电压引出峰值$Ca^{2+}$电流，待电流稳定后，分别加入20μmol/L硝苯地平（L型$Ca^{2+}$通道阻断剂，美国sigma公司，57h1139），2μmol/Lω-Conotoxin MVIIC（P/Q型$Ca^{2+}$通道阻断剂，美国sigma公司，017k4765）或2μmol/Lω-Conotoxin MVIIA（N型$Ca^{2+}$通道阻断剂，美国sigma公司，028k4801），再给予-10mv（或0mv），时程80ms的刺激电压记录电流。电流抑制率=($I_{加药前}$－$I_{加药后}$)/$I_{加药前}$*100%。

### 6. 统计学处理

采用Clamfit8.1和SigmaPlot10.0软件进行数据采集与处理。计量数据以均数±标准差（$\bar{x}\pm s$）表示，$V_{a1/2}$，$V_{i1/2}$，电流密度及电流比例各组间比较均采用单因素方差分析，进一步两两比较采用q检验。采用SPSS16.0软件进行数据统计学分析，P＜0.05为差异有统计学意义。

## 二、结果

### 1. 三组神经元HVA-$Ca^{2+}$电流I-V曲线的比较

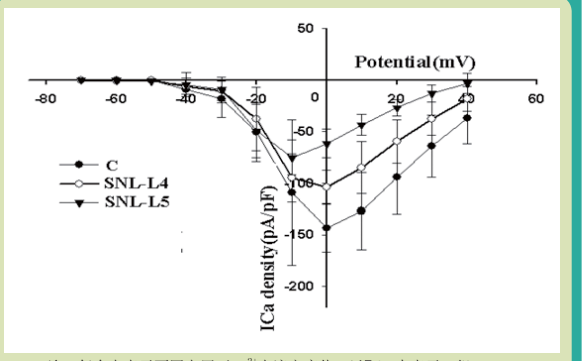
与C组HVA-$Ca^{2+}$峰电流密度值(143.6±23.7)pA/pF相比，SNL-L4组（103.5±16.6）pA/pF以及SNL-L5组（75.1±17.0）pA/pF均减低(P<0.05)，差异有统计学意义。与SNL-L4组相比，SNL-L5组时的峰电流密度进一步减小（P<0.05）。同时，HVA-$Ca^{2+}$峰值电流的激活电压C组及SNL-L4组时为0mv，SNL-L5组向超级化方向移动至-10mv,见图1。

### 2. 三组神经元HVA-$Ca^{2+}$电流激活和稳态失活曲线的比较

SNL-L5组神经元$Ca^{2+}$电流激活曲线的半数激活电压$V_{a1/2}$为（-20.7±0.3）mV，较C组（-16.2±1.9）mV与SNL-L4组的(-16.0±0.4)mV分别向超级化方向移动了4.5mV和4.7mV,差异

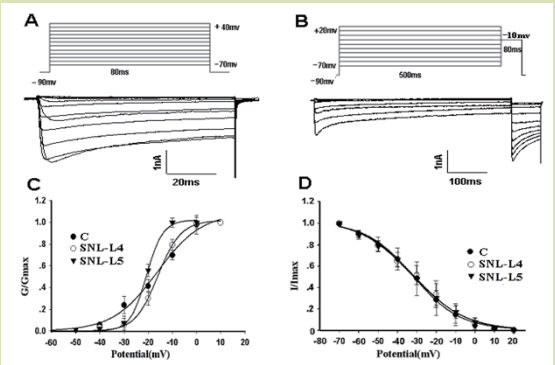
具有统计学意义(P<0.05)，而SNL-L4组与C组的$V_{a1/2}$无显著性差异(P>0.05，图2C)。三组$Ca^{2+}$电流稳态失活曲线均无显著性差异（P>0.05，图2D）。

**图1** DRG神经元HVA-$Ca^{2+}$电流I-V曲线的比较




注：每个点表示不同电压下$Ca^{2+}$电流密度值，以x±s来表示,C组n=7；SNL-L4组n=5；SNL-L5组n=8.

**图2** DRG神经元HVA-$Ca^{2+}$电流激活和稳态失活曲线

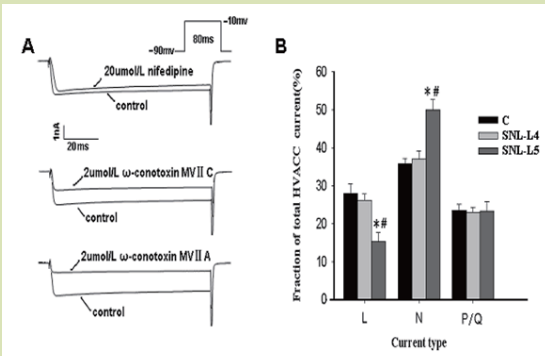



注：每个点表示相对应值的x±s.A、C：分别为按图中所示刺激方案记录到的HVA-$Ca^{2+}$激活电流和数据平均后经Blotzman方程拟合出的激活曲线（C组n=10;SNL-L4组n=5;SNL-L5组n=8.）；B、D：分别为按图中所示刺激方案记录到的HVA-$Ca^{2+}$失活电流和数据平均后经Blotzman方程拟合出的失活曲线（C组n=6组;SNL-L4组n=6;SNL-L5组n=7.）

### 3. 三组神经元中各型HVA-$Ca^{2+}$电流比例的比较

加入20μmol/L硝苯地平，2μmol/Lω-Conotoxin MVIIC或2μmol/Lω-Conotoxin MVIIA后，SNL-L5组DRG神经元峰值电流的抑制率分别为(15.4±2.3)%，(23.4±2.4)%和（50.0±2.7）%,此即代表SNL-L5组中L、P/Q和N型$Ca^{2+}$电流占总HVA-$Ca^{2+}$电流的比例（图3A）。C组及SNL-L4组L、P/Q、N型$Ca^{2+}$电流比例分别为：(27.9±2.5)%、(23.5±1.6)%、(35.9±1.4)%和(26.1±1.8)%、(22.9±1.3)%和(37.1±2.0)%。与C组及SNL-L4组相比，SNL-L5组N型$Ca^{2+}$电流比例均升高(P<0.05)，L型$Ca^{2+}$电流比例均下降(P<0.05)，差异有统计学意义。三组P/Q$Ca^{2+}$电流比例均无显著性差异(P>0.05)。在C和SNL-L4两组中，三型$Ca^{2+}$电流比例的变化均无显著性差异(P>0.05)，见图3B。

**图3** DRG神经元中三型HVA-$Ca^{2+}$电流比例




注：A:膜钳制电位为-90mv,对SNL-L5组DRG神经元施以-10mv时程80ms的刺激电压引出$Ca^{2+}$电流(control)，待电流稳定后，分别加入20umol/L硝苯地平,2umol/Lω-Conotoxin MVIIC或2umol/Lω-Conotoxin MVIIA，再施一相同刺激后电流的变化情况；B：C，SNL-L4，SNL-L5三组中，各亚型$Ca^{2+}$电流占总HVA-$Ca^{2+}$峰电流比例的变化情况。与C组比较，*P<0.05;与SNL-L4比较，#P<0.05（每根条形表示亚型$Ca^{2+}$电流占总HVA-$Ca^{2+}$峰电流的百分比，以x±s表示，n=10）

## 讨论

神经损伤所引起的DRG神经元功能的紊乱是导致神经病理性痛发病的重要原因。有研究表明，SNL后损伤侧L4和L5 DRG神经元膜电生理特性明显不同[6]。本研究所采用的SNL模型是模拟临床神经病理性痛的经典模型，SNL损伤大鼠表现为长时程的痛觉过敏和机械性痛觉超敏。该模型的优点是损伤变异程度小，动物个体间的差异仅来自于动物生物学变异，尽可能排除了实验误差。同时，可以将损伤与邻近未损伤DRG从解剖学上完全分开，有利于比较在神经病理性痛中，两组神经元HVA-$Ca^{2+}$电流变化的异同。

本研究结果表明，神经病理性痛模型大鼠损伤和邻近未损伤DRG神经元HVA-$Ca^{2+}$峰电流密度均较正常神经元降低，且与邻近未损伤神经元相比，损伤神经元峰电流密度进一步降低。$Ca^{2+}$通过VDCCs内流的一个重要功能就是调节钙激活钾通道（calcium-dependent potassium channels，$K_{Ca}$)的功能。$K_{Ca}$是调节神经元活性的关键离子通道，该通道开放的减少可导致神经元兴奋性增高。Hogan等的研究已证明，SNL损伤引起的损伤DRG神经元$Ca^{2+}$电流的降低可减少$K_{Ca}$电流，$K_{Ca}$电流的减少可引起膜后超级化幅度和持续时间的减少，最终导致神经元兴奋性增高和神经病理性痛的产生[7]。因此，损伤和邻近未损伤DRG神经元$Ca^{2+}$峰电流密度的降低提示在SNL损伤后，两组DRG神经元兴奋性均增高，这可能是诱发神经病理性痛的原因之一。本研究中，与正常和邻近未损伤神经元相比，损伤DRG神经元HVA-$Ca^{2+}$峰电流的电压值向超级化方向移动了10mV，且其半数激活电压$V_{a1/2}$亦向超级化方向移动，表明SNL损伤引起损伤DRG神经元HVA-$Ca^{2+}$激活阈值降低，更易

激活。

脊神经损伤可引起脊髓背角和DRG神经元上VDCCs重要辅助亚基$\alpha_2\delta$表达增多，后者可促进神经病理性痛的发生[8-10]。$\alpha_2\delta$可通过对核心亚基$\alpha_1$的调节来影响$Ca^{2+}$内流。此外，$\alpha_2\delta$亚基与其他亚基的共表达可加速VDCCs的激活，并使其电流-电压关系向超级化方向移动。因此，损伤DRG神经元激活曲线的改变可能与脊神经损伤后DRG神经元上$\alpha_2\delta$表达增多有关。Li等的研究也发现，与正常小鼠相比，高表达$\alpha_2\delta$的转基因小鼠DRG神经元VDCCs电流的激活曲线向超级化方向移动[8]。损伤DRG神经元的激活曲线向超级化方向移动，稳态失活曲线未移动，提示窗口电流增大，$Ca^{2+}$内向电流应增多，然而我们记录到的HVA-$Ca^{2+}$电流却是降低的；同时，邻近未损伤神经元激活和失活曲线均无明显变化，表示其窗口电流未发生变化，但记录到的HVA-$Ca^{2+}$电流亦是降低的，此表明HVA-$Ca^{2+}$通道激活动力学和失活动力学的变化可能不是导致神经病理性痛大鼠DRG神经元HVA-$Ca^{2+}$电流降低的原因。

本研究结果显示，与正常和邻近未损伤神经元相比，损伤DRG神经元HVA-$Ca^{2+}$电流比例变化表现为L型$Ca^{2+}$电流比例下降，N型$Ca^{2+}$电流比例升高，而正常与邻近未损伤DRG神经元的各亚型HVA-$Ca^{2+}$电流比例则无显著性差异。目前认为，N型$Ca^{2+}$通道与疼痛的关系最为密切，被公认为是镇痛的首选靶点。Yang等在小鼠部分坐骨神经结扎模型[11]以及Matthews等在大鼠SNL模型[12]中均发现DRG神经元N型$Ca^{2+}$电流比例升高。这些结果均提示，N型$Ca^{2+}$通道可能在神经病理性痛的发生及维持中占主导作用。有研究表明，在大鼠神经病理性痛模型中L型$Ca^{2+}$通道mRNA表达降低，而N型$Ca^{2+}$通道mRNA的表达无明显变化[13]，因此我们推测，损伤神经元上亚型$Ca^{2+}$电流比例的改变可能与SNL损伤后DRG上各型$Ca^{2+}$通道密度的变化有关。

邻近未损伤传入神经元在神经病理性痛的发病过程中可能发挥了重要作用[14,15]。本研究发现，与正常神经元相比，邻近未损伤DRG神经元仅$Ca^{2+}$电流密度是降低的，提示其神经元兴奋性是增高的。邻近未损伤DRG神经元兴奋性的增高可能促进了SNL损伤后痛觉过敏和异常性疼痛的发生[16]。此外，我们发现，在SNL损伤后，损伤与邻近未损伤DRG神经元HVA-$Ca^{2+}$电流特性的变化并不一致，这可能是两组神经元在SNL损伤后遭受了不同病理损伤的结果。目前认为，SNL损伤后，损伤神经元的轴突残端可发生变质退化，释放大量细胞因子和炎性介质，这些炎性反应物作为刺激源可引起邻近未损伤神经元的激活和过度兴奋，从而导致邻近未损伤神经元离子通道分布和活性状态的改变，而损伤神经元电生理特性的改变可能主要是由SNL直接损伤所引起[2]。

在本实验条件下，神经病理性痛模型大鼠损伤DRG神经元HVA-$Ca^{2+}$电流密度降低，电流激活曲线向超级化方向移动，其$Ca^{2+}$电流中与疼痛密切相关的N型$Ca^{2+}$电流比例升高，而邻近未损伤DRG神经元仅HVA-$Ca^{2+}$电流密度降低。这些变化提示，损伤DRG神经元HVA-$Ca^{2+}$电流可能在诱发神经病理性痛的过程中起主导作用。

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## 2010年中华医学会麻醉学分会疼痛医学年会

为了加强可视化技术在麻醉镇痛与危重急救领域中的应用，加强国内外临床疼痛诊断、治疗、管理与学科建设的学术交流与合作，增进涉及临床疼痛的各专业医师之间的互相了解，由中华医学会麻醉学分会主办，四川大学华西医院承办的2010年中华医学麻醉学分会疼痛医学年会暨可视化技术在麻醉镇痛与危重急救中的应用大会将于2010年8月12～15日在四川成都召开。届时大会将邀请J. Clinical Pain和Pain Medicine主编、加拿大、西班牙及香港的专家作大会主题演讲，同时将邀请国内知名疼痛学和麻醉学专家做专题学术报告。

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## 摘要

目的：探讨七氟醚预处理对右肝癌切除患者肝脏缺血再灌注损伤的保护作用及其机制。

方法：择期全麻下行右肝癌手术切除患者40例，ASA Ⅰ或Ⅱ级，术中经第一肝门阻断，血流阻断时间10～30min，随机分为2组（n=20）：缺血再灌注组（IR组）和七氟醚预处理组（S组）。两组麻醉维持期间均保持脑电双频谱指数40～50。S组麻醉诱导后吸入1MAC七氟醚（呼气末浓度），30min后洗脱15min。于麻醉诱导前（T0）、缺血再灌注即刻（T1）、1h（T2）、6h（T3）抽血测血清中谷丙转氨酶（ALT）、谷草转氨酶（AST）、乳酸脱氢酶（LDH）的含量以及肝脏组织匀浆中丙二醛（MDA）含量和超氧化物岐化酶（SOD）活性，并行肝组织病理学观察。

结果：与麻醉诱导前比较，两组缺血再灌注即刻、1h、6h血清ALT、AST、LDH含量均显著增加（P＜0.05）；与IR组比较，S组肝脏缺血再灌注后相应各时点血清ALT、AST、LDH含量均降低，肝组织匀浆MDA含量减少，SOD活性增加（P＜0.05）；肝组织病理学损伤减轻。

结论：七氟醚预处理对右肝癌切除患者肝脏缺血再灌注损伤有保护作用，可能与其抑制氧自由基生成，减少脂质过氧化有关。

关键词：七氟醚；肝脏；缺血再灌注损伤；最低肺泡有效浓度

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# 七氟醚预处理对右肝癌切除患者肝脏缺血再灌注损伤的保护作用

# Protective Effects of Sevoflurane Preconditioning on the Right Liver Cancer Ischemia Reperfusion Injury

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## Abstract

**Objective**:To investigate the protection and mechanism of sevoflurane preconditioning on right liver cancer ischemia reperfusion injury.

**Methods**:Forty ASA I or II patients for right liver cancer operation in the technique blocks after the first liver gate,hepatic inflow occlusion time 10～30min, were allocated randomly into 2 group (n=20):ischemia reperfusion group (group IR) ,sevoflurane preconditioning group (group S). During maintenance of anesthesia, BIS value was maintained at 40-50 in both groups. In group S patients inhales 1MAC sevoflurane for 30 min followed by 15 min of wash-out after induction of anestheia. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) were determined before induction of anestheia(T0) ,immediated ischemia-reperfusion（T1）,at 1h （T2）and 6h（T3）after ischemia-reperfusion. Superoxide dismutase (SOD) activities and malondialdehyde (MDA) content in liver tissue were measured,and histopathological changes of liver were determined.

**Results**:As compared to before induction of anestheia, the levels of serum ALT, AST, and LDH in both groups immediated ischemia-reperfusion,at 1h and 6h after ischemia-reperfusion were significantly higher; As compared to those of IR group, the serum levels of ALT,AST,LDH, and the content of MDA in liver tissue of the S group were lower, and the content of SOD was higher(P <0.05),the abnormal changesof themorphology of hepatocyte in the S group were reduced.

**Conclusion**:Sevoflurane preconditioning can protect right liver caner from ischemia and reperfusion injury. The protective mechanisms maybe related to reduceing the release of oxyradical and inhibiting the lipid peroxidation.

**Key Words**：Sevoflurane；Liver；Ischemia -reperfusion injury；Minimal alveolar concentration

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肝脏缺血再灌注损伤(hepatic ischemia andeperfusion injury, HIRI) 是临床广泛关注的问题，肝切除、肝外伤、出血性休克和肝移植等均可引起HIRI，它直接影响到疾病的预后、手术成功率和病人存活率[1]。因此，如何预防或减轻HIRI具有重要的临床意义。七氟醚是一种新型的吸入麻醉药，已广泛应用于临床麻醉，最近研究显示七氟醚预处理对心、脑、肾、肺的缺血再灌注损伤有保护作用，并且揭示了部分的作用机制[2-4]，但对HIRI的影响研究较少。本研究探

讨七氟醚预处理对右肝癌切除患者HIRI的保护作用。

## 一、材料与方法

### 1. 病例资料

本研究经本院伦理委员会批准和患者的知情同意。拟在全麻下择期行右肝癌切除患者40例，ASAI或II级，术中均行第一肝门阻断，阻断时间10～30min。随机分为2组（n＝20）:缺血再灌注（IR组）和七氟醚预处理组（S组）。心、肺、肾功能未见明显异常，肝功能Child-Pugh分级均为A级，肿瘤直径1.5cm～8.0cm，所有患者经病理诊断证实为原发性肝细胞性肝癌。对于术中未进行肝门阻断、阻断时间在10min内、重复多次阻断肝门累计总时间超过60min、出血总量超过1500ml的患者，均予以剔除，不计在入选范围内。

### 2. 麻醉方法与术中管理

术前常规禁食6h，禁水2h。麻醉前30min肌肉注射咪达唑仑2mg和盐酸戊乙奎醚0.5mg。入室后开放静脉通路，常规监测心电图、平均动脉压（MAP）、脉搏血氧饱和度和脑电双频谱指数（BIS）。麻醉诱导：静脉注射咪达唑仑0.08～0.1mg/kg，依托咪酯0.2～0.3mg/kg，芬太尼8～10μg/kg及罗库溴铵0.6～0.8mg/kg，气管插管后行间歇正压机械通气，潮气量8～10ml/kg，呼吸频率12次/min，吸呼比1:1.5，氧流量2L/min，维持呼气末二氧化碳30～35mmHg（1mmHg＝0.133kpa）。左侧桡动脉穿刺置管用于监测MAP，右侧颈内静脉穿刺置管用于采血。麻醉维持：静脉输注异丙酚50～100ug·$kg^{-1}$.$min^{-1}$和瑞芬太尼0.1μg·$kg^{-1}$·$min^{-1}$，间歇静脉注射维库溴铵0.04mg/kg。S组麻醉诱导后吸入1MAC七氟醚，30min后洗脱15min。术中静脉输注乳酸钠林格液和羟乙基淀粉130/0.4氯化钠注射液10～12ml·$kg^{-1}$·$h^{-1}$，补充失血和失液量，晶胶比1：1，间断行血气分析，Hb＜80g/L或Hct＜24%时，输红细胞悬液。

### 3. 标本采集及检测方法

分别于麻醉诱导前（T0）、再灌注即刻（T1）、1h（T2）、6h（T3），右侧颈内静脉取血样，3500r/min离心15min，取上清，采用AU2700型全自动生化分析仪（Olympus公司，日本）测定血清谷丙转氨酶（ALT）、谷草转氨酶（AST）、乳酸脱氢酶（LDH）的含量。于再灌注1h取右肝组织约5g，分成两份，－20℃保存备用。一份冰浴中制成10%匀浆，4℃3500r/min离心10min，取上清，再用生理盐水按1：9稀释成1%组织匀浆，采用比色法测定丙二醛（MDA）含量，采用黄嘌呤氧化酶法测定超氧化物歧化酶的（SOD）活性（试剂盒均购自南京建成生物工程研究所）；另一份用10%甲醛固定石蜡包埋，4μm切片，HE染色，光镜下观察肝组织形态学改变。

### 4. 统计学处理

采用SPSS13.0统计软件包进行处理，计量资料以均数±标准差（$\bar{x}$±S）表示，方差齐时，组间比较用单因素方差分析，方差不齐时，组间比较采用F’检验。

## 二、结果

**1. 两组患者一般情况各指标、肿瘤直径、肝门阻断时间、出血量及手术时间比较差异无统计学意义**（P＞0.05），见表1。

**表1** 两组患者一般情况各指标、肿瘤直径、肝门阻断时间、出血量及手术时间的比较（n＝20）

| 组别 | 年龄（岁） | 性别构成（男/女，例） | 体重（kg） | 肿瘤直径（cm） | 肝门阻断时间(min) | 出血量（ml） | 手术时间（min） |
|---|---|---|---|---|---|---|---|
| IR组 | 54±11 | 16/4 | 65±9 | 4.3±1.8 | 19±6 | 425±27 | 132.3±21.2 |
| S组 | 49±13 | 15/5 | 67±11 | 4.5±1.6 | 20±7 | 436±19 | 138.6±19.2 |

### 2. 血清酶、SOD和MDA的变化

与麻醉诱导前比较（T0），两组缺血再灌注即刻（T1）、1h（T2）、6h（T3）血清ALT、AST、LDH含量均显著增加（P＜0.05）。S组与IR组比较，肝脏缺血再灌注后相应各时点ALT、AST、LDH含量均降低（P＜0.05）；肝组织匀浆MDA含量减少、SOD活性增加（P＜0.05），见表2、3。

**表2** 两组不同时相血清ALT、AST、LDH的含量（n＝20，IU/L）

| 组别 | T0 | T1 | T2 | T3 |
|---|---|---|---|---|
| ALT | | | | |
| IR | 49.57±1.62 | 73.03±3.34* | 105.64±9.69* | 141.73±12.42* |
| S | 50.4±3.44 | 65.77±2.23*# | 90.41±4.33*# | 114.08±9.38*# |
| AST | | | | |
| IR | 39.41±4.5 | 64.29±4.38* | 89.24±7.43* | 128.84±15.75* |
| S | 39.42±5.12 | 52.53±5.94*# | 69.63±4.61*# | 100.38±6.99*# |
| LDH | | | | |
| IR | 173.44±43.39 | 685.53±73.43* | 1049.94±145.52* | 1270.52±158.95* |
| S | 170.74±45.98 | 473.62±73.24*# | 552.24±82.54*# | 814.32±112.35*# |

与T0组比较，*P<0.05；与IR组比较，#P<0.05

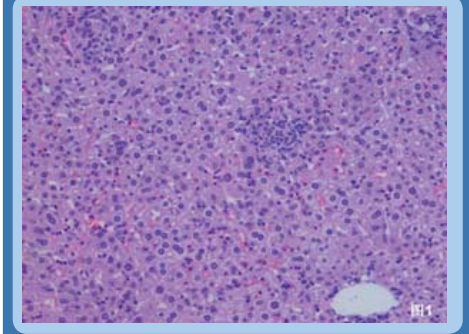
**表3** 缺血再灌注1h肝组织SOD活性、MDA含量（n＝20）

| 组别 | SOD(NU/mg) | MDA(nmol/ml) |
|---|---|---|
| IR | 35.12±3.74 | 38.48±4.33 |
| S | 51.59±4.12 | 26.80±5.07 |

### 3. 肝组织病理学改变

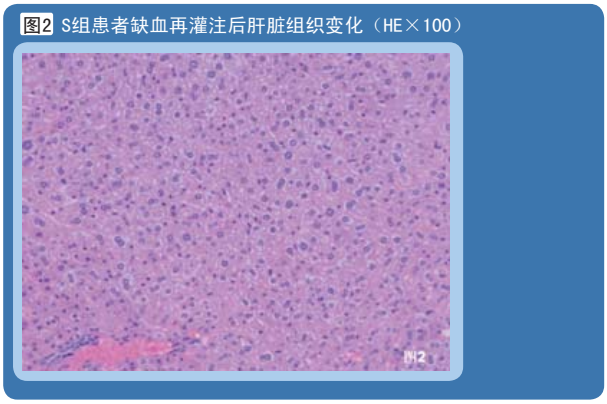
光镜下可见，IR组肝细胞肿胀，肝窦扩张，有大量红细

**图1** IR组患者缺血再灌注后肝脏组织变化（HE×100）



胞淤积，可见水肿变性和点状坏死，有大量炎性细胞浸润（图1）；S组肝组织结构尚清楚，肝细胞轻、中度水肿，少量炎性细胞浸润，但其程度和范围明显小于IR组（图2）。

图2 S组患者缺血再灌注后肝脏组织变化（HE×100）



## 三、讨论

肝脏缺血再灌注是外科常见的病理生理过程，可导致肝脏组织坏死、细胞凋亡、肝功能下降甚至衰竭[1]。最近研究[4]显示在使用七氟醚等吸入性麻醉药后，肝脏缺血再灌注损伤减轻,体现在各肝细胞酶指标明显下降,提示吸入性麻醉药可能具有肝保护作用。研究结果表明,与麻醉前比较，两组于缺血再灌注后各时点ALT、AST和LDH水平明显升高,表明随着肝缺血再灌注的发生，肝细胞功能受到严重损害；但S组与IR组相比，缺血再灌注后各时点ALT、AST和LDH水平明显下降，提示七氟醚预处理对缺血再灌注的肝细胞有保护作用。在本研究中，我们仅选择了1MAC的七氟醚吸入，主要是考虑这一剂量范围具有临床相关性，而更高浓度的吸入虽有可能进一步增强其效果[6]，但随之带来的不良反应也相应增加[7]。

HIRI的发生机制复杂，受多种因素影响。氧自由基急剧升高及其引发的脂质过氧化反应是主要影响因素[6]。肝脏缺血再灌注时，机体通过多种途径产生大量氧自由基，引起细胞生物膜不饱和脂肪酸发生脂质过氧化反应，导致机体组织损伤，而超氧化物歧化酶(Super－oxide dismutase，SOD)则能清除氧自由基，保护细胞免受损伤，对机体的氧化与抗氧化平衡起着至关重要的作用[6]。丙二醛 (malondialdehyde,MDA)是自由基攻击生物膜引发的脂质过氧化反应产物，组织中的含量可反映脂质过氧化程度，间接地反映出细胞受自由基攻击和损伤的程度[8]。本研究IR组SOD显著降低而MDA显著升高亦证明了这一点；与IR组比较，S组SOD升高而MDA降低，说明临床麻醉剂量的七氟醚预处理能减轻肝脏缺血再灌注中氧自由基介导的组织脂质过氧化反应，这可能是七氟醚预处理减轻HIRI的机制之一。

本研究结果表明，七氟醚预处理对于HIRI有一定的保护作用，这可能是通过抑制氧自由基生成，减少脂质过氧化来实现的，对于七氟醚预处理使用最佳浓度以及其保护机制还有待于进一步研究。此外，本研究只观察了七氟烷预处理对再灌注后1h、6h时间点的结果，而对更长时间再灌注（再灌注晚期）损伤的影响仍需进一步探讨。

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## 第八届全国麻醉学新进展学术会议暨学习班

中华医学会批准，由中华医学杂志英文版编辑部（国内唯一被SCI核心版收录的综合性医学期刊）和中华医学电子音像出版社培训部联合上海瑞金医院以及北京协和医院、江西省医学院第一附属医院等共同主办的“第八届全国麻醉学新进展学术会议暨学习班”，邀请国内知名的麻醉学专家莅临授课会议，定于2010年7月9—13日在江西省井冈山市召开。本次会议的宗旨是务实、互动，它将是一个前沿的、务实的、内容丰富的会议，以全面提高学员的临床诊治水平为宗旨，进行全面系统地讲授，通过学习，可以使大家开阔思路、解决问题，对麻醉科新的理念、新的技术有一个全面的了解和掌握。相信通过本次大会，与会代表必将受益匪浅，满载而归。

我们真诚地邀请您能莅临本次盛会，推动我国麻醉学科事业的发展做出贡献！本次会议可授予国家级Ⅰ类继续医学教育学分10分，项目编号：2010－04－11－093（国）。欢迎广大麻醉科正副主任、医疗骨干及相关人员积极参会。

会议报名处：中华医学会电话：010－85158757、85158758，邮箱：jixiacao@yahoo.com.cn，联系人：曹继霞，严正

朱倩林 罗艳 薛庆生 张富军 于布为*

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## 摘要

背景：术中知晓和术后认知功能障碍是困扰麻醉医师的棘手问题。以往多认为与全身麻醉药物对神经系统的影响有关。但近来不断有实验研究证实，低浓度吸入麻醉气体在特定环境下反而会兴奋大脑功能，甚至产生脑保护的作用。显然全麻药物对大脑认知功能的影响机制仍未明瞭。全身麻醉药物七氟醚已广泛应用于各类临床手术，其对哺乳类动物中枢神经系统是否及如何产生影响是我们一直在探讨的课题。细胞骨架蛋白ARC可在大脑海马结构大量表达，已证实可依据其表达情况来考察神经元的活性，以及突触可塑性的变化。目前认为其表达程度可作为检测学习记忆形成的指标。近来有学者发现，较低浓度的七氟醚可引发中枢神经兴奋现象，并猜测亚麻醉剂量对于中枢神经系统具潜在保护作用。为进一步证实这一现象，本研究拟结合ARC蛋白和抑制性逃避（inhibitory avoidance，IA）这一行为学实验来进行深入探讨。方法：250～300g雄性SD大鼠随机分为3组：空白组、极低浓度七氟醚吸入组（0.11%SEV）和低浓度七氟醚吸入组（0.3%SEV）。依据分组依次将大鼠安置于连接有低流量（0.5L/min）闭合环路吸入麻醉系统的特制容器内，分别给予吸入空气、0.11%SEV（0.05MAC）和0.3%SEV（0.14MAC）各45min。结束后马上进行单次IA训练（0.4mA，2s），24小时后进行IA记忆（潜伏期）检测。另取一批大鼠在IA初次训练后45min处死取材，以Western-blotting方法检测脑内海马ARC蛋白的表达水平，以real-time PCR方法检测ARC的mRNA转录水平。结果：与吸入空气组相比，0.11%SEV组的24小时IA记忆潜伏期明显延长，而0.3%SEV组的24小时IA记忆潜伏期缩短；相应地，0.11%SEV组的海马ARC蛋白表达增加，而0.3%SEV组ARC蛋白的表达减少。但ARC的mRNA水平却始终无显著差异。结论：吸入不同浓度的七氟醚能对大鼠的学习记忆能力产生双相作用，这种现象伴有海马蛋白ARC表达的相应改变，却没有相应mRNA水平的改变。提示全麻药物七氟醚对于记忆的双向调节存在即可早期基因如ARC对神经元突触可塑性的作用，但这种干预可能体现在转录后水平。

关键词：七氟醚；ARC；海马；抑制性逃避；学习记忆

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# 不同浓度七氟醚可双向调节大鼠学习记忆及海马ARC蛋白表达

## Sevoflurane Inhalation at Different Dosage Regulate Hippocampal ARC Protein Expression and Memory Formation Bidirectionally

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## Abstract

**Background**: Central nervous system (CNS) disorder such as intra-operative awareness and post operative cognitive dysfunction are major concerns of anesthesiologists, general anesthetics have been discovered to have controversial impact on CNS. Studies showed that low dose of inhalational gas may excite the brain function in specialized environment, this is much different from their negative effect at clinical dosage and therefore the exact modulating mechanism is still unclear. Sevoflurane is widely applied in routine operation room work, so how this agent affect the CNS is becoming a popular topic. Activity-regulated cytoskeleton protein (Arc) can be fastly expressed in hippocampus, and evidence has shown that it is a powerful factor for investigating the activity of neuronal work, even the modulation of synaptic plasticity. Recently, researchers have discovered that lower dose sevoflurane would have neuronal excitatory effect in CNS, and thus proposing that certain subanesthetic dose of sevoflurane can display a memory enhancing phenomenon. To further investigate it, we conducted the following study by associating Arc protein expression and “inhibitory avoidance” (IA) behavioral training.

**Methods**:250~300g, male SD rats were randomly assigned into three groups: sham group, 0.11% SEV group and 0.3% SEV group. Anesthesia was given by target dosage of sevoflurane for 45min and IA training (0.4mA，2s) was given to every subject immediately after inhalation. The memory retention latency was observed 24hs after. Another serial of rats were killed for hippocampal tissue after first IA training, both western-blotting and real-time PCR for Arc

mRNA level were applied.

**Results**: Statistical difference of the 24-h inhibitory avoidance memory retention performance was compared among groups. 0.11% SEV group displayed a significant elevation of memory retention while 0.3% SEV group showed descendent of memory retention, both compared with the sham (air) group. PCR analysis of relative Arc mRNA levels showed that subanesthetic doses of sevoflurane inhalation did not change Arc transcription level, when compared to sham group. 0.11% sevoflurane significantly increased Arc protein in the hippocampus, while 0.3% sevoflurane reversed this phenomenon and even suppress the Arc expression (* P < 0.05, compared with the sham group).

**Conclusion**: Inhalation of different subanesthetic dosage of sevoflurane have bidirectional regulation on rat's learning and memory function. Arc protein level varies according to this regulation while Arc mRNA level keeps still. This demonstrates that hippocampal ARC protein expression influences the sevoflurane induced bidirectional regulation of memory, potentially in a posttranslational level.

**Key Words**: Sevoflurane；ARC；Hippocampus；Inhibition Escape；Learning and memory

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大量研究证明吸入性全身麻醉药在达到0.3的最小肺泡浓度（MAC）时即可抑制哺乳动物的学习能力并产生遗忘效应[1-7]。Gorski[8]等人更通过逃避性抑制（Inhibitory avoidance, IA）这项检测大鼠学习记忆能力的实验得出，达到一个24小时的长时遗忘效应的药物剂量不仅与麻醉药本身种类有关，而且所需最小浓度低于预期估计值。然而意外的是，Alkire等还发现了预先给予极低浓度的氟烷（如0.1MAC）能显著改善IA实验结果，尤其是24小时后的记忆保留度。七氟醚为广泛应用于临床的吸入性全身麻醉药物，因此其安全性和精确应用剂量为临床所关注，而目前七氟醚对中枢系统的具体作用机制尚不明朗，因此，若能检测不同剂量七氟醚在记忆调节中的作用，并进一步探索这些浓度是如何作用于大脑神经系统的，必将丰富我们对七氟醚的临床和理论认识。

细胞骨架蛋白（activity-regulated cytoskeletal protein, ARC）[9]不但在突触可塑性形成和长时记忆的巩固中发挥重要的作用，它的表达也可作为检测长时记忆巩固的指标，已证明在海马、皮层等部位它较为活跃，而大脑的海马结构被认为是“掌管”学习记忆能力的关键部位，因此本实验基于上述背景，建立不同浓度七氟醚吸入的大鼠模型，利用检验大鼠学习记忆的经典行为学实验——抑制性逃避，检验麻醉药对记忆习得与巩固的调节，并以海马ARC蛋白表达的变化作为评判记忆在海马巩固加工的指标。

## 材料与方法

### 1. 动物

选取健康清洁级雄性SD大鼠45只（体重250-300g），由上海交通大学医学院动物科学部提供。在严格的生物实验条件下饲养一周,并培养固定的昼夜节律。按照将要给于的药物剂量将大鼠平均分为空气吸入组（sham组），极低浓度七氟醚吸入组（0.11SEV组，0.05MAC）和低浓度七氟醚吸入组（0.3%SEV组，0.14MAC）。

### 2. 麻醉

在IA训练当日从各笼中取出大鼠，称重后按分组依次放入自制的链接麻醉紧闭环路的无色透明有机玻璃箱中，箱中早已预冲目标浓度的相关气体，麻醉气体按0.5L/min的流量持续从挥发罐吹出并维持整个麻醉期间（至少45min）箱中的恒定药物浓度。在麻醉结束之后，快速从箱中取出大鼠，放入IA训练箱中，进行学习训练。

### 3. 行为实验

IA训练是利用大鼠趋暗喜黑的天性，检测大鼠情绪相关记忆的一种方法。单次IA训练的原理和方法：IA训练仪由一个亮室和一个暗室组成，两室之间有一道梯形升降门。首先将大鼠背朝隔离门置入IA训练仪的亮室中，当大鼠面向升降门时，把门升起，暴露暗室。喜暗的天性会使大鼠选择进入暗室探索，当大鼠四足全部迈进暗室时即将梯形升降门关闭，给予大鼠足部单次电击（0.4mA，2秒）。随后将大鼠取出。大鼠在亮室时间上限为100秒，超过即剔除。

24小时后检测大鼠IA记忆：将大鼠再次背朝隔离门置入IA训练仪的亮室中，当大鼠面向升降门时，把门升起，暴露暗室。记录大鼠在亮室停留的时间（潜伏期），潜伏期越长代表大鼠记忆越好（因为记住了暗室的恶性电击事件，而不急于依照天性“贸然行事”）。在记忆检测的过程中，大鼠进入暗室后不再给予足底电击。潜伏期上限为600秒，超过亦记作600秒。

在完成记忆检测后即刻在乙醚深麻醉下断头处死，冰上操作取出大鼠脑组织，迅速完整分离出双侧海马组织置于液氮保存。

### 4.Western-blotting：

每侧海马组织加入1mL裂解液。匀浆器冰上操作，粉碎后4度，9500r/min离心20min，取上清液经BCA（bicinchoninic acid）法定量组织蛋白，加入上样缓冲液变性，每孔上样25μg。电泳、湿转、封闭后加入一抗1：1000稀释，4℃孵育过夜。TBST洗膜3次，加入二抗室温孵育1h。TBST洗膜3次，ECL发光。

### 5.Real-time PCR：

根据GenBank提供序列，利用Primer Premier5.0软件进行设计，设计序列为：β-actin：上游引物为5′-CTCTTCCAGCCTTCCTTCCT-3′，下游引物为

5′-TCATCGTACTCCTGCTTGCT-3′；目的基因ARC：上游引物为5′-AGGGAGGTCTTCTACCGTCT-3′，下游引物为5′-AGTGTAGTCGTAGCCATCAGC-3′。

完整分离大鼠海马组织，以Trizol法抽提海马总RNA，采用Promega试剂盒逆转录体系合成cDNA，将反转录获得的cDNA稀释10倍（模板量要求为50pg-100ng），反应体系10ul为：($ddH_2O$ 2.5ul)+(mixture 5ul)+(probe/primers 0.5ul)+(cDNA 2ul)。反应条件为：50℃2min—95℃10min—(92℃15sec—60℃1min)×40cycles，以Roche LC480 PCR仪进行real-time PCR。

### 6. 统计

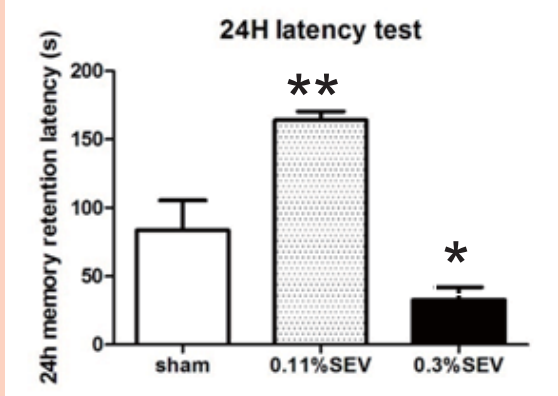
采用SPSS 11.5软件包行统计分析。所有数据表示为均数和标准差的形式。组间比较采用方差分析法(ANOVA)。随后采用Dunnett post hoc tests确定组间比较的统计学差异（sham组为对照组）。所有的统计分析中，P<0.05认为有统计学差异。

## 结果

45只大鼠均顺利完成行为IA实验。sham组大鼠(n=15)，平均潜伏期为83.63±43.57s；0.11%SEV吸入组大鼠(n=15)表现为记忆增强，其潜伏期为164.13±12.54s(与sham组相比，P=0.003)；0.3%SEV吸入组大鼠(n=15)表现为存在遗忘，其潜伏期为32.75±18.46s（与sham组相比，P=0.031）。（见图1）

与sham组相比较，0.3%SEV显著降低ARC蛋白的表达，而0.11%SEV却增强了ARC蛋白的表达(P值均小于0.05，见图2)。real-time PCR检测显示与sham组相比较，0.11%SEV组和0.3%SEV组的mRNA表达均无显著改变(P值均大于0.05，见图3)。

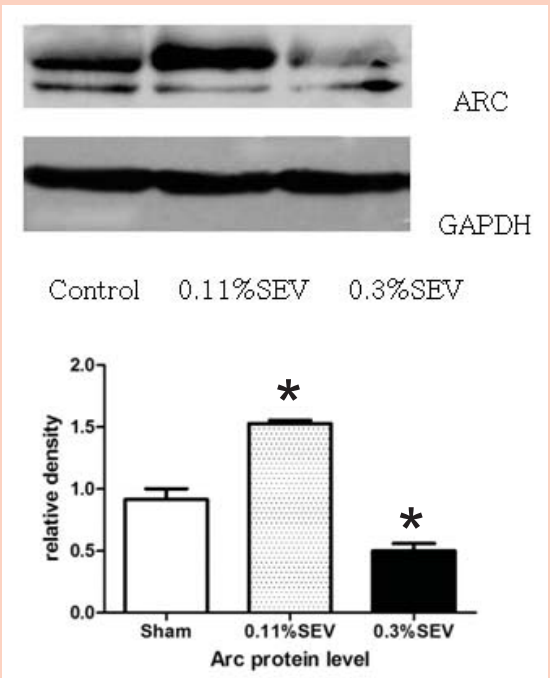
图1 24小时IA记忆检测结果比较




## 讨论

作为全身麻醉的重要特性之一，全麻药物影响大脑认知功能的机制仍未阐明。学术界公认的理想全身麻醉药物应具

图2 （上）Western-Blot 检测3组动物ARC (55 kd)蛋白表达水平,GAPDH为对照。
（下）七氟醚组（0.11%SEV组，0.3%SEV组）与对照组（SHAM组）之间ARC蛋白表达的差异。




备两个条件：首先，在药物作用期间能完全阻断记忆的形成；其次，药物应没有神经毒性，在代谢清除之后对学习记忆功能不再有影响。但现有的全麻药物并没有我们所期盼的调节记忆的“全或无”的特征，而是通过作用于多个环节对记忆产生影响。术中知晓（Intraoperative Awareness）和术后认知功能障碍（Postoperative cognitive dysfunction，POCD）作为困扰麻醉医师的棘手问题，它们的发生与术中施行全身麻醉关系密切；而近来不断有实验发现低浓度吸入麻醉气体反而出现脑功能兴奋甚至脑保护（特定环境下）作用。经典药物异氟醚已在临床和部分动物实验中被证实对哺乳动物中枢神经活性的抑制效应，并呈剂量依赖性；近来七氟醚因其较令人舒适的气味和更低的血气分布而迅速得到普及，研究者更开始关注低浓度吸入七氟醚引发的中枢或外周神经兴奋现象。Alkire[10,11]的实验得出将小鼠暴露于遗忘剂量的七氟醚环境下，小鼠将出现学习障碍，而本实验亦证实给予大鼠约等于遗忘剂量七氟醚（相当于0.14MAC）确可产生IA训练的记忆减退，而在给予更低浓度七氟醚（相当于0.05MAC）的时候也出现了类似氟烷的IA记忆增强现象，这与研究者对于七氟醚神经兴奋作用的猜测不无一致。

近年来相继在海马发现并分别命名为ARC和Arg3.1的细胞骨架相关蛋白被统称为ARC（又称为ARC/Arg3.1），这是一种

与诱导其转录的刺激在时间与空间上都相关的活性诱导基因(activity-induced gene)。如今越来越多的研究者依靠检测ARC的转录或表达水平来考察神经元的活性，以及神经元突触可塑性的变化。细胞在静息状态下，ARC的表达量很低；当细胞被“激活”后，ARC则迅速转录与表达。研究证实，凡能诱发LTP的刺激都能够诱发该基因的转录，且转录后的mRNA迅速移动、积聚在被激活神经元的树突，从而也使其蛋白表达产物定位于刺激到达的部位。而且，ARC mRNA的定位并不会被蛋白合成抑制剂阻断[12]。Guzowski等人于1999年采用荧光原位杂交技术（即catFISH）考察了ARC在细胞不同区域的分布，证实在行为训练或其它刺激诱导神经元活化的2分钟之内，ARC的mRNA前体即在核内出现。随后，经过大约20分钟，前体mRNA加工为成熟的mRNA并移至胞浆。这项研究首次为ARC的转录过程提供了时间曲线，也为以后分析神经元被激活时程的研究作出了贡献。其它研究还发现大鼠在新环境探索后，海马神经元和顶叶皮层神经元内ARC基因的转录水平与蛋白表达水平之间在30分钟至2小时内密切关联，在此期间还出现ARC蛋白表达的第一个高峰。蛋白表达的另一高峰则在8-12小时出现，有学者推测这一峰值的出现可能预示着大脑对该行为的学习加工过程已进入了下一个阶段--记忆的巩固阶段[13]。目前已认为ARC蛋白的表达可作为检测长时记忆巩固的指标，长时记忆形成时需要大脑结构在突触水平发生改变，这种学习变化即“突触可塑性（synaptic plasticity）”的具体表现。改变神经结构可能需要合成新的细胞蛋白，ARC在其中也许发挥着关键作用[14]。对于即可早期基因而言，增加蛋白表达需要更多mRNA的合成。而蛋白翻译本身是个复杂的过程，全麻药物可能通过抑制ARC转录水平、降解新合成的mRNA、抑制mRNA翻译，或是将翻译好的蛋白降解等多种途径达到减少ARC蛋白表达目的。

已证实全麻药物通过调节神经突触可塑性对学习记忆等认知功能产生影响。而作为学习记忆的中枢关键部位，海马神经元的突触可塑性与认知功能之间关系尤为引人注目，多种全麻药物均可通过该途径来干扰认知功能[15,16]。因此本实验通过观察活动刺激后海马部位ARC的表达变化，及细胞内ARC的mRNA总体水平的改变，从突触重塑的角度来检验记忆的形成。结果显示ARC的蛋白表达的确因为七氟醚吸入的浓度改变而变化，且极度浓度的吸入反而引起ARC表达的增加，这提示IA训练中出现的记忆增强效应存在海马神经元突触构造的相应改变，也符合突触可塑性改变是学习记忆的神经生物学机制这一理论。但是在检测mRNA时我们发现，给予不同浓度七氟醚吸入后ARC的mRNA增加与对照组比较并未有显著改变，这强烈提示七氟醚并非通过影响ARC转录前的记忆加工阶段来阻断学习的。结合蛋白部分的结果可以认为七氟醚对长时记忆的遗忘效应可能源自其干扰了翻译或更下游的修饰部分。当然，这些猜测都有待进一步的研究验证。

本研究得出极低浓度七氟醚（0.05MAC）可引起大鼠的IA学习记忆增强，而遗忘浓度七氟醚（0.14MAC）则导致IA学习减退。此现象与大鼠海马部位ARC蛋白的表达改变呈正相关，而ARC在海马部位的转录水平却不受麻醉药物吸入的干扰。这提示全麻药物七氟醚对于记忆的双向调节存在即可早期基因如ARC对神经元突触可塑性的作用，但这种干预可能体现在转录后水平。

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## 广东省医学会麻醉学分会心胸麻醉学组成立大会暨第一届心胸麻醉学学术交流会议

为了加强省内心、胸麻醉学科的交流与合作，我会定于2010年7月3日（周六）下午在广州白云宾馆举办广东省医学会麻醉学分会心胸麻醉学组成立大会，同时，召开第一届心胸麻醉学学术交流会议。此次大会将邀请省内心胸麻醉学方面的专家就心脏及胸科麻醉等方面的热点问题进行学术交流。

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## 摘要

目的：探讨异丙酚在不同靶控浓度下，罗库溴铵对脑电双频指数（Bispectral index,BIS）监测麻醉深度的影响。

方法：ASA Ⅰ级或Ⅱ级择期手术患者60例，随机分为4组（n=15）：实验组（R2和R3）和对照组（C2和C3）。设定异丙酚初始效应室浓度(effect-site concentration ,Ce）为4.0μg/mL，当患者镇静警觉评分（OAA/S评分）≤1时置入喉罩，机械通气，调节异丙酚靶控浓度，使Ce维持在2.0μg/mL或3.0μg/mL，达到靶浓度后稳定20min，实验组(R2和R3）静脉注射2倍$ED_{95}$剂量的罗库溴铵0.6mg/kg，对照组(C2和C3） 注射生理盐水（5ml）。记录异丙酚诱导前即刻（$T_1$）、静脉注射罗库溴铵或生理盐水即刻（$T_2$）、TOF消失为0时（$T_3$）、TOF的第一个肌颤搐恢复到5%时（$T_4$）BIS、HR、MAP值。

结果：四组患者性别、年龄、体重之间差异无显著性差异(P>0.05)；对照组$T_1$～$T_4$各时点BIS值比较差异无统计学意义(P>0.05) ；与$T_2$时比较，R2组$T_3$和$T_4$时BIS降低(P<0.05)，但R3组、C2组和C3组变化差异无统计学意义(P>0.05)。实验组与相同异丙酚效应室浓度对照组比较，R2组、C2组与R3组、C3组在静脉注射罗库溴铵或生理盐水前后变化差异无统计学意义(P>0.05)。

结论：罗库溴铵对BIS值的影响与镇静深度有关，异丙酚靶控浓度维持在2.0μg/mL较浅的镇静状态下，静脉注射2倍$ED_{95}$剂量的罗库溴铵可引起BIS数值的下降，但在3.0μg/mL较深的镇静状态下，2倍$ED_{95}$剂量的罗库溴铵对BIS值无影响。

关键词：罗库溴铵；脑电双频指数；靶控输注；镇静深度

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# 全麻患者在异丙酚不同靶控浓度下罗库溴铵对脑电双频指数的影响

# Influence of Rocuronium on Bispectral Index During Different Effect-site Concentration of Propofol

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## Abstract

**Objective**:To investgate whether rocuronium can affect bispcetral index during different effect-site concentration of propofol .

**Methods**:Sixty ASA Ⅰ or Ⅱ patients undergoing elective surgery were enrollded in the study,based on Ce of propofol,the patients randomly divided into four groups (R2 and R3)and(C2 and C3)(n=15).When the Ce of propofol reached 4.0μg/mL and OAA/S score was below one,a laryngeal mask airway was inserted,Ce was then maintained at 2.0μg/mL or 3.0μg/mL for 20min.Rocuronium $2ED_{95}$0. 6 mg/kg was gived in groups R2and R3, normal saline(5ml) was gived in the other two groups . BIS、heart rate (HR) and mean arterial pressure(MAP)values were recorded before induction of propofol immediately($T_1$),injection rocuronium or normal saline immediately($T_2$),TOF reached 0($T_3$), The first TOF twitch of muscle recovered to 5 % ($T_4$).

**Results**:There was no significant difference in sex, age, body weight among four groups(P>0. 05). There was no significant difference in BIS between groups C2 and C3 when$T_1$～$T_4$(P > 0. 05).The BIS of $T_3$and $T_4$ were significantly lower than $T_2$ in group R2（P>0.05) but not in group R3, C2 and C3（P>0.05). Compared with the same Ce,there was no significant difference between group R2,C2 and groupR3,C3(P>0.05).

**Conclusion**:Rocuronium alters the BIS scores in moderately sedated patients but not in deeply sedated patients,the scores of BIS were decreased after a bolus 2 times $ED_{95}$ of rocuronium when Ce of propofol set at 2. 0μg/mL ,but Ce of propofol set at 3. 0μg/mL,there were no change in BIS scores.

**Key Words**：Rocuronium; Bispectral index ;Target controlled infusion ;Depth of sedation

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脑电双频指数（BIS）是监测镇静水平的脑电效应指标，已普遍用于临床麻醉。研究表明BIS受肌松药的影响[1]。本研究拟探讨在2.0μg/mL或3.0μg/mL不同异丙酚效应室浓度下，静脉注射2倍$ED_{95}$剂量的罗库溴铵对BIS值的影响，以进一步了解肌松药对脑电效应指标的影响。

## 一、资料和方法

### 1. 一般资料

行择期非头面部手术患者60例，ASA分级Ⅰ级或Ⅱ级，年龄24～55岁，体重48～76kg，根据异丙酚的不同靶控浓度，随机分成四组（n=15）：实验组（R2和R3）和对照组（C2和C3）。心、肝、肾、肺、中枢性神经功能未见异常，无神经肌肉阻滞药过敏史，无喉罩使用禁忌症，无长期服用镇静催眠或抗精神病药物。

### 2. 麻醉与监测

所有患者均不用术前药，入室后开放左肘静脉通路，监测心率（HR）、平均动脉压（MAP）和脉搏血氧饱和度（$SpO_2$）。使用DSL-XP型BIS监测仪（Aspect公司，美国)监测BIS值；手掌式定量肌松监测仪（华翔公司，中国）监测姆内收肌肌颤搐；TCI-1型输液泵(北京思路高高科技发展有限公司)靶控输注（TCI）异丙酚（批号:EK733,AstraZeneca公司，意大利），麻醉诱导设定异丙酚的初始效应室浓度(effect-site concentration,Ce)为4.0μg/mL，当患者镇静警觉评分(OAA/S评分)≤1时置入喉罩，机械通气，潮气量8ml/kg，呼吸频率10～15次/分，维持呼气末二氧化碳分压（$P_{ET}CO_2$）35～40mmHg，调节异丙酚靶控浓度，使Ce维持在2.0μg/mL或3.0μg/mL，达到靶浓度后稳定20min[期间启动肌松监测仪的自动校准设置，进行肌松定标，调整肌颤搐幅度，待第1次肌颤搐稳定在100%5min后，给予四个成串刺激法（TOF），刺激电流40～60mA，脉冲宽度0.2ms，频率2Hz，串间距15s]。实验组（R2和R3）静脉注射2倍ED95剂量的罗库溴铵（批号:905993 ,荷兰欧加农公司）0.6mg/kg，另外2组对照组(C2和C3)注射生理盐水（5ml）。麻醉诱导过程中，由同一医师进行托下颌及置入喉罩操作。

### 3. 监测项目

记录异丙酚诱导前即刻（$T_1$）、静脉注射罗库溴铵或生理盐水即刻（$T_2$）、TOF消失为0时（$T_3$）、TOF的第一个肌颤搐恢复到5%时（$T_4$）BIS、HR、MAP值 。

### 4. 统计学处理

采用SPSS14.0统计学软件分析，计量资料以均数$\bar{x}\pm s$表示，组内比较采用重复测量数据的方差分析，组间比较采用单因素方差分析，计数资料采用$\chi^2$检验，P<0.05为差异有统计学意义。

## 二、结果

1. 患者一般情况

见表1。由表1可见，4组性别比、年龄、体重比较差异均无统计学意义(P> 0.05)。

表1 四组患者的临床资料比较（n=15,$\bar{x}\pm s$）

| 组别 | n | 性别比（男/女） | 年龄（岁） | 体重量（kg） |
|---|---|---|---|---|
| C2组 | 15 | 7/8 | 35±12 | 63±9 |
| C3组 | 15 | 6/9 | 35±11 | 59±7 |
| R2组 | 15 | 7/8 | 38±12 | 60±6 |
| R3组 | 15 | 7/8 | 40±9 | 56±8 |

### 2. 监测指标的变化

对照组$T_1$～$T_4$各时点BIS值比较差异无统计学意义(P>0.05)；与$T_2$时比较，R2组$T_3$和$T_4$时BIS降低( P<0.05)，但R3组、C2组和C3组变化差异无统计学意义(P>0.05)。实验组与相同异丙酚效应室浓度对照组比较，R2组、C2组与R3组、C3组在静脉注射罗库溴铵或生理盐水前后变化差异无统计学意义(P>0.05)，见表2。

表2 实验组和对照组不同时点BIS值的变化（n=15,$\bar{x}\pm s$）

| 组别 | $T_1$ | $T_2$ | $T_3$ | $T_4$ |
|---|---|---|---|---|
| R2组 | 98±1 | 62±6 | 51±8* | 52±8* |
| R3组 | 97±1 | 46±7 | 45±8 | 44±6 |
| C2组 | 97±1 | 60±7 | 60±7 | 60±7 |
| C3组 | 97±1 | 45±7 | 45±7 | 45±7 |

注：与$T_2$比较，*P<0.05

各组患者静脉注射罗库溴铵或生理盐水前后各时点血流动力学稳定，HR、MAP变化差异无统计学意义(P>0.05)，见表3。

表3 实验组和对照组不同时点HR、MAP值的变化（n=15,$\bar{x}\pm s$）

| 指标 | 组别 | $T_1$ | $T_2$ | $T_3$ | $T_4$ |
|---|---|---|---|---|---|
| HR（次/min） | R2组 | 84±12 | 80±11 | 81±13 | 82±14 |
| | R3组 | 80±16 | 83±9 | 85±10 | 85±13 |
| | C2组 | 80±14 | 77±14 | 78±10 | 77±12 |
| | C3组 | 79±13 | 82±11 | 83±13 | 83±12 |
| MAP（mmHg） | R2组 | 96±15 | 85±11 | 84±18 | 83±19 |
| | R3组 | 97±13 | 75±15 | 74±12 | 73±17 |
| | C2组 | 99±14 | 87±9 | 88±7 | 87±12 |
| | C3组 | 97±15 | 74±13 | 74±11 | 73±17 |

## 三、讨论

BIS能有效地监测异丙酚的镇静程度[2,3,4]，但可能受到肌电活动的干扰，影响监测结果的准确性。Bruhn等[5]于2000年首次报道了2例由肌电活动变化而非镇静深度改变引起的BIS数值变化。

本研究结果显示，在异丙酚Ce为2.0μg/mL的浅麻醉状态下，R2组注射2倍$ED_{95}$剂量的罗库溴铵后，随着肌颤搐的抑制BIS出现明显降低，其原因可能为：一方面，肌松药引起BIS数值降低可能与其采集脑电图的波谱范围有关，BIS采集47Hz以下的信号，而肌电信号的频率范围是30～300Hz，所以BIS包含一部分肌电信号，所以额肌肌电活动可能混入脑电图的测量信号之中，使BIS计算出伪值。肌颤搐抑制后，额肌肌

电活动对BIS的干扰被消除[6,7]。Messner等[8]发现，清醒志愿者静脉注射1.5mg/kg琥珀胆碱后BIS值迅速降低，于此同时，额肌EMG活动亦随之消失，BIS的恢复与额肌EMG活动的恢复显示出了很好的相关性；另一方面，肌颤搐的抑制使得镇静水平加深，从而使BIS降低。肌肉松弛可减少来自肌肉牵拉感受器的信号，而根据“肌梭传入理论”肌肉的收缩和舒张可增加大脑觉醒中枢的传入信号，肌肉松弛后,觉醒中枢传入信号减少，故肌松药可间接影响意识状态水平。本研究结果表明，异丙酚Ce为3.0μg/mL的深度镇静状态下给予罗库溴铵后BIS无明显变化，可能原因是，当患者处于深度镇静时，肌肉的紧张度已降低，对维持大脑兴奋状态的作用很小，同时头面部肌肉的自主活动也减弱，此时使用罗库溴铵对肌电活动的影响有限，BIS则不再出现明显变化。

综上所述，罗库溴铵对BIS值的影响与镇静深度有关，异丙酚靶控浓度维持在2.0μg/mL较浅的镇静状态下，静脉注射2倍$ED_{95}$剂量的罗库溴铵可引起BIS数值的下降，但在3.0μg/mL较深的镇静状态下，2倍$ED_{95}$剂量的罗库溴铵对BIS值无影响。因此，BIS应用于临床时，需要考虑肌肉松弛情况对其监测价值的影响。

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## 2010首都医科大学麻醉学系年会

2009，祖国60华诞，举国欢庆；60年沧桑巨变，祖国母亲为我们演绎了一个东方大国崛起的神奇。祖国的医药事业也经历了日新月异的变革，在变革的激流中，首都医科大学麻醉学系已成长为国内规模最大、亚学科群建设最为完整的集临床、教学和科研为一体的综合性麻醉学培养和临床考核基地。

2010，为推动中国麻醉学事业的全面发展，由首都医科大学麻醉学系联合首都医科大学及其附属宣武医院、北京友谊医院、北京朝阳医院、北京同仁医院、北京天坛医院、北京安贞医院、北京复兴医院、北京口腔医院、北京佑安医院、北京儿童医院、北京妇产医院、康复医学院（中国康复研究中心）、北京中医医院、北京胸科医院等14家医院麻醉科联合主办，北京麦迪卫康广告有限公司承办的“首届首都医科大学麻醉学系年会”将于2010年11月5-7日，在国家会议中心（暂定）隆重召开！

首都医科大学麻醉学系年会将以“专业、分享、收获、促进”为宗旨，传递麻醉学及相关领域的最新进展与学术成果。届时我们将整合最顶级的专家团队，带来丰富精彩的学术专题演讲和医院手术室现场观摩体验。理论与实践相结合，教学相长将为麻醉学及相关领域医生搭建一个创新实用的学术大舞台，各获所需，全面提升和切实促进麻醉领域医生的学术和临床实践水平。

首都医科大学麻醉学系年会，坚持立足领域学术前沿，促进领域医生的学习与交流、打造中国麻醉学领域最具影响力学术品牌之一，全力推动我国麻醉学事业的发展！

我们诚挚邀请您参加此次会议，共同演绎麻醉学领域的饕餮盛宴，谱写2010年中国麻醉学领域的华彩乐章！

会议名称：2010首都医科大学麻醉学系年会
会议时间：2010年11月5—7日
会议地点：北京国家会议中心（待定）
会议规模：1000人
会议受众：全国麻醉学科专业人员,包括麻醉科医生、ICU医生、疼痛诊疗相关人员及其他相关专业人员
学分授予：国家级Ⅰ类继续教育学分

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## 摘要

目的：雷米芬太尼作为一种新型的麻醉性镇痛药在临床已经广泛应用于静脉全麻，目前发现在静脉全麻中雷米芬太尼可以明显减少肌肉松弛药的用量，这是否是雷米芬太尼与肌松药的协同作用还不清楚，本研究应用Organon–TOF–WATCH$^{R}$SX肌松监测仪观察全凭静脉麻醉下腹腔镜手术中靶控输注不同剂量的雷米芬太尼对肌松药罗库溴铵的起效、作用和恢复时间的影响，以此来判断雷米芬太尼与肌松药之间是否有协同作用。方法：选择ASA Ⅰ－Ⅱ级，年龄25–55岁，妇科及普外科腹腔镜择期手术病人75例随机分为三组，全麻诱导：咪唑安定0.04mg.kg$^{-1}$，丙泊酚TCI血药浓度3ug.ml$^{-1}$，罗库溴铵0.6mg.kg$^{-1}$，麻醉维持：A组单纯用TCI丙泊酚，B组用TCI丙泊酚加上TCI雷米芬太尼效应室浓度2ng.ml$^{-1}$，C组用TCI丙泊酚加上雷米芬太尼效应室浓度5ng.ml$^{-1}$，三组异丙酚TCI效应室浓度维持在3ug.ml$^{-1}$左右，根据病人的反应调整，将麻醉深度控制在满足手术需要和术中BIS在40–60之间，用Organon–TOF–WATCH$^{R}$SX肌松监测仪记录罗库溴铵(0.6mg.kg$^{-1}$)的起效时间（从给药至TOF比值下降到25%的时间）、维持时间（从TOF值低于25% 至恢复到25%）、恢复时间（从TOF比值恢复到25%至TOF比值恢复到75%）用美国Aspect公司的BIS–XP监测仪控制麻醉深度。结果：罗库溴铵的起效时间三组分别为0.96±0.35min，1.12±0.51min，1.11±0.34min，三组之间无统计学差异(P>0.05)；罗库溴铵的作用时间三组分别为39.94±10.17min，42.45±11.07min，42.46±11.25min，各组间没有统计学差异(P>0.05)，罗库溴铵的恢复时间三组分别为11.68±4.99min，13.44±5.93min，12.20±2.61min，各组间没有统计学差异(P>0.05)。结论：不同TCI效应室浓度的雷米芬太尼没有明显延长单次注射罗库溴铵(0.6mg.kg$^{-1}$)的起效、作用和恢复时间，提示雷米芬太尼减少静脉全麻中肌松药用量的作用机制是中枢性的。

关键词：雷米芬太尼；罗库溴铵；TOF–WATCH；药物的相互作用

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# 全凭静脉麻醉中雷米芬太尼减少肌松药用量的机制探讨

# To Investigate the Mechanism of Remifentanil Reducing the Requirements of Muscle Relaxants in Total Intravenous Anesthesia

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## Abstract

**Objective**:It is found that remifentanil can reduce the requirements of muscle relaxants in intravenous anesthesia .Whether the mechanism is relative to the synergistic effect between remifentanil and muscle relaxants is not clear. We aimed to investigate the effects of remifentanil on the onset、duration and recovery times of rocuronium in different remifentanil concentration groups, in which the patients undergoing elective celioscope operations with TOF-WATCH monitoring in intravenous anesthesia.

**Method**: Seventy-five patients, ASA1-2, aged 20-55yr, weighing 50-75kg,scheduled for the operation of elective celioscope. Anesthesia induction :midazotam 0.04mg.kg$^{-1}$, rocuronium 0.6mg.kg$^{-1}$,and propofol deliverd by TCI at blood concentration of 3ug.ml$^{-1}$. According to the dosage of remifentanil,the patients were divided into three groups ,Group A : the patients without remifentanil, Group B: the patients were infused with remifentanil by TCI in the effect-site concentration of 2ng.ml$^{-1}$, Group C: the patients were infused with remifentanil by TCI in the effect-site concentration of 5ng.ml$^{-1}$, The onset time of rocuronium (from beginning to decreasing to twenty-five percent of TOF)、the duration time of rocuronium (from decreasing to twenty-five percent to recovering to twenty-five percent of TOF)、the recovery time of rocuronium (from recovering to twenty-five percent to recovering to seventy-five percent of TOF)were recorded by the Organon-TOF-WATCH$^{R}$SX.

**Results**: BIS in three groups were not different significantly（P>0.05）.The onset times of rocuronium among there groups (0.96±0.35min，1.12±0.51min,1.11±0.34min)were no different significantly (P>0.05); The duration time of rocuronium among there groups (39.94±10.17min，42.45±11.07min，42.46±11.25min) were no different significantly; The recovery time of rocuronium among there groups 11.68±4.99min，13.44±5.93min，12.20±2.61min )(P>0.05) were no different significantly（P>0.05）.

**Conclusion**: remifentanil in different effect-site concentration of TCI does not prolong the onset、duration and recovery times of rocuronium in intravenous anesthesia. It is suggested that the mechanism of remifentanil reducing the requirements of muscle relaxants in total intravenous anesthesia is due to the effect on CNS.

**Key Words**：remifentanil；rocuronium；TOF-WATCH；interaction

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雷米芬太尼作为一种新型的麻醉药在临床已经广泛应用于静脉全麻，众所周知吸入麻醉药与肌松药有明显的协同作用，这是吸入麻醉药直接作用于运动终板-神经肌肉接头所至。麻醉深度相同时，如果用了挥发性麻醉药肌松药的用量就明显减少。近来发现静脉全麻中联合应用雷米芬太尼也可以明显减少术中肌松药的用量。但这种作用是因为阿片类药物的中枢性呼吸抑制作用所致（例如：能够耐受机械通气和维持较深的麻醉状态），还是它直接对神经肌肉传递的抑制作用造成的，目前还不能肯定。本研究的目的就是应用肌松监测仪TOF-WATCH观察静脉全麻中雷米芬太尼对罗库溴胺的起效、作用和恢复时间的影响，以此来判断全凭静脉麻醉中雷米芬太尼减少肌松药用量的可能机制。

## 资料与方法

### 1. 病例选择

ASA1-2级，年龄25-55岁，体重50-70公斤，妇科卵巢和子宫腹腔镜及普外科胆囊腹腔镜择期手术病人75例，手术时间2-3小时。有心肝肾疾病及阿片类药物过敏的病人，有明显电解质及酸碱失衡的病人，术前应用影响神经肌肉传导功能的药物的病人予以排除。

### 2. 研究方法

根据术中雷米芬太尼的效应室浓度不同随机将病人分为三组(n=25)，A组:单纯用TCI丙泊酚；B组:用TCI丙泊酚加上TCI雷米芬太尼效应室浓度2ng.ml$^{-1}$；C组:用TCI丙泊酚加上雷米芬太尼效应室浓度5ng.ml$^{-1}$。三组丙泊酚TCI麻醉诱导为血药浓度为3ug.ml$^{-1}$和维持为效应室浓度3ug.ml$^{-1}$，术中根据病人的反应进行调整,将麻醉深度控制在满足手术需要和术中BIS控制在40-60之间。

麻醉方法：入室后常规开放上肢静脉，用惠普监护仪行血压、心率和脉氧和鼻温监测，麻醉诱导：咪唑安定0.04 mg.kg$^{-1}$,分别用思路高TCI和Graseby-3500泵TCI雷米芬太尼（除外A组）和TCI丙泊酚，待病人意识消失后给予罗库溴胺0.6mg.kg$^{-1}$，10秒之内推完，然后行气管内插管。药品名称：瑞芬太尼（宜昌人福药业有限责任公司提供，规格1mg/瓶，批号：050903）罗库溴铵（南京欧加农制药有限公司提供，规格50mg/瓶，批号：862984）丙泊酚（英国阿斯利康公司生产，规格，500mg/支，批号：TH153）。

### 3. 肌松监测

待患者入室，在右侧尺神经处，先用酒精消毒，然后放置刺激电极，连接和开启Organon-TOF-WATCH$^{R}$SX肌松监测仪及数据输出电脑，进行校正后开始监测神经肌肉功能，采用四个成串刺激连续监测，每15秒一次刺激，监测尺神经-拇内收肌神经功能。罗库溴铵的起效时间（从给药至TOF值低于25%的时间）、维持时间（从给药后TOF值低于25% 至恢复到25%）、恢复时间（从TOF值恢复到25% 至恢复到75%）。用美国Aspect公司的BIS-XP监测仪控制麻醉深度。术中记录患者入室、给药时、给药后、TOF值低于25%、TOF值恢复到25%、TOF值恢复到75%的心率、血压、、BIS值和体温，T1、T4和TOF值，观察罗库溴铵的一个肌松周期后试验结束。

### 4. 统计方法

所有计量资料以均数士标准差表示，组间比较用方差分析，用sPPSS11.5软件包进行处理，以P<0.05为差异有显著性。

## 结果

**表1** 三组病人一般情况（n=25）

| | A组 | B组 | C组 |
|---|---|---|---|
| 年龄（岁） | 40.6±8.7 | 42.1±7.2 | 43.2±7.6 |
| 体重（千克） | 59.7±4.9 | 57.8±6.3 | 60.5±6.1 |
| 身高（厘米） | 164.3±6.6 | 163.2±8.6 | 165.0±7.3 |
| 性别比(男/女) | 9/16 | 10/15 | 9/16 |

与A组比较,*P<0.05 **P<0.01；与B组比较,▲P<0.05 ▲▲P<0.01；与C组比较，#P<0.05 ##P<0.01

**表2** 三组病人BIS和体温（n=25）

| | | 诱导前 | TOF值低于25% | TOF恢复到25% | TOF恢复到75% |
|---|---|---|---|---|---|
| BIS | A | 99.0±8.3 | 45.3±7.6 | 49.6±9.9 | 58.7±11.4 |
| | B | 101.±6.5 | 42.62±3.4 | 47.6±10.5 | 54.5±13.5 |
| | C | 98.5±5.8 | 40.8±6.6 | 44.5±11.7 | 51.7±9.7 |
| 体温 | A | 37.2±0.5 | 36.7±0.3 | 36.7±0.2 | 36.6±0.2 |
| | B | 36.9±0.4 | 36.6±0.3 | 36.5±0.1 | 36.5±0.5 |
| | C | 37.0±0.3 | 36.0±0.6 | 36.8±0.4 | 36.7±0.3 |

与A组比较,*P<0.05 **P<0.01；与B组比较,▲P<0.05 ▲▲P<0.01；与C组比较，#P<0.05 ##P<0.01

**表3** 罗库溴铵的起效时间（n=25）

| 成串刺激 | $T_1$（min） | $T_4$（min） | TOF（min） |
|---|---|---|---|
| A组 | 0.96±0.35 | 0.96±0.52 | 0.96±0.35 |
| B组 | 1.12±0.41 | 1.12±0.41 | 1.12±0.41 |
| C组 | 1.11±0.34 | 1.11±0.34 | 1.11±0.34 |

与A组比较,*P<0.05 **P<0.01；与B组比较,▲P<0.05 ▲▲P<0.01；与C组比较，#P<0.05 ##P<0.01

**表4** 罗库溴铵的作用时间（n=25）

| 成串刺激 | $T_1$（min） | $T_4$（min） | TOF（min） |
|---|---|---|---|
| A组 | 34.35±10.71 | 42.29±13.75 | 39.94±10.17 |
| B组 | 38.49±11.29 | 4558±11.91 | 4245±11.07 |
| C组 | 39.58±10.68 | 45.87±11.25 | 42.46±11.25 |

与A组比较,*P<0.05 **P<0.01；与B组比较,▲P<0.05 ▲▲P<0.01；与C组比较，#P<0.05 ##P<0.01

**表5** 罗库溴铵的恢复时间（n=25）

| 成串刺激 | $T_1$（min） | $T_4$（min） | TOF（min） |
|---|---|---|---|
| A组 | 11.33±5.86 | 7.79±4.46 | 11.68±4.99 |
| B组 | 14.15±7.08 | 10.56±5.64 | 13.44±5.93 |
| C组 | 11.34±2.46 | 10.82±3.09 | 12.20±2.61 |

与A组比较,*P<0.05 **P<0.01；与B组比较,▲P<0.05 ▲▲P<0.01；与C组比较，#P<0.05 ##P<0.01

1、三组间病人的年龄、身高、体重、性别比、ASA分级、手术种类差异无显著性(P>0.05)，见表1。

2、三组间各时点的BIS值、HR、MAP和体温无统计学差异(P>0.05)，见表2。

3、罗库溴铵的起效时间三组分别为0.96±0.35min，1.12±0.51min，1.11±0.34min三组之间无统计学差异(P>0.05)（见表3）；三组间罗库溴铵的作用时间分别为39.94±10.17min，42.45±11.07min，42.46±11.25min没有统计学差异(P>0.05)（见表4）；三组间罗库溴铵的恢复时间分别为11.68±4.99min，13.44±5.93min，12.20±2.61min没有统计学差异(P>0.05)（见表5）。

## 讨论

罗库溴铵的起效时间快已接近琥珀胆碱，能迅速产生优良的气管插管条件，其作用时间中等，神经肌肉阻滞强度约为维库溴铵的1/6[1]。

肌松药作用时间长短与下列因素密切相关:(1)个体差异，由于老人和小儿对肌松药的反应与青壮年不同，为了减少个体差异带来的影响，我们规定入选病人的年龄在25-55岁，体重在50-70kg之间。(2)麻醉深浅，由于病人的麻醉深度影响着肌松药的作用和代谢，所以术中用BIS控制麻醉深度，使麻醉深度在一定范围内，这就减少了由于麻醉深度不同对肌松药作用时间的影响。(3)吸入麻醉药浓度及吸入时间，本研究中采用静脉麻醉药诱导及维持，避免了吸入麻醉药的影响。(4)肝肾功能，术前肝肾功能异常的病人予以排除。(5)体外循环下低温等因素，术中监测鼻温较少体温对肌松药作用时间的影响。（6）药物之间的相互作用，试验期间没有应用其它阿片类药物，同时术前应用影响神经肌肉传导功能的药物的病人予以排除。（7）酸碱平衡及电解质紊乱[2]，排除术前有明显电解质及酸碱失衡的病人。

静脉全麻中通常是几种药物联合应用，那各种药物之间就可能会产生协同作用，药物在体内的相互作用体现在药效学效应和药代动力学效应这两个方面[3]。在药效学方面除$N_2O$外，现有吸入麻醉药均能抑制神经肌肉的兴奋传递，与非、去极化肌松药有明显的协同作用，且与剂量相关，作用部位同属神经肌肉终板[4]。作用强的吸入麻醉药可减少非去极化松药的需要量，而且可使剂量一反应曲线左移[4]。

麻醉性镇痛药雷米芬太尼是一种最新型的芬太尼衍生物，具有独特的药理学特点 ，被誉为二十一世纪的阿片类镇痛药。长时间输注后，消除半衰期甚短(9.5min),中央室和外周室平衡迅速,起效快,无蓄积作用,不会延长麻醉后苏醒时间,与其他阿片类药比较 ,更适宜于静脉输注给药[6]。以往人们认为中枢性镇痛药虽然在临床上没有表现出明显的肌松作用，但可能有增强肌松药的趋势，到目前还没有关于雷米芬太尼抑制神经肌肉的兴奋传递的报道。本研究中不同TCI效应室浓度的雷米芬太尼没有明显延长单次注射罗库溴铵(0.6mg.kg$^{-1}$)的起效、作用和恢复时间，这说明雷米芬太尼并没有抑制神经肌肉的兴奋传递。雷米芬太尼对中枢神经系统的影响有明显的呼吸抑制作用，因此静脉全麻中使用雷米芬太尼的病人能够更好的耐受机械通气和维持足够的麻醉深度，从而可能减少了罗库溴胺的用量。

总之静脉全麻中持续应用雷米芬太尼与罗库溴胺没有协同作用，不同TCI效应室浓度的雷米芬太尼没有明显延长单次注射罗库溴铵(0.6mg.kg$^{-1}$)的起效、作用和恢复时间，这提示雷米芬太尼减少静脉全麻中肌松药用量的作用机制是中枢性的。

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## 2010年天津医学会疼痛学分会年会

经天津医学会批准，天津医学会疼痛学分会将于2010年10月下旬在天津市召开学术年会。届时会议将总结天津疼痛学近年的工作、知识更新讲座、学术交流、疑难病例讨论以及疼痛微创介入治疗最新进展等内容。现将会议的有关事宜通知如下：

一、会议将邀请中华医学会疼痛学分会专家讲演，题目待定；

二、会议代表：天津疼痛学会全体代表，以及各级医院疼痛科、麻醉科、骨科、神经科、康复医学科、肿瘤内科、中医科以及相关学科医生；

三、论文交流：经大会学术委员会审定，您的论文如果被录用为大会交流，请按时出席并按要求作好幻灯。

四、会议时间、地点：2010年10月下旬，会议地点：根据人数待定

五、征文截止日期：为2010年9月30日，请投稿投稿的代表在规定时间内把稿件以电子邮件（E-mail）方式发送到本次会议的专用邮箱：tianjinpain@163.com并附联系方式（单位、职称、手机号码、电子邮箱等）。

# *The Year in Cardiothoracic and Vascular Anesthesia: Selected Highlights From 2009*

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## Abstract

The hybrid operating room is the venue for transcatheter therapy with the convergence of 3 specialties: cardiac surgery, cardiovascular anesthesiology, and interventional cardiology. Transcatheter aortic valve replacement is proof that cardiac specialists have embraced the endovascular revolution. Because pharmacologic conditioning and ischemic myocardial conditioning are safe and effective, they are currently the focus of multiple trials. Angiotensin blockade, anemia, and endoscopic saphenous vein harvesting worsen outcome after coronary artery bypass graft (CABG) surgery. Although off-pump CABG surgery is equivalent to on-pump CABG surgery, it may improve outcomes in high-risk groups. Although percutaneous coronary intervention (PCI) significantly decreases mortality after myocardial infarction, the evidence is less convincing for intra-aortic balloon counterpulsation. Even though prasugrel recently was approved for platelet blockade in PCI, it may be superseded by ticagrelor. Although PCI and CABG surgery appear equivalent for multivessel coronary disease, CABG surgery lowers revascularization rates and also has superior outcomes in diabetics and the elderly. Hetastarch and N-acetylcysteine both increase bleeding and transfusion in cardiac surgery. Factor VII can treat life-threatening bleeding, but its safety requires further evaluation. Because eltrombopag and romiplostim stimulate platelet production, they may have a future role in hemostasis after cardiac surgery. Even though fenoldopam, atrial natriuretic peptide, and sodium bicarbonate are nephroprotective, further trials must confirm these findings. Intensive insulin therapy offers no further outcome advantage and significantly increases hypoglycemic risk. The past year has witnessed the advent of a new clinical venue, new devices, and new drugs. The coming year will most likely advance these achievements.

***Key Words***: hybrid operating room, transcatheter aortic valve replacement, transcatheter mitral valve repair, ischemic preconditioning, pharmacologic conditioning, levosimendan, volatile anesthetics, angiotensin-converting enzyme inhibitors, anemia, hetastarch, coronary artery bypass graft surgery, endovascular saphenous vein graft harvesting, percutaneous coronary intervention, intra-aortic balloon counterpulsation, sodium bicarbonate, atrial natriuretic peptide, fenoldopam, intensive insulin therapy, prasugrel, ticagrelor, eltrombopag, romiplostim

This article the second in the annual series for the Journal of Cardiothoracic and VascularAnesthesia.[1]The authors thank the Editor-in-Chief, Dr Kaplan, for the opportu-nity to continue this series, namely the research highlights of the year that pertain to the specialty of cardiothoracic and vascular anesthesia. The introduction of this article will outline the major themes selected for 2009, each of which is then reviewed in detail in the main body of the article.

The literature highlights in this specialty for 2009 begin with the rapid advances in transcatheter valve therapy and the advent of a new perioperative venue, the hybrid operating room. Transcatheter aortic valve replacement (both via the transfemo-ral and transapical routes) will generalize further throughout North America after regulatory agency approval of the first-generation

valves. The venue for this revolutionary technology, the hybrid operating room, is a blend of the traditional cardiac catheterization laboratory and the traditional operating room.The advances in transcatheter mural repair, which until now have taken place in the cardiac catheterization laboratory, may transfer to this new perioperative venue as cardiac surgeons embrace the endovascular revolution in cardiovascular medicine.

The advances in perioperative myocardial conditioning have continued throughout 2009, strengthening the evidence to exploit this protective mechanism to improve outcomes. Pharmacologic conditioning with agents such as volatile anesthetics and levosimendan delivers incremental outcome benefit after cardiac surgery in randomized trials, large observational cohort series, and metaanalyses. Furthermore, ischemic preconditioning of the myocardium, whether local or remote, consistently protects the heart during ischemia and reperfusion both in the catheterization laboratory and the operating room. Both pharmacologic conditioning and ischemic conditioning currently are being further evaluated in multiple randomized trials throughout cardiovascular practice. It is likely that these trials will show clinical benefit to initiate a paradigm shift in the practice and facilitate the incorporation of these interventions into daily practice. The advances in the management of coronary artery disease (CAD) have been a major theme in 2009. Perioperative angiotensin blockade and anemia worsen outcome after coronary artery bypass graft (CABG) surgery.Based on large observational studies, off-pump CABG surgery is clinically equivalent to on-pump CABG surgery, except in high-risk patients in whom it may offer outcome advantages. Although endoscopic saphenous vein harvesting has advantages, it recently has been associated with significant increases in coronary graft thrombosis and adverse outcomes after CABG surgery.

In the practice of interventional cardiology, large randomized trials and meta-analyses in 2009 consistently show the significant outcome advantage from percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) managed with or without systemic fibrinolysis. In contrast. however. the outcome benefits of intra-aortic balloon counterpulsation are not striking in contemporary analysis,challenging recommendations in current PCI guidelines. Advances in oral platelet blockade continue with the advent of the thienopyridine prasugrel, which was shown to be more efficacious than clopidogrel in randomized trials and recently was approved in 2009 by the Food and Drug Administration in the United States. Prasugrel, however, may be superseded by ticagrelor, a thienopyridine that inhibits platelets directly and reversibly. Although further trials are indicated, it is likely that ticagrelor will be widely available in the near future to achieve powerful short-acting oral platelet blockade for PCI that is rapidly reversible in appropriate clinical scenarios such as emergent CABG surgery after complicated PCI for STEMI. Now that PCI is a viable option for multivessel CAD, trials in 2009 have continued to compare PCI versus CABG surgery for multivessel CAD. The data suggest that in appropriate patient groups, these techniques produce equivalent clinical outcomes, although CABG surgery has a significantly lower revascular-ization rate and superior outcomes in diabetics and patients>65 years old. Now that clinicians are in the era of the hybrid operating room, the interventional management of multivessel CAD can be further individualized. This therapeutic approach allows coronary artery bypass and coronary stenting to be performed as indicated at a single venue under the auspices of the new specialist trio, which includes a coronary surgeon, a cardiovascular anesthesiologist, and an interventional cardiologist. Hybrid coronary revascularization (PCI and CABG surgery) will likely represent the future approach to multivessel CAD, thus shifting the focus away from a contest between techniques to best complementary therapy in a hybrid environment.

Bleeding after cardiac surgery continues to adversely affect clinical outcomes. Hetastarch and N-acetylcysteine appear to aggravate bleeding and transfusion risk in adult cardiac surgical patients. Although factor VII can be a magic bullet in lifethreatening bleeding in cardiac surgery, its safety must be explored further in adequately powered randomized trials. Platelet production by megakaryocytes can be stimulated by thrombopoietin agonists such as eltrombopag and romiplostim; their perioperative application could be very significant in the future management of coagulopathy after cardiac surgery.

Because renal dysfunction independently predicts adverse outcome after cardiac surgery, perioperative nephroprotective strategies remain a clinical priority. Recent data show that fenoldopam, atrial natriuretic peptide, and sodium bicarbonate significantly reduce the incidence of

renal dysfunction. Further randomized trials are indicated to confirm these encouraging findings and to explore their safety in adult cardiac surgery before they can be incorporated into clinical practice.

Although perioperative glucose management (goal glucose level≤180 mg/dL) improves outcome in adult cardiac surgical patients, recent evidence shows that these outcome benefits do not apply to all hospital settings. Furthermore, intensive insulin therapy for a target glucose range of 80-110 mg/dL does not improve outcome further and significantly increases the risk of hypoglycemia.

The themes selected for this second highlights article have only sampled the advances in the specialty for 2009. If all the significant articles had been included, indeed this review could be developed into a yearbook. Many significant advances in 2009 also have been featured in the expert review section of the Journal.

## TRANSCATHETER VALVE THERARY: THE EMERGENCE OF THE HYBRID OPERATING ROOM

*Aortic Valve*

Transcatheter aortic valve replacement has remained in focus throughout 2009, with prominent attention given to anesthetic challenges emerging from recent case series (transfemoral and transapical approaches) and recent major developments in the literature.[2-5] This technology will generalize further in the United States after completion of the landmark PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial: full details available at www.clinicaltrials.gov [NCT00530894]) and ultimate FDA approval for the first-generation transcatheter aortic valve. As this revolution in aortic valve replacement unfolds, it remains essential for the cardiovascular anesthesiologist to be in command of the accompanying challenges, namely understanding the procedure in detail and its complications, adapting to the new environment of the hybrid operating room, and working with a dedicated multidisciplinary team to introduce this technology safely within each institution.

The detailed understanding of the procedure is mandatory for the optimal conduct and success of transcatheter aortic valve replacement.[6-8] The procedure can be divided into the following major parts: vascular access, aortic annular sizing, testing of transvenous ventricular pacing, balloon aortic valvuloplasty, aortic valve positioning, and aortic valve deployment. The major complications can be understood in relation to the different parts of the procedure. Vascular access carries the risk of dissection and rupture with significant hemorrhage. Errors in aortic annular sizing can lead to valve embolization, aortic annulus rupture, and aortic dissection.[9] Transvenous ventricular pacing to achieve pulseless ventricular tachycardia is essential for brief cessation of transaortic ejection to facilitate balloon valvuloplasty and aortic valve deployment. Inadequate pacing can interfere with balloon positioning and result in valve malposition. Aortic valve positioning and subsequent deployment are typically guided with a combination of fluoroscopic and echocardiographic imaging, although it is entirely feasible with echocardiography alone.[10] The major risk at this point is aortic valve malposition with the possibilities of valve prolapse into the left ventricle, valve embolization downstream into the thoracic aorta, coronary ostial occlusion, and aortic root rupture. Although complications will occur, patient survival will depend on timely recognition and effective management. [11]

The hybrid operating room enables treatments traditionally available only in the catheterization laboratory with those tra-ditionally available only in the operating room to offer patients the best therapy for a given cardiovascular lesion such as coronary artery disease or aortic stenosis.[12] The design of this hybrid space must balance the work requirements of a multidisciplinary team of cardiovascular anesthesiologists, cardiac surgeons, and interventional cardiologists.[13] Imaging modalities typically include fluoroscopy, echocardiography, and even computed axial tomography scans. It remains important to guarantee radiation safety in this innovative but challenging environment.[14] The hybrid approach will likely revolutionize not only the management of aortic stenosis but also the management of CAD. [15] A recent study (N=366 patients with a total of 796 vascular grafts) showed that routine completion angiography after CABG surgery detected important angiographic lesions in 12% of grafts that were subsequently all immediately addressed with surgical revision or PCI.[15]

The learning curve of the multidisciplinary

team (anesthesiologist, surgeon, and cardiologist) for transcatheter aortic valve replacement is significant.[16] It is essential that the team always functions superbly for optimal patient outcome. At the University of Pennsylvania Medical Center, there is a dedicated team (1 lead cardiac anesthesiologist, 1 lead cardiac surgeon, and 1 lead interventional cardiologist) who perform and/or supervise all the transcatheter procedures. Based on peer discussions, this approach appears to be the team model at multiple leading centers around North America and Europe. Even as this technology matures for widespread clinical application, this team focus will remain a priority in the successful and safe generalization of this revolutionary technology into cardiovascular practice.[17]

*Mitral Valve*

The revolution in the management of mural valve disease is extensive and consequently is the subject of a forthcoming expert review article in itself.[18,19] Transcatheter mural valve repair is currently under rigorous evaluation.[18-20] The principles of surgical mural valve repair have largely influenced the transcatheter approach to mural regurgitation. Percutaneous leaflet edge-to-edge repair("transcatheter Alfieri mural valve repair") is feasible with an array of technologies. Percutaneous mural annuloplasty is also feasible with stenting of the coronary sinus to reshape the mural annulus. Based on the surgical principles of mural repair, it is likely that a durable percutaneous repair will require both leaflet apposition and annuloplasty.

These innovations in transcatheter mural valve therapies have to date had the traditional cardiac catheterization laboratory as their venue. It is likely that they will transfer to the hybrid operating room as cardiothoracic surgeons embrace and master these disruptive technologies.[21] The rapidly evolving devices must be subjected to rigorous evaluation in controlled trials to guarantee safety and efficacy before being allowed to generalize into clinical management of valvular heart dis-ease.[22,23] The emergence of the hybrid operating room is part of the endovascular revolution in cardiothoracic and vascular surgery and will likely be a mainstream clinical venue in every cardiovascular center in the near future.

## PERIOPERATIVE MYOCARDIAL CONDITIONING

*Pharmacologic Conditioning*

***Volatile Anesthetics***

Perioperative myocardial protection in cardiac surgery remains a clinical priority that is achievable by both pharmacologic and ischemic conditioning.[24] Volatile anesthetics have emerged as important pharmacologic myocardial protectants in cardiac surgery as clinical evidence of their efficacy is consistently measurable.[25,26] A recent Italian cohort study (N=34,310: 64 medical centers) investigated whether exposure to volatile anesthetics influenced mortality after CABG surgery.[27] Risk-adjusted analysis showed that volatile anesthesia significandy decreased operative mortality(p=0.035). Furthermore, this mortality reduction was even more significant with a longer duration of exposure to volatile anesthetics(p=0.022) or at those medical centers that used volatile anesthetics in at least 25% of their coronary cases(p=0.003). Isoflurane was associated with the most significant mortality decrease (p=0.039). These outcome data provide yet more evidence to include volatile anesthesia as part of the anesthetic plan for adult cardiac surgical patients.

***levosimendan***

Levosimendan, a calcium-sensitizing inodilator, has augmented pharmacologic effects when administered early after anesthetic induction before cardiopulmonary bypass.[28] A recent meta-analysis of 5 randomized trials (cumulative N=139)showed that levosimendan exposure significantly reduced the release of cardiac troponin after cardiac surgery (weighted mean difference=2.5 ng/dL, p=0.0003) and also significandy shortened the time to hospital discharge (weighted mean difference=-1.38 days, p=0.05).[29] A second meta-analysis of 10 randomized trials (cumulative N=440) showed that levosimendan exposure significantly reduced mortality after cardiac surgery (odds ratio=0.35: 95% confidence interval. 0.18-0.71;P=0.003).[30]

These perioperative outcome benefits of levosimendan are being evaluated in multiple randomized controlled trials in cardiac surgical patients. A survey of a clinical trials registry revealed the following trials in progress (full details available at www.clinicaltrials.gov): high-risk adult heart valve surgery (NCT00154115), myocardial

protection in elective CABG surgery with cardiopulmonary bypass (NCT00610350 and NCT00130871), prophylactic application in infant heart surgery (NCT00549107), and the use of levosimendan in pediatric heart surgery compared with milrinone (NCT00695929). Given the positive results from recent meta-analyses, it is highly likely that levosimendan will protect the myocardium after cardiac surgery to result in significantly improved outcomes.

### *Ischemic Conditioning*

#### ***Myocardial Ischemic Conditioning***

Ischemic preconditioning has shown clinical benefit in cardiac surgery, making it a highlight in the specialty in 2008.[1] A recent meta-analysis of 22 trials (cumulative N=933) showed that ischemic preconditioning significantly reduced ventricular arrhythmias (odds ratio=0.11;95% confidence interval. 0.04-0.29; p=0.001), inotrope requirements (odds ratio=0.34: 95% confidence interval, 0.17-0.68; p=0.002), and intensive care unit stay (weighted mean difference=-3 hours: 95% confidence interval. -4.6 to-1.5 hours; p=0.001).[31] The authors concluded that ischemic preconditioning may provide additional myocardial protection over cardioplegia alone and that a large randomized controlled clinical trial was indicated.

#### ***Remote Ischemic Conditioning***

Ischemic preconditioning also can be remote, in that brief ischemia of a remote tissue induces ischemic protection in the heart. This type of approach has received increasing clinical focus in proof-of-concept studies, making it a highlight for the specialty in 2008.[1]

A recent meta-analysis of 4 randomized controlled trials (cumulative N=184) showed that remote ischemic precondi-boning in cardiac surgery significantly reduced biomarkers of cardiac injury (standardized mean difference=-0.81;95% confidence interval.-1.29to-0.33; p=0.0010).[32] This finding was confirmed in a recent randomized trial in PCI, taking the clinical application of remote ischemic preconditioning yet a step further.[33,34] In this trial (N=242), remote ischemic preconditioning was induced by three 5-minute infiadons of a blood pressure cuff to 200 mmHg around the upper arm. This simple intervention significantly lowered cardiac troponin release after elective PCI(p=0.040), as well as the 6-month major adverse cardiac and cerebral rate(p=0.018).[33] This powerful effect of remote ischemic preconditioning was recently highlighted again in a small randomized trial in elective CABG surgery (N=45) in which this simple intervention reduced troponin release by 42.4%(p=0.019).[35]The search is underway to isolate the humoral factors responsible for this ischemic preconditioning of 1 tissue remote from another.[36] This targeted research also could result in a future parenteral agent for perioperative protection against myocardial ischemia.

The clinical promise and immediate applicability of remote ischemic preconditioning is reflected in the multiple perioperative clinical trials currently in progress, 16 in cardiac surgery and 25 in noncardiac surgery (full details available at www. clinicaltrials.gov). As these trials are completed, it is likely that this intervention will become an anesthetic consideration throughout perioperative practice both in cardiac and noncardiac procedures. It represents a major research opportunity for the cardiothoracic and vascular community.

## CORONAR ARTER DISEASE

### *Clinical Outcomes After CABG Surgery*

#### ***Perioperative Angiotensin Blockade***

Angiotensin-converting enzyme inhibitor (ACEI) therapy already has been highlighted as an independent predictor for significant perioperative hypotension.[36-38] A recent observational cohort study (N=10,023: 1996-2008) evaluated the outcome effects of exposure to ACEI in adults undergoing CABG surgery.[39] From this large cohort, the ACEI cohort (N=3,052) was matched to a control group by propensity analysis. Overall mortality was 1 %. Preoperative exposure to ACEI doubled the mortality risk (odds ratio=2.00; 95% confidence interval, 1.17-3.42; p=0.013). Furthermore, preoperative exposure to ACEI significantly increased the risks of renal dysfunction (odds ratio=1.36; 95% confidence interval. 1.1-1.67; p=0.006), atrial fibrillation (odds ratio=1.34; 95% confi-dente interval, 1.18-1.51; p<0.0001), and increased inotropic support (odds ratio=1.22; 95% confidence interval, 1.1-1.36; p<0.0001). Multivariate analysis showed that preoperative ACEI exposure independently predicted mortality(p=0.04), renal dysfunction(p=0.0002), atrial fibrillation(p<0.0001),

and inotropic support (p<0.0001).

These data provide support for preoperative discontinuation of ACEI in patients scheduled for CABG surgery, as is currently recommended in noncardiac surgery.[40] This concept has been supported further by a recent clinical trial (N=300) that showed that perioperative hemodynamic instability caused by ACEI exposure in adult cardiac surgical patients was dose dependent.[41] Further trials should determine the optimal time for preoperative discontinuation of ACEI in cardiac surgery to avoid the outcome disadvantages associated with this drug class in the perioperative period. Besides the avoidance of ACEI, future clinical trials also will likely show outcome improvements for adult cardiac surgical patients with perioperative steroids, statins, and endothelin antagonists, as has been recently reviewed.[42]

***Preoperative Red Cell Mass***

The risks of preoperative anemia in outcomes after elective CABG surgery continue to be elucidated. A recent observational trial (N=10,025: 1998-2007) investigated whether preoperative hemoglobin affects survival after elective coronary surgery. Multivariate analysis showed that low hemoglobin level as a continuous variable was an independent risk factor for perioperative mortality. [43] In a follow-up study, the same group of investigators showed that a low preoperative hemoglobin level is also an independent risk factor for postoperative renal dysfunction. [44] The focus of future trials in this research area should be whether preoperative augmentation of red cell mass (eg, erythropoietin) in high-risk patient subgroups would improve clinical outcomes after cardiac surgery with and without cardiopulmonary bypass.

*Techniques in CABG Surgery*

***Endoscopic Saphenous Vein Graft Harvesting***

Although endoscopic saphenous vein harvesting is widely used to reduce postoperative wound complications after CABG surgery, its effects on long-term graft patency remain unknown.

A landmark observational study investigated whether endoscopic vein harvesting is significantly associated with vein graft failure and adverse outcomes (n=1,753 in the endoscopic harvest group; n=1,247 in the open harvest group).[45] Venous graft failure was defined as at least 75% stenosis as evaluated on angiography 12 to 18 months after CABG surgery. The selected trial endpoints were death, myocardial infarction, and repeat myocardial revascularization.

The study subgroups had similar baseline clinical profiles. Endoscopic venous graft harvesting was associated with a significantly higher rate of graft failure (46.0% v 38.0%, p<0.001). Furthermore, endoscopic venous harvesting was associated with significantly increased risks of death, myocardial infarction, or repeat revascularization as an endpoint (hazard ratio=1.22; 95% confidence interval, 1.101-1.47; p=0.04), death, or myocardial infarction as an endpoint (hazard ratio=1.38; 95% confidence interval, 1.07-1.77; p=0.01) and death alone as an endpoint (hazard ratio=1.52; 95% confidence interval, 1.13-2.04; p=0.005). [45] The investigators concluded that graft failure and adverse outcomes after CABG surgery are significantly worsened by endoscopic venous harvesting. They suggested that the safety of this vascular graft harvesting technique should be evaluated further in randomized trials. The pathophysiology behind this observation may be the increased venous endothelial trauma that is possible with the endovascular harvest technique.

***Cardiopulmonary Bypass: On-Pump Versus Off-Pump***

The search for the optimal CABG technique has been ongo-ing after the development of off-pump CABG surgery in the 1990s.[46] The off-pump CABG technique has now matured and generalized throughout cardiac surgery, making large cohort comparisons possible. An extensive cohort comparison (N=63,047: n=48,658 on-pump CABG surgery patients; n=14,389 off-pump CABG surgery patients) with multivariate analysis recently evaluated the clinical outcome differences between the 2 established techniques. [47]

There were no significant differences in perioperative mortality (on-pump 3.0% v off-pump3.2%; p=0.14) and stroke (on-pump 1.8% v off-pump 1.7%; p=0.53). Despite similar baseline demographics and comorbidities, the off-pump cohort had significantly longer hospital stays (off-pump mean stay=10.2 days v on-pump mean stay=9.9 days, p<0.0001) and higher hospital costs (off-pump mean cost=$38,793 v on-pump mean cost=$37,806; p=0.0005).

Multivariate analysis showed that the off-pump technique was associated with 0.6 extra hospital days (95% confidence interval, 04-0.8; p<0.0001) and $1,497 extra in hospital costs (95%confidence interval, $779-$2,216; p<0.01). Although these differences may be statistically significant, their clinical significance is weak at best.

A second cohort study (N=14.766 from 1997-2007: n=7,083 off-pump CABG surgery patients; n=7,683 on-pump CABG surgery patients) analyzed clinical outcomes between the 2 techniques based on risk quartiles derived from the predicted risk of operative mortality calculated from the Society of Thoracic Surgeons validated predicted risk of operative mortality formula.[48,49]

In the lower 2 risk quartiles, there was no difference in perioperative mortality associated with the CABG technique. In the higher-risk quartiles, the off-pump technique was associated with improved survival (odds ratios=0.62 and 0.45 for third and fourth risk quartiles, respectively). Further analysis confirmed that the off-pump technique preferentially reduced mortality in high-risk patients(p=0.005). Based on these recent large "real-world" analyses, it appears that clinical outcomes after surgical coronary revascularization are equivalent between techniques in low-risk patients but that the off-pump technique offers a survival advantage in the high-risk subgroups.

### *Techniques in PCI*

#### ***PCI for Myocardial Infarction***

Primary PCI has been compared with fibrinolytic therapy in STEMI in multiple randomized controlled trials and metaanalyses.[50] However, because randomized trials may have limited applicability to "real-world" settings, a recent meta-analysis included randomized trials (N=8,140; 23 trials) and observational studies (N=185,900: 32 studies).[51] Primary PCI reduced short-term mortality by 34% in randomized trials (odds ratio=0.66; 95% confidence interval, 0.51-0.82) and 23% in observational studies (odds ratio=0.77: 95% confidence interval, 0.62-0.95). In randomized trials, primary PCI significandy reduced 1-year mortality by 24%(odds ratio=0.76: 95% confidence interval, 0.58-0.95)and reinfarction by51% (odds ratio=0.49; 95%confidence interval, 0.32-0.66). However, in observational studies, primary PCI had no significant long-term clinical outcome benefits. It is important to interpret evidence in the light of study design. Although randomized trials are often regarded as high-quality evidence, their applicability outside strict study criteria in the real world may be limited.

Patients with STEMI may present to hospitals that do not have primary PCI capability and so will receive fibrinolysis. The optimal timing of PCI after fibrinolysis has not been established. A recent randomized trial evaluated the efficacy of prompt PCI within 6 hours after fibrinolysis for STEMI (N=1,059).[52] The defined trial endpoint was the composite of death, reinfarction, recurrent ischemia, congestive heart failure, or cardiogenic shock within 30 days.

Routine early PCI after fibrinolysis in STEMI significantly decreased the incidence of the defined study endpoint (11.0% v 17.2%: relative risk=0.64: 95% confidence interval. 0.47-0.87; p=0.004).[52] The incidence of clinically significant bleeding was similar between groups. The authors concluded that early routine PCI after fibrinolysis for STEMI significantly reduced ischemic complications. Taken together, these recent PCI studies show the consistent benefit of PCI in STEMI managed with or without fibrinolysis.

#### ***Intra-aortic Balloon Pump Therapy in Myocardial Infarction***

Recent cardiology guidelines recommend intra-aortic balloon counterpulsation (IABP) in STEMI with cardiogenic shock.[53] A recent meta-analysis examined the evidence supporting this strong recommendation by the American Heart Association and American College of Cardiology.[54] The first analysis pooled data from 7 randomized trials (N=1,009) to show that IABP did not improve survival or ejection fraction and was significantly associated with higher rates of stroke and bleeding.

The second analysis pooled data from 9 STEMI cohort studies (N=10,529). In STEMI treated with thrombolysis, IABP decreased mortality by 18% (95% confidence interval, 16%-20%; p<0.0001). In contrast, in STEMI treated with primary PCI, IABP was associated with a 6% (95% confidence interval. 3%-10%; p<0.0008) increase in mortality. The investigators concluded that the current recommendation for IABP in high-risk STEMI is

only partially supported by the current evidence. The only supporting evidence for IABP is derived from observational studies of STEMI managed with thrombolysis.

***Advances in Platelet Blockade: The Advent of Prasugrel and Ticagrelor***

Mechanical reperfusion with PCI and stenting during STEMI is accompanied by platelet blockade with aspirin and clopidogrel, a second-generation thienopyridine.[53] Coronary stmt thrombosis after PCI is a serious complication with a high mortality rate.[55] Resistance to platelet blockade with clopidogrel has received ongoing attention because of its importance as a risk factor for coronary stmt thrombosis.[56]

Prasugrel is a novel third-generation thienopyridine that pro-duces more consistent platelet inhibition than clopidogrel be-cause it a more potent blocker of the platelet adenosine diphos-phate $P2Y_{12}$ receptor.[57] However, like clopidogrel, prasugrel is a prodrug that requires hepatic biotransformation to form the active drug.[57]

A randomized trial in patients with acute coronary syndromes undergoing PCI (N=13,608) showed that prasugrel, as compared with clopidogrel, significantly reduced ischemic events including stmt thrombosis (hazard ratio=0.81; 95%confidence interval, 0.73-0.90; p<0.001) but at an increased risk of bleeding (hazard ratio=1.32; 95% confidence interval, 1.03-1.68; p=0.03).[58]

A second randomized trial (N=3,534; 707 medical centers in 30 countries) showed in patients with STEMI undergoing PCI that prasugrel compared with clopidogrel significantly reduced the rates of the following 2 composite endpoints: cardiovascular death, nonfatal myocardial infarction or nonfatal stroke (hazard ratio=0.68; 95% confidence interval, 0.54-0.87; p=0.0017); and, cardiovascular death, myocardial infarction or urgent target vessel revascularization (hazard ratio=0.75; 95% confidence interval, 0.59-0.96; p=0.0205).[59] There was no additional increase in major bleeding(p=0.3359), except after CABG surgery in which adverse bleeding was increased significantly with prasugrel(p=0.0033).

In the United States, the Food and Drug Administration approved prasugrel on July 10, 2009, for application in patients with unstable angina or myocardial infarction who undergo PCL.[60] Although this new agent offers additional profound platelet blockade for PCI in the cardiac catheterization laboratory, it poses a significant risk for severe perioperative bleeding in patients who subsequently undergo CABG surgery. There is still an unmet clinical priority to have rapidly reversible oral platelet blockers to minimize the occurrence of significant platelet blockade in the subset of patients who require CABG surgery after PCI. The development of a short-acting reversible oral thienopyridine would be a major pharmacologic break-through in the management of acute coronary syndromes.

Clopidogrel and prasugrel bind irreversibly to the platelet ADP $P2Y_{12}$ receptor after biotransformation in the liver; they are therefore classified as indirect irreversible platelet inhibi-tors.[61] In contrast, ticagrelor is a novel drug that binds directly and reversibly to the platelet ADP $P2Y_{12}$ receptor: it is therefore classified as a direct reversible oral platelet inhibitor.[61] A recent randomized trial evaluated ticagrelor versus clopidogrel for the prevention of cardiovascular events in patients with acute coronary syndromes, with or without STEMI (N=18,624).[62] The defined trial endpoint was a composite of death from vascular causes, myocardial infarction, or stroke at 12 months. Ticagrelor significantly decreased the incidence of the endpoint (9.8% v 11.7%; hazard ration=0.84; 95% confidence interval, 0.77-0.92; p<0.001) as well death from any cause (4.5% v 5.9%, p<0.001). Although the incidence of major bleeding was similar, ticagrelor was associated with higher rates of bleeding that were not related to CABG surgery (4.5% v 3.8%, p=0.03). Ticagrelor is the first thienopyridine that is a direct reversible platelet inhibitor. If randomized trials continue to show outcome improvement with this new drug in acute coronary syndromes, the Food and Drug Administration should approve ticagrelor in the near future.

***Choice of Coronary Revascularization Technique***

With the advent of drug-eluting stems and further refinemenu in PCI, the management of multivessel CAD may be with multivessel PCI or CABG surgery.[63,64] A recent observational study (N=3,720 from a single medical center (2004-2005) evaluated clinical outcomes in multivessel coronary disease 3 years after CABG surgery or PCI.[65] Although the PCI cohort was typically younger with fewer comorbidities, PCI with drug-eluting stems

was associated with significantly higher rates of target-vessel revascularization, death (hazard ratio=1.62; 95% confidence interval, 1.07-2.47), and myocardial infarction (hazard ratio=1.65; 95% confidence interval, 1.15-2.44). The risk-adjusted stroke rate was similar between groups (hazard ratio=0.92; 95% confidence interval,0.69-1.51).

A second trial pooled data from 10 randomized trials (N=7,812) to evaluate long-term mortality in multivessel coronary artery disease managed with CABG surgery or PCI (balloon angioplasty in 6 trials and bare-metal stems in 4 trials).[66] The mortality rate at 5.9 years was similar regardless of the revascularization technique (15% for CABG surgery and 18% for PCI; hazard ratio=0.91;95% confidence interval, 0.82-1.02; P=0.12). Mortality rates, however, were significantly lower after CABG surgery for diabetics (hazard ratio=0.70; 95% confidence interval, 0.56-0.87; p=0.014) and patients >65 years of age (hazard ratio=0.82; 95% confidence interval, 0.70-0.97; p=0.002). The investigators concluded that long-term mortality in multivessel disease is similar after PCI or CABG surgery, except for diabetics and patients >65 years in whom CABG surgery offered a significant survival benefit.

## ADVANCES IN PERIOPERATIVE BLEEDING AND HEMOSTASIS

Bleeding after cardiac surgery remains an important clinical challenge that significantly worsens clinical outcome and economic costs.[67] A recent observational study (N=1,118) identified a 6% rate of excessive bleeding after adult cardiac surgery defined as mediastinal bleeding≥200 mL per hour or ≥2mL/kg per hour for 2 consecutive hours.[67] Patients with excessive bleeding had significantly increased risks of blood transfusion and mediastinal re-exploration (p<0.001), prolonged mechanical ventilation and intensive care unit stay(p<0.001),and death (22% v 6%, p<0.001).

Although moderate exposure to allogeneic blood products has been shown recently not to affect long-term survival after CABG surgery, the risks of blood transfusion are still highly significant in the perioperative period.[68] Even though CABG surgery performed off-pump reduces the perioperative bleeding and transfusion risk, these risks are still present.[69] A recent randomized clinical trial examined the hematologic effects of volume resuscitation with the artificial colloid hetastarch in off-pump CABG surgery (N=156: 1 L of hetastarch v 1 L of albumin).[70] The study was terminated early because hetastarch administration significantly increased the risk of transfusion (46.2% v 25.6%, p=0.012), the amount of transfusion (packed red blood cells 1.14 v 0.40 U, p=0.017; fresh frozen plasma 0.57 v 0.15 U, p=0.009, and platelets 0.35 v 0.10 U, p=0.013) and the volume of chest tube drainage in the first 12 hours postoperatively (732 mL v 563.6 mL, p<0.001).

A second placebo-controlled randomized trial evaluated the hematologic effects of intravenous N-acetylcysteine (100-mg/kg bolus followed by infusion at 20 mg/kg/h until 4 hours after cardiopulmonary bypass) administered during cardiac surgery in patients with moderate renal dysfunction defined as glomerular filtration rate ≤60 mL/min (N=177).[71] Exposure to N-acetylcysteine significantly increased 24-hour chest tube drainage (mean=261 mL; 95% confidence interval, 93-488mL; p=0.008), red blood cell transfusion (mean=1.6 U; 95% confidence interval, 0.4-3.1 U; p=0.02) and the risk of receiving≥5 U of red blood cells (relative risk=2.09; 95% confidence interval, 1.24-3.83; p=0.005). The investigators concluded that although this agent may offer perioperative nephroprotection, its adverse effects on bleeding and transfusion should be considered in the perioperative risk-benefit profile.

Although factor VII can be lifesaving in refractory bleeding after cardiac surgery, its perioperative safety and efficacy have not been adequately evaluated.[69] A recent meta-analysis pooled data from 5 trials (cumulative N=298: 1 randomized, 3 propensity matched, and 1 case matched) to address the perioperative safety and efficacy of this therapy.[72] Factor VII therapy was associated with a nonsignificant reduction in surgical re-exploration for bleeding (odds ratio=0.25: 95% confidence interval. 0.01-7.01;P=0.42), equivalent mortality (odds ratio=0.96; 95% confidence interval, 0.50-1.86; p=0.90), and a trend toward increased stroke (odds ratio=3.17; 95% confidence interval, 0.83-12.10; p=0.09). The authors concluded that these proposed effects of perioperative factor VII should be explored further in a large randomized controlled trial.

A recent small randomized trial has begun this process. Adult cardiac surgical patients with refractory bleeding (N=172) were randomized to placebo (n=68), factor VIi at

40μg/kg(n=35), or factor VII at 80μg/kg(n=69).[73] Exposure to factor VII was associated with significantly reduced rates of exploration for bleeding(p=0.03) and allogeneic transfusion (p=0.01). Although serious adverse events were more common in the factor VII groups, these differences were not statistically significant (placebo 7%, 40 μg/kg 14%, and 80 μg/kg 12%; p=0.43). The authors concluded that this therapy is effective for refractory bleeding in cardiac surgery but that larger clinical trials are required to document its safety. This is a major research opportunity for the specialty in the form of a large multicenter trial through a clinical research collaboration such as the cardiothoracic trials network (full details available at www.ctsurgerytnet.org).

A frequent etiology in bleeding after cardiac surgery is platelet dysfunction.[69] Recently, it has become possible to directly stimulate platelet production by megakaryocytes in the bone marrow by means of thrombopoietin-receptor agonists such as eltrombopag and romiplostim.[74] Although these agents are still in late-stage clinical development, they seem promising. It is a small leap to apply these agents preoperatively in adult cardiac surgical patients to allow the facilitation of autologous platelet harvest for the management of perioperative coagulopathy as a means to minimize allogeneic transfusion in a manner analogous to the application of erythropoietin in cardiac surgery.[69] Because platelet dysfunction is a major mechanism in acquired coagulopathy after cardiopulmonary bypass, this concept may have major perioperative application in the future.

## RENAL PROTECTION AFTER CARDIAC SURGERY

Renal dysfunction independently predicts for adverse outcome after cardiac surgery.[75] As a result, perioperative nephrotection is a clinical priority. A recent trial investigated whether fenoldopam is nephroprotective in renal dysfunction after cardiac surgery (N=92: 46 patients exposed to fenoldopam infusion and 46 case-matched patients as the control group).[76] The 48-hour exposure to fenoldopam was associated with a significantly reduced need for renal replacement therapy (17% v 39%, p=0.037). These findings merit a larger randomized trial in adult cardiac surgical patients.

Atrial natriuretic peptide in conjunction with hydration recently was shown in a randomized trial (N=254) to significandy protect against contrast nephropathy in coronary angiography (3.2% v 11.7%, p=0.015).[77] In multivariate analysis, exposure to atrial natriuretic peptide was nephroprotective (odds ratio=0.24, p=0.016). A similar randomized trial in on-pump CABG surgery patients (N=504) also found that perioperative exposure to atrial natriuretic peptide is nephroprotective(p<0.0001) and significantly reduces postoperative complications(p=0.0208).[78] The authors concluded that atrial natriuretic peptide reduces complications including renal failure after cardiac surgery.

A pilot randomized trial (N=100) recently showed that perioperative sodium bicarbonate infusion significantly reduces renal dysfunction after cardiac surgery with cardiopulmonary bypass (odds ratio=0.43; 95% confidence interval. 0.19-0.98: V=0.043).[79] These promising data are being explored in more than 50 randomized trials throughout cardiovascular medicine and nephrology (full details available at www.clinicaltrials.gov).

A single-center observational study in adult cardiac surgical patients (N=563) showed that pentastarch was significantly associated with renal injury, defined as a 50% rise in serum creatinine within 4 days after cardiac surgery.[80] The incidence of renal injury was 10%. Exposure to pentastarch independently predicted renal injury (odds ratio per mL/kg=1.08; 95% confidence interval, 1.04-1.12; p=0.001). The risk was dose dependent with a cutoff of 14 mL/kg. Hence, this group of colloids (hetastarch and pentastarch) may increase the risks of bleeding, allogeneic transfusion, and renal injury after cardiac surgery. Although N-acetylcysteine also interferes with hemostasis in cardiac surgery, it does not appear to contribute to renal injury.[81] Although studies have shown that N-acetylcysteine is nephroprotective, these results have not been consistent in the perioperative period.[81]

## PERIOPERATIVE GLYCEMIC CONTROL

Perioperative management of glucose has been a major focus, given its relationship to important clinical outcomes.[82] However, a landmark trial randomized critically ill adults (N=6,014) to intensive glucose control (defined as target glucose range 81-108 mg/dL) versus conventional glucose control (defined as target glucose range ≤180 mg/dL).[83] The

trial primary endpoint was defined as death within 90 days after randomization. The 2 cohorts had similar baseline characteristics. Intensive insulin therapy significantly increased mortality (27.5% v 24.9%; odds ratio=1.14: 95% confidence interval, 1.02-1.28; p=0.02). This significantly increased mortality associated with intensive glucose control applied to surgical and medical patients equally (odds ratio for intensive glucose control=1.31, odds ratio for conventional control group=1.07, p=0.10). Severe hypoglycemia (defined as blood glucose ≤40mg/dL) was significantly associated with intensive insulin therapy (6.8% v 0.5%, p<0.001). There was no significant difference between groups with respect to hospital stay(p=0.86), intensive care unit stay(p=0.84), duration of mechanical ventilation(p=0.56), or requirement for renal replacement therapy(p=0.39). The authors concluded that conventional glucose control reduced mortality in critically ill adults as compared with intensive glucose control.

Hypoglycemia is not only more common with intensive glucose management but has been associated with increased mortality in patients admitted to the hospital with acute myocardial infarction.[84] A follow-up large cohort observational trial (N=7,820) investigated whether spontaneous or iatrogenic hypoglycemia was responsible for the increased mortality risk observed in myocardial infarction.[85] Multivariate analysis showed that hypoglycemia predicted mortality in patients not treated with insulin (odds ratio=2.32; 95% confidence interval, 1.31-4.12) but not in patients managed with insulin (odds ratio=0.92; 95% confidence interval, 0.58-1.45). This issue merits further investigation in perioperative cardiovascular practice.

In light of these recent studies, an updated meta-analysis was conducted to summate all relevant evidence on the relationship between intensive glucose therapy with insulin and mortality in the intensive care unit (N=13,567: 26 trials).[86] The relative risk of hypoglycemia with intensive insulin therapy was 6.0 (95% confidence interval, 4.5-8.0). Intensive insulin therapy decreased mortality in the surgical intensive care unit (relative risk=0.63; 95% confidence interval, 0.44-0.91) but not in medical (relative risk= 1.0: 95% confidence interval. 0.78-1.28) or mixed intensive care units (relative risk=0.99; 95% confidence interval, 0.86-1.12). The authors concluded that intensive glucose therapy with insulin significantly increased the risk of hypoglycemia and reduced mortality only in the surgical intensive care unit setting. The recent guideline from the Society of Thoracic Surgeons on glucose management in adult cardiac surgery endorses insulin infusion therapy to maintaro perioperative glucose levels below 180 mg/dL.[87]

## CONCLUSIONS

The 2009 highlights in the specialty begin with the emergence of the hybrid operating room as the venue for transcatheter valve and coronary therapies with the convergence of the 3 specialties: cardiac surgery, cardiovascular anesthesiology, and interventional cardiology. Transcatheter aortic valve replacement will expand exponentially around the world to usher in the global paradigm shift in perioperative cardiovascular practice. The venue for this disruptive innovation, the hybrid operating room, will stimulate further transcatheter innovations for the management of disease entities such as mural regurgitation, atrial fibrillation, and ascending aortic aneurysm. Cardiac specialists have embraced the endovascular revolution in the management of cardiovascular pathology.

Progress in myocardial conditioning in 2009 has strengthened the evidence to exploit this protective mechanism perioperatively. Pharmacologic conditioning with volatile anesthetics and levosimendan significantly improves cardiac surgical outcomes in randomized trials, large observational trials, and meta-analysis. Ischemic myocardial conditioning consistently protects the heart during ischemia and reperfusion both in the catheterization laboratory and the operating room. Myocardial conditioning is the focus of multiple randomized trials throughout cardiovascular practice. It is likely that these large trials will show clinical benefit to facilitate the integration of these interventions into the specialty.

Advances in the management of CAD have continued in 2009. Perioperative angiotensin blockade and anemia significandy worsen outcome after CABG surgery. Although current data show that off-pump CABG surgery is clinically equivalent with on-pump CABG surgery, it appears to improve outcomes in high-risk subgroups. Although endoscopic saphenous vein harvesting has proven advantages over the open technique, a landmark trial has shown that it significantly increases graft thrombosis and adverse outcome rates after CABG surgery.

In interventional cardiology, the latest data consistently show the significant outcome advantage from PCI in STEMI managed with or without fibrinolysis. In contrast, however, recent evidence suggests that IABP does improve outcome in highrisk STEMI, challenging current PCI guidelines. The new oral platelet blocker, prasugrel, was approved in 2009 by the Food and Drug Administration in the United States. Prasugrel, however, may be superseded by ticagrelor, a thienopyridine that inhibits platelets directly and reversibly. Although further trials are indicated, it is likely that ticagrelor will be approved in the near future to allow powerful short-acting oral platelet blockade that is rapidly reversible for PCI. Now that PCI is a viable therapy for multivessel CAD, recent trials have compared PCI versus CABG surgery for multivessel CAD. The data suggest that in appropriate patient groups, these techniques are equivalent, although CABG significantly lowers revascularization rates and improves outcome in diabetics and patients >65 years old. The hybrid operating room will allow CABG surgery and PCI to be performed as indicated at a single venue supervised by the specialist trio including a coronary surgeon, a cardiovascular anesthesiologist, and an interventional cardiologist. Hybrid coronary revascularization will likely be the future approach to multivessel CAD, thus shifting the focus away from a contest between techniques for best complementary therapy in a hybrid environment.

Bleeding after cardiac surgery continues to adversely affect clinical outcomes. Hetastarch and N-acetylcysteine appear to aggravate bleeding and transfusion risk in adult cardiac surgical patients. Although factor VII can be a magic bullet in life-threatening refractory bleeding in cardiac surgery, its safety remains to be explored further in randomized trials. Because platelet production can be stimulated by thrombopoietin agonists such as eltrombopag and romiplostim, they may be very significant in the future management of coagulopathy after cardiac surgery.

Because renal dysfunction decreases survival after cardiac surgery, perioperative nephroprotection remains a clinical priority. Recent data show that fenoldopam, atrial natriuretic peptide, and sodium bicarbonate significantly reduce the incidente of renal dysfunction. Further randomized trials must confirm these encouraging findings and confirm their safety before they can be incorporated into clinical practice.

Although perioperative glucose management (goal glu-cose level≤180 mg/dL) improves outcome in adult cardiac surgery, recent evidence shows that these outcome benefits do not apply to all hospital settings. Furthermore, intensive insulin therapy for a target glucose range of 80 to 110 mg/dL offers no outcome advantage and significant hypoglycemic risk.

These selected highlights have only sampled the advances in the specialty for 2009. The past year has witnessed major advances in cardiovascular practice. There are new devices, new clinical venues, and new drugs. The coming year will most likely advance these achievements.

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## 摘要

全文汇总了2009年心胸血管麻醉领域权威性和学术性较高的临床研究资料，对去年本专业相关热点问题进行了概括性介绍。杂交手术室是心外科、心血管麻醉和心内科介入治疗三种专业人员进行经导管治疗的场所，经导管行主动脉瓣膜置换术的开展证明人们对腔内治疗技术变革的认同。通过药物预处理和缺血预处理实施的心肌保护具安全、有效的临床特点，因此它们是目前多项临床试验关注的重点。血管紧张素抑制、贫血以及内窥镜取大隐静脉技术可对冠状动脉旁路移植术（CABG）的预后造成不良影响。不停跳CABG与停跳CABG的临床预后对低风险患者等同，但后者有利于改善高风险患者预后。经皮冠状动脉介入治疗(PCI)能明显降低心肌梗死患者的病死率，然而主动脉内球囊反搏技术对此类患者的有效性证据却不尽如人意。普拉格雷已被批准用于PCI后的血小板抑制，但有可能被替卡格雷取代。PCI与CABG技术对冠脉血管多支病变患者临床预后的影响相似，但CABG对降低患者行再血管化治疗可能性、对糖尿病和年龄>65岁患者术后生存率的提高更有益。羟乙基淀粉和N-乙酰半胱氨酸都能够增加心脏手术患者围术期出血量和输血量。VII因子能够治疗致命性出血，但它的安全性有待进一步论证。具有够刺激血小板生成作用的血小板生成素拟肽等药物可能在未来改善心脏手术后止血功能方面发挥作用。非诺多泮、心房利钠肽以及碳酸氢钠的肾保护作用有待进一步试验证实。强化胰岛素治疗并无改善临床预后作用，却明显增加低血糖的发生率。

关键词：杂交手术室；经导管主动脉瓣膜置换术；二尖瓣成形术；缺血预处理；药物预处理；左西孟旦；吸入麻醉药；血管紧张素转化酶抑制剂；贫血；羟乙基淀粉；冠状动脉搭桥手术；内窥镜取大隐静脉技术；经皮冠状动脉介入治疗；主动脉内球囊反搏；心房利钠肽；强化胰岛素治疗

# 2009年心胸血管麻醉热点问题

# The Year in Cardiothoracic and Vascular Anesthesia:Selected Highlights From 2009

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## 一、杂交手术室内进行的经导管瓣膜手术

### 1. 经导管进行主动脉瓣手术

2009年，经导管行主动脉瓣膜置换术仍备受关注。最近的系列病例报道和文献进展使其对麻醉带来的挑战引起了格外的关注[2-5]。当美国完成了具有里程碑意义的PARTNER试验（AoRTic TraNscathetER 瓣膜试验）后，这项技术进一步获得重大进展（了解细节请登陆www.clinicaltrials.gov[NCT00530894]），并最终导致FDA批准第一代经导管主动脉瓣置换技术的使用。随着此项技术的开展，其对心血管麻醉医生也带来一系列的挑战，包括对手术细节及其可能并发症的了解、对杂交手术室环境的适应、与多学科精英团队的协作以保障此技术在各机构的安全推广。

为确保最佳管理模式和经导管主动脉瓣膜置换术的成功，必须对手术步骤有详尽了解[6-8]。手术主要分为以下几部分：开放入径血管、确定主动脉瓣环大小、调试经静脉心室起搏器、主动脉瓣球囊成形、确定主动脉瓣位置以及开放主动脉瓣伞。其主要并发症可以理解为与几个主要操作步骤相关。如开放入径血管有导致主动脉夹层或主动脉破裂引发大出血的危险。瓣环大小错误可导致瓣膜血栓形成、瓣环破裂以及主动脉夹层[9]。经静脉心室起搏器产生无脉性室速才能短暂中止经主动脉瓣的射血，从而便于主动脉瓣球囊成形术及瓣膜伞的打开。起搏不适将影响球囊定位，导致瓣膜位置不当。虽然单纯的超声心动监测足以引导手术的进行，但是典型的方法还是结合荧光X线透视和超声心动成像引导瓣膜定位和瓣膜伞的打开[10]。此步骤主要风险为瓣膜位置不正可能导致瓣膜脱落入左心室、瓣膜血栓顺血流进入胸主动脉、堵塞冠状动脉开口以及主动脉根部破裂。尽管可能发生这些并发症，但患者转归取决于发现及时和有效处理[11]。

杂交手术室结合了传统导管室和传统手术室才能开展的治疗技术，为已知的心血管病患者（如冠状动脉疾病或主动脉瓣狭窄）提供了最佳的治疗方法[12]。杂交手术室的设计必须平衡多学科团队工作的需要，如心血管麻醉医生、心脏外科医生和心脏内科介入治疗医生[13]。其影像学设备主要包括荧光显影、超声心动、甚至是X线断层扫描。在此创新性的挑战环境中确保射线防护也是很重要的一点[14]。杂交手术操作对主动脉瓣狭窄和冠心病的治疗均产生变革性的影响[15]。最近的一项研究显示（366名CABG患者，共计796支移植血管），CABG术后的常规血管造影发现12%的移植血管出现严重病变，并随即进行了手术修复或PCI治疗。

多学科团队（麻醉医师、外科医师和心内科医师）对经导管主动脉瓣膜置换术的学习曲线具有显著意义[16]。团队功能在于能提供优越理想的患者转归。宾夕法尼亚大学医学中心就有这样一个非常优秀的多学科团队（一个主职心血管麻醉医生、一个主职心脏外科医生、一个主职心内科介入治疗医生），他们负责并监督所有的经导管治疗。经同行审议，这种团队工作模式已为北美和欧洲众多领先医学中心所采用。尽管随着这项技术的成熟，广泛推广于临床，但这种团队集中的工作方式仍对此项心血管领域革新技术的成功和

安全起有重要的作用[17]。

### 2. 经导管进行的二尖瓣手术

二尖瓣病变的治疗技术已有广泛革新发展，即将有专家就此方面内容进行综述[18, 19]。目前对经导管二尖瓣成形术正进行严格的评估[18-20]。手术修复二尖瓣的原则极大影响了二尖瓣返流的经导管治疗。在一系列技术条件下经皮二尖瓣瓣叶缘对缘成形术是可行的。经冠状静脉窦放置固定装置进行的经皮二尖瓣瓣环成形技术已具临床可行性。基于二尖瓣成形的手术原则，似乎经皮修复的持久性既需要瓣叶对位又需要瓣环成形。

到目前为止，各种经皮二尖瓣治疗技术都以传统的心导管技术为评判标准。似乎只有当心胸外科医生都熟练掌握了此项颠覆性的革新技术后，它才能转入杂交手术室[21]。迅速发展的相关设备也必须经过严格的对照研究验证，以确保其在心脏瓣膜疾病临床治疗中的安全性和有效性[22, 23]。作为心胸血管手术腔内治疗技术革新的一部分，杂交手术室在不久的将来会成为每个心血管疾病治疗中心的主流临床标准。

## 二、围术期心肌调节

### 1. 药物调节

（1）吸入麻醉药

心脏手术围术期心肌保护是临床的首要考虑因素，目前主要方法是药物调节和缺血预处理[24]。吸入麻醉药是重要的心肌保护药物，临床研究已经观察到其心肌保护的有效性[25, 26]。最近一项意大利的队列研究（34310名患者，64家医学中心），观察了吸入麻醉药是否会影响CABG术后患者的死亡率[27]。经危险性校正分析后显示，吸入麻醉药确能明显降低手术死亡率（p=0.035）。进一步的研究表明，延长吸入麻醉药的时间，死亡率下降更显著（p=0.022）；至少给25%的CABG患者使用吸入麻醉的医学中心中，死亡率也显著降低（p=0.003）。异氟烷降低手术后死亡率的效果最明显（p=0.039）。此结果为将吸入麻醉药纳入成人心脏手术的麻醉计划提供了进一步的依据。

（2）左西孟旦

左西孟旦是一种钙增敏剂，是新型的正性肌力药和血管扩张剂。在麻醉诱导后、体外循环前早期应用可获得放大的临床药理学作用[28]。最近一项针对5个随机试验的荟萃分析结果表明（累积病例139），使用左西孟旦能够显著降低心脏手术后肌钙蛋白的释放，并且显著减少患者住院时间[29]。另一项含10个随机试验的荟萃分析结果显示（累积病例440），左西孟旦能明显降低心脏手术后的死亡率[30]。

多项随机对照临床试验证实了心脏手术围术期应用左西孟旦的益处。一项针对临床研究注册情况的问卷调查显示以下研究正在进行中：成人高风险心脏瓣膜手术中(NCT00154115)、择期体外循环下行CABG术患者的心肌保护(NCT00610350和NCT00130871)、婴儿心脏手术中的预防性使用(NCT00549107)和小儿心脏手术中应用左西孟旦与米力农的对比研究(NCT00695929)（详情请登陆www.clinicaltrials.gov）。如果最近这些荟萃分析的结果是肯定的，那么左西孟旦将有助于心脏手术后的心肌保护，从而显著促进患者转归。

### 2. 缺血处理

（1）心肌缺血处理

缺血预处理在心脏手术中有明显的心肌保护作用，是该领域2008年的亮点之一[1]。最近一项含22个研究的荟萃分析结果显示（累积病例933），缺血预处理能显著降低室性心律失常、减少对正性肌力药的需求量并能缩短ICU停留时间[31]。该作者认为，缺血预处理可在心肌停跳液的基础上提供额外的心肌保护作用，这尚需大样本量的随机对照试验进行验证。

（2）远端缺血处理

缺血预处理也可以在远端进行，远端组织的短暂缺血会诱导心肌的缺血保护作用。这一方法已经在临床概念验证研究中受到越来越多的关注，成为此专业2008年的亮点之一[1]。

最近一项含4个随机对照试验的荟萃分析结果显示（累积病例184），远端缺血预处理能显著降低心脏手术后心肌损伤生物标志物的水平[32]。该发现被近期一个PCI随机试验所证实，由此对远端缺血预处理的临床推广起到一定的推动作用[33, 34]。在该研究中，远端缺血预处理通过连续3次将上臂血压计袖带压力充到200mmHg，每次持续5分钟，这个简单的措施明显降低择期PCI术后患者的肌钙蛋白水平，同样也降低了术后6个月严重心脑血管不良事件的发生率[33]。远端缺血预处理的强大效应在最近的一项择期CABG小样本随机研究中再一次得到了证实，这一简单的操作使肌钙蛋白释放减少了42.4%[35]。目前研究者正在鉴别产生预处理效果从一个远端组织到另一个组织的体液因子[36]。此靶向研究可能在不久的将来会产生围术期心肌缺血保护的肠道外药物。

远端缺血预处理的临床效应和应用取决于目前正在进行的一项多中心临床研究，包括16个心脏外科中心和25个非心脏外科中心（详情请登陆www.clinicaltrials.gov）。随着这些试验的完成，远端缺血预处理将可能成为心脏手术或非心脏手术围术期麻醉处理的一项可供选择的措施，并将成为心胸血管领域未来的研究热点。

## 三、冠心病

### 1. CABG术后的临床转归

（1）围术期血管紧张素抑制剂

血管紧张素转换酶抑制剂（ACEI）已经是围术期严重低血压的独立危险因素[36-38]。最近的一项观察队列研究评估了成年CABG患者使用ACEI对手术预后的影响[39]。在此项大样本队列研究中，ACEI与对照组进行倾向性分析。结果显示，该研究的总体死亡率为1%，而术前服用ACEI的死亡率翻倍。此外，术前应用ACEI还显著增加肾功能障碍、房颤的风险，增加正性肌力药物的使用。多因素分析结果显示，术前

使用ACEI药物是CABG术后死亡率、肾功能衰竭、房颤和使用正性肌力药物的独立危险因素。

由于这些数据的支持，择期CABG术前已经开始停止服用ACEI类药物，近期这一措施也被推荐到非心脏手术中[40]。这一观念被最近的一项临床研究进一步证实：成人心脏手术患者术前服用ACEI类药物与围术期血流动力学的不稳定性呈剂量依赖性特点[41]。下一步要做的研究就是确定心脏手术患者术前停用ACEI的最佳时间，从而避免服用这类药物对围术期转归的不良影响。除了避免使用ACEI类药物外，进一步的临床试验还需要对成年人心脏手术围术期使用类固醇、他汀类药物以及内皮素拮抗剂对预后的改善作用进行研究[42]。

（2）术前红细胞水平

术前贫血对择期CABG术后转归的影响仍是目前被关注的问题之一。近期的一项试验观察了术前血色素水平对择期CABG术后生存率的影响。多因素分析结果表明，低血色素做为一个连续变量是围术期死亡率的独立危险因素[43]。一项随访调查发现，术前低血色素同样是术后肾功能障碍的独立危险因素[44]。未来的关注点应该是对于高危患者术前使用促红细胞生成素增加红细胞水平，对体外循环或非体外循环下心脏手术后患者的预后是否具有促进作用。

**2. CABG中的相关技术**

（1）内窥镜取大隐静脉

尽管内窥镜取大隐静脉技术被临床广泛应用以降低CABG术后的并发症，但目前该技术对远期血管通畅性的影响还不清楚。一项具有重要意义的研究观察了内窥镜取大隐静脉是否与静脉桥失败和临床不良预后有关。静脉桥失败的定义是CABG后12～18个月，经血管造影证实静脉桥发生大于75%的狭窄。观察的终点是死亡、心肌梗塞以及行再次心肌血管重建。

各组间的基础临床状况相似。结果显示，内窥镜取大隐静脉与较高的静脉桥失败发生率有显著相关。而且，其也显著增加死亡、心肌梗塞或再次心肌血管重建的发生率[45]。文章结论认为，内窥镜取大隐静脉使CABG术后血管桥失败和不良转归的情况更加严重。他们建议，这种移植血管获取技术的安全性应经随机试验进一步评估。这种技术的潜在病理机制可能是其增加了血管内皮损伤。

（2）体外循环：停跳与不停跳手术的比较

自从90年代出现了不停跳CABG术后，人们一直在寻求最佳的搭桥技术[46]。不停跳CABG技术现已非常成熟，普遍应用于心脏手术中，也便于进行大规模的队列比较研究。最近一项大规模的队列比较研究(总例数＝63,047；停跳CABG例数＝48,658，不停跳CABG例数＝14,389)用多元分析法评估了两种技术在临床转归间的差异[47]。

结果显示，两者围术期死亡率和脑卒中发生率之间没有统计学差异。尽管两组患者一般流行病学资料及合并症相似，但不停跳CABG组患者的住院时间明显较长、住院费用也较高。多元分析显示，应用不停跳技术患者的住院天数多0.6天，住院费用多1.497美元。尽管这些差异具有统计学意义，但临床意义尚不明显。

另一项队列研究（总例数：14,766，不停跳CABG：7,083，停跳CABG：7,683）评估了二种技术在不同危险性患者临床转归间的差异，危险性采用胸外科医师学会验证的手术死亡率危险预示方程。[48, 49]结果显示，四级危险度中，较低二级患者围术期死亡率在两种CABG技术之间没有差异。危险度较高患者中，不停跳组的生存率较高，进一步的分析显示，不停跳CABG更倾向于降低高危患者的死亡率。基于此项大样本的“实例”分析显示，两种冠脉血管重建术对低危患者的临床预后影响等同，但是对高危患者，不停跳CABG更利于改善预后。

**3. PCI技术**

（1）PCI在心肌梗塞中的应用

多元随机对照研究和荟萃分析比较了PCI与溶栓治疗在STEMI（ST段抬高性心肌梗塞）患者中的应用。由于随机试验应用于“真实环境”有其局限性，最近的一项荟萃分析包含了随机试验以及观察性研究[50, 51]。在随机试验中，PCI降低了34%的短期死亡率，在观察性研究中降低了23%。在随机试验中，PCI显著降低了24%的1年死亡率，降低了51%的再梗率。然而在观察性研究中，PCI对远期临床预后无明显改善作用。

发生STEMI的患者可能在发病时被没有能力进行PCI的医院收治，从而接受溶栓治疗。目前尚未确定溶栓治疗后进行PCI的最佳时机。一项最近的随机试验评估了STEMI患者在溶栓治疗后6小时内实施PCI的有效性[52]。试验定义的终点包括死亡、再次心肌梗塞、再次心肌缺血、充血性心力衰竭和30天内的心源性休克。

结果显示，STEMI患者溶栓后早期行常规PCI，可明显降低上述终点事件的发生率。两组间具有临床意义的出血发生率相似。结论认为，STEMI溶栓后早期行常规PCI能够明显降低缺血性并发症的发生率。总之，近期关于PCI的研究表明对STEMI患者不论是否进行了溶栓治疗，PCI都改善了预后。

（2）主动脉内球囊反搏在心肌梗塞患者中的应用

最近，心脏内科指南建议对有心源性休克的STEMI患者应用主动脉内球囊反搏(IABP)[53]。最近的一项荟萃分析验证了这项AHA以及ACC强烈推荐的治疗措施[54]。第1项分析集中了7项随机试验，证实IABP并不能改善患者的生存情况和射血分数，反且与脑卒中及出血的发生显著相关。

第2项分析集中了9项STEMI队列研究的数据。在接受溶栓治疗的STEMI患者中，IABP降低了18%的死亡率，但是在首先接受PCI治疗的STEMI患者中，IABP却增加了6%的死亡率。研究者认为，目前的证据仅部分支持对高危STEMI患者使用IABP。唯一支持IABP的证据来自于接受溶栓治疗的STEMI患者的观察性研究。

（3）血小板抑制药物的进展：普拉格雷和替卡格雷的应用

PCI和安放支架的STEMI患者常需服用血小板抑制药如阿司匹林和第2代噻吩吡啶类药物氯吡格雷[53]。PCI后冠脉支

架内血栓形成是具有较高死亡率的严重并发症。氯吡格雷抗血小板作用抵抗现象已受到越来越多的关注，它是冠脉支架血栓形成的重要危险因素[56]。

普拉格雷是新型的第3代噻吩吡啶类药物，由于其能更强效的阻滞血小板二磷酸腺苷$P2Y_{12}$受体，产生比氯吡格雷更持续的血小板抑制作用。当然，普拉格雷和氯吡格雷一样也是一种前体药物，需要经肝脏(内)的生物转化才能形成有活性的药物[57]。

一项关于急性冠脉综合征患者进行PCI的随机试验结果表明，与氯吡格雷相比，普拉格雷能够明显降低包括支架内血栓形成在内的心肌缺血事件的发生率，但却增加出血的风险[58]。另一项随机试验结果显示，与氯吡格雷相比，接受PCI治疗的STEMI患者使用普拉格雷能够明显降低以下两组终点结局的发生率，即心血管死亡、非致命性心肌梗塞、非致命性脑卒中；心血管死亡、心肌梗塞、急性靶血管重建术[59]。除了CABG手术患者以外，应用普拉格雷没有显著增加重大出血事件。

美国FDA于2009年7月10号批准普拉格雷用于不稳定性心绞痛或心肌梗塞后行PCI的患者[60]。虽然这一新药为心脏导管室内行PCI的患者提供了很好的血小板抑制作用，但却显著增加了CABG围术期严重出血的危险。至今临床上尚无起效快速、作用可逆的口服血小板抑制药物满足PCI后行CABG患者的需要。生产一种短效、作用可逆的噻吩吡啶类口服药物将成为急性冠脉综合症药物治疗方面的突破。

经肝脏生物转化后，氯吡格雷和普拉格雷与血小板ADP P2Y12受体不可逆性结合。因此它们属于间接作用、不可逆的血小板抑制剂。与此相反，替卡格雷是直接与血小板ADP P2Y12受体发生可逆性结合的新药[61]。一项最近的随机试验评估了替卡格雷与氯吡格雷对伴有或不伴有STEMI的急性冠脉综合症患者心血管事件的预防作用[62]。试验终点定义为12个月内因血管因素、心肌梗塞或脑卒中导致的死亡。替卡格雷显著降低了终点事件的发生率，包括任何原因引起的。虽然严重出血事件的发生率相似，但替卡格雷的高发生率与CABG无关。替卡格雷是第一个具有直接、可逆作用的噻吩吡啶类血小板抑制药物。如果随机试验继续显示其对急性冠脉综合症患者转归的改善作用，美国FDA应该在不远的将来批准其上市。

### 4. 冠脉重建术的选择

随着药物洗脱支架的出现以及PCI技术的改进，多支冠脉病变可采用多支血管PCI或CABG进行治疗[63，64]。一项近期的单一中心观察性研究评估了多支病变冠心病患者CABG或PCI后3年的临床转归[65]。尽管PCI组年龄较小，并发症较少，但放置药物洗脱支架的PCI患者，其靶血管重建术、死亡以及心肌梗塞的发生率较高，两组间校正危险因素后，脑卒中的发生率相似。

另一个集中了10项随机试验的研究，评估了多支冠脉病变患者接受CABG或PCI（其中6个试验使用球囊血管成形术，4个试验使用金属裸支架）后的远期死亡率[66]。结果显示，无论使用何种血管重建术，5.9年的远期死亡率相似。然而，年龄>65岁的糖尿病患者行CABG后死亡率明显下降。研究者总结认为，多支冠脉病变的患者接受PCI或CABG后的远期死亡率相似，但CABG对年龄>65岁的糖尿病患者术后生存率提高更加有益。

## 四、围术期出血和止血的进展

心脏手术后出血仍然是一项重要的临床挑战，因其显著恶化临床转归[67]。最近的一项观察性研究显示，成人心脏手术后严重出血的发生率为6%，严重术后出血定义为纵膈引流血量≥200ml/h或每h出血量≥2mL/kg并持续2h以上[67]。严重出血患者的输血、再次开胸、机械通气以及ICU停留时间和术后死亡均明显增加。尽管最近研究显示中等量使用同种异体血制品不会影响CABG后患者的远期生存情况，但围术期输血带来的相关风险还是明显增高[68]。即便在不停跳下行CABG中能减少围术期出血以及输血的可能性，但其相关风险依旧存在[69]。一项新近的随机试验，观察不停跳CABG中使用羟乙基淀粉进行容量复苏对血液系统的影响[70]，但研究在早期就被中止，因为输注羟乙基淀粉明显增加输血风险，增加输血总量、新鲜冰冻血浆量和血小板用量，以及术后最初12小时内的胸腔引流量。

另一项安慰剂随机对照试验评估了中度肾功能不全的心脏手术患者（肾小球滤过率≤60mL/min)静脉注射N -乙酰半胱氨酸对血液系统的影响[71]。输注N-乙酰半胱氨酸(100mg/kg推注后，以20mg/kg/h的速度持续至体外循环后4小时)明显增加24小时的胸腔引流量、红细胞输注量以及输注红细胞量≥5U的风险性。研究者认为，虽然这种胶体液具有围术期肾功能的保护作用，但是从围术期风险-利益层面看效应看，其增加出血和输血的副作用应予重视。

尽管VII因子用于心脏手术后难治性出血可以拯救患者生命，但其围术期应用的安全性和有效性还未得到充分证实[69]。最近一项集合了5个试验的荟萃分析评估了围术期使用VII因子的安全性和有效性[72]。结果显示，VII因子治疗没有显著降低因出血导致的再次开胸的机率,与未用患者的死亡率相似，有增加脑卒中发生的趋势。结论认为围术期VII因子的应用效果应进行更大规模的随机对照试验研究。

近期一个小样本的随机试验已经开始进行此方面的研究。成人难治性出血的心脏手术患者被随机分为安慰剂组、40ug/kgVII因子组和80ug/kgVII因子组[73]。VII因子组再次开胸止血和输注异体血均显著下降。尽管严重不良事件的发生在VII因子组更常见，但尚未达到统计意义。结论认为，VII因子治疗心脏手术的难治性出血是有效的，但仍需大规模的临床试验证实其安全性，这是相关专业进行多中心临床合作研究的一个方向。（详情请登陆www.ctsurgerytnet.org)。

心脏术后出血的常见原因是血小板功能障碍[69]。近期，通过血小板生成素受体激动剂艾曲波帕（eltrombopag）

和血小板生成素拟肽（romiplostim）直接刺激骨髓内的巨核细胞产生血小板的方法已成为可能[74]。尽管这些药物仍处于后期临床开发阶段，他们似乎很有发展前景。现在有倾向于对成年心脏手术患者术前使用这些药物，以便于自体血小板收集，治疗围术期凝血障碍，减少异体输血。类似于心脏手术中使用促红细胞生成素[69]。由于血小板功能障碍时体外循环获得性凝血障碍的一大重要机制，此理念在将来有重大的围术期应用价值。

## 五、心脏术后的肾功能保护

肾功能障碍是心脏手术后不良预后的独立危险因素[75]，因此，围术期肾保护是临床优先重视的问题。新近一项临床试验研究了非诺多泮对心脏手术后肾功能障碍是否有保护作用[76]。持续48小时的非诺多泮治疗显著降低了对肾脏替代疗法的需求。该发现值得针对成人心脏手术进行更大规模的研究。

近来，一项随机试验证实了心房利钠肽的水合作用对冠脉造影导致的肾病具有显著的保护作用[77]。多元分析显示，心房利钠肽具有肾保护效应。另一项针对心肺转流下行CABG术的随机试验(N=504)也发现，围术期使用心房利钠肽具有肾脏保护作用，并可显著降低术后并发症[78]。结论认为，心房利钠肽能够降低包括肾功能衰竭在内的心脏术后并发症。

最近一项试验性随机研究显示，围术期输注碳酸氢钠可显著降低心肺转流下心脏术后肾功能障碍的发生率[79]。这些可喜的数据目前正在50多个心血管和肾脏科的随机试验中进行验证（详情请登陆www.clinicaltrials.gov）。

一个针对成人心脏手术的单中心观察性研究显示,喷他淀粉(pentastarch)与肾脏损伤有显著相关性。肾损伤定义为血清肌酐浓度在心脏手术后4天内上升50%[80]。肾损伤的发生率为10%。喷他淀粉是肾损伤的独立危险因素，呈剂量依赖性，封顶剂量为14mL/kg。因此胶体组（羟乙基淀粉以及喷他淀粉）可能增加心脏术后出血、输注异体血以及肾损伤的风险。虽然N-乙酰半胱氨酸同样会影响心脏手术患者的止血能力，但其似乎与肾损伤无关[81]。尽管有研究显示，N-乙酰半胱氨酸具有肾保护作用，但该作用在围术期的效果并不一致[81]。

## 六、围术期血糖控制

由于血糖与手术预后的重要关系，围术期血糖控制一直是临床关注的重点[82]。一项标志性的随机对照研究，对比了成年危重患者(N=6,014)严格控制血糖（目标血糖为81-108mg/dL）和常规控制血糖（目标血糖为≤180mg/dL）的临床预后[83]。主要试验终点定义为随机化后90天内的死亡，两组患者的一般情况相似。结果显示，严格控制血糖组的死亡率明显上升，内、外科患者的结果相同。严重低血糖（血糖≤40mg/dL）与严格控制血糖有显著相关性，两组在住院时间、ICU停留时间、机械通气时间以及需要肾替代治疗的机率之间没有明显差异。结论认为，与严格控制血糖相比，常规控制血糖能够降低危重患者的死亡率。

低血糖并非仅常见于严格控制血糖时，而且与急性心梗入院患者的死亡率增加相关[84]。一个后续的大样本队列观察性研究(N=7,820)观察了自发性和医源性低血糖是否增加了心梗患者的死亡率[85]。多因素分析结果显示，对没有接受胰岛素治疗的心梗患者低血糖是死亡率的危险因素，对接受胰岛素治疗患者的死亡率无预测作用。这个问题有必要在心血管手术围术期实践中进一步研究。

鉴于近期的研究成果，一项更新的荟萃分析对胰岛素严格控制血糖和ICU死亡率相关性之间的所有相关证据进行了总结[86]。严格胰岛素治疗的低血糖相对风险为6.0。严格胰岛素治疗降低了SICU内患者的死亡率，但是没有降低内科或综合性ICU内患者的死亡率。结论认为，强化胰岛素治疗能够明显增加低血糖的风险，仅在SICU内能降低患者死亡率。胸外科医师学会近期的一项关于成人心脏手术患者血糖控制的指南建议胰岛素控制围术期血糖水平低于180mg/dL[87]。

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## 摘要

迄今越来越多的存在心脏高危疾病的患者进行各种手术治疗，由此产生的围术期心肌梗塞（PMI）日益受到关注。依据导致PMI的病理生理机制可以将PMI分为两种类型：1型为围术期出现急性冠脉综合征，2型则是由于在稳定的冠脉病变的基础上(在围手术期间)出现过长时间供氧与耗氧的不平衡而发生的。在围术期对心肌缺血细致严密的监护、在保证血压的基础上严格的控制心率、降低心输出量及预防心脏失代偿的发生，对PMI的预防具有积极的意义。而冠脉血管的外科干预治疗并不是推荐的预防PMI的治疗手段，常规的抗血栓治疗可能加重围术期出血。

关键词：围术期心肌梗塞

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# 围术期心肌梗塞的诊疗进展

# The Latest Progress in Perioperative Myocardial Infarction

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## Abstract

More high-risk cardiac patients will undergo surgery and perioperative myocardial infarction (PMI) can be an increasing problem. Two distinct mechanisms may lead to PMI: acute coronary syndrome and prolonged myocardial oxygen supply-demand imbalance in the presence of stable coronary artery disease, designated type 1 and type 2 by the universal definition of MI. Careful perioperative monitoring for ischemia, a low threshold for treating and preventing tachycardia while avoiding hypotension, decreased cardiac output, and/or cardiac decompensation help prevent PMI. Coronary intervention is rarely indicated as the first line of treatment and antithrombotic therapy may exacerbate bleeding.

**Key Words**：Perioperative Myocardial Infarction

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全世界每年所进行的外科手术超过了2亿3千万台，中至高危非心脏手术的30天死亡率超过2%，而在高危心脏疾病的患者中超过了5%。心脏疾患已成为术后并发症及死亡率的首要影响因素，并造成住院时间及费用的延长。

## 一、围术期心肌梗塞（PMI）的再定义

世界卫生组织对心肌梗塞（MI）的传统定义主要体现在心电图及心酶的变化两方面。现行的MI定义是基于一系列心肌缺血特异的生物标记物（尤其是肌钙蛋白水平）的综合指标，包括：心梗的症状、心电图的变化及影像学的相关征象。大量研究利用肌钙蛋白的连续变化展示了大手术应激后PMI的发生一般在术后的24-48小时内。

## 二、PMI病理生理变化

为了便于指导治疗，依据导致PMI的病理生理机制可以将PMI分为两种类型：1型为围术期出现急性冠脉综合征(ACS)，2型则是由于在稳定的冠脉病变的基础上(在围手术期间)出现过长时间供氧与耗氧的不平衡而发生的心梗。

### 1. 急性冠脉综合征(1型PMI)

急性冠脉综合征是由于不稳定的(脆弱的)粥样斑块出现脱落、撕裂或溃疡后导致冠脉急性栓塞继而引起心肌缺血缺氧，造成心肌梗塞。尽管当前认为粥样斑块内发生的炎症反应在斑块的不稳定性及自发性ACS的病理进展过程中起关键的作用，但是在围手术期所出现的多种应激因子也在PMI的进展中起着不可忽视的作用：

（1）体液因素

与一般的MI相同的是，在围手术期间，患者均会面对生理及情感上的应激，而且后者的程度更高。在围术期的应激中，由于疼痛、创伤、贫血及低温等外科因素使机体的儿茶酚胺及皮质醇激素等应激相关体液因素水平上调，继而通过交感兴奋引起全身血流动力学改变、冠脉收缩及促凝因子的活性上调，最终导致了粥样斑块的崩解。

（2）循环因素

围手术期间的心动过速及高血压将会通过血管内的剪切应力及高血流量的摩擦分别对粥样斑块造成外部(局部断裂)及内部(纤维帽、血管内皮溃疡及条状脱落)的形态重朔，继而加重冠脉的狭窄。

（3）凝血功能

围手术期间凝血功能的亢进体现为：促凝物质(如纤维蛋白原、因子VIII、因子VII及α-抗胰蛋白酶)的增加，血小板活性的上调、内源性抗凝物质(C-蛋白、AT-III及α-巨球蛋白)的下调以及纤溶的下调。然而，结合术后患者活动不足及血液凝滞等因素，围手术期间由于凝血功能异常导致的并发症主要时静脉系统血栓形成，而心肌缺血、梗塞或者侧支栓塞较为少见。

**2.心肌氧供及氧耗不平衡（2型PMI）**

通过在围术期对高危心脏疾病患者进行连续的24小时心电图监测(Holter心电图)发现术后常见的ST段压低与心率相关且不伴随躯体症状，而且这与住院时间及远期的死亡率有相关性。包括猝死在内的术后心脏并发症将会在上述无症状的ST段压低持续一定时间(30分钟、2小时或5小时以上不等)后出现。上述的发现同样在结合肌钙蛋白水平及12导联心电综合评价的临床研究中得到证实。相反，在PMI发病原因研究中，仅有不到2%出现ST段的抬高。因此，可以认为过长时间的ST段压低为主的心肌缺血是PMI的常见原因。进一步利用高灵敏性肌钙蛋白检测方法的研究提示，在高危心脏疾患的患者中，术后出现低水平但具有诊断意义的肌钙蛋白上升并非一定伴随有心肌缺血的心电图表现。较高的肌钙蛋白上升水平往往伴随出现较长时间的ST段压低及较严重的肺充血或胸痛。因此，术后心肌缺血时间过长，心肌损伤及2型PMI是一个由轻到重的变化范围：从无症状性的伴有轻度TnT上升的心肌损伤，继而出现低频率持续时间逐渐延长的心肌缺血心电表现，最后表现为心电图多导联的心肌缺血、明显的TnT上升最终发生PMI。

心动过速是术后出现氧供-氧耗不平衡常见原因。在术前基础心率为50-60次/分的确诊冠心病患者中，当心律高于80-90次/分水平时将会导致心肌缺血及PMI，并表现为较低的术后心肌缺血承受力。同样，术后低血压、高血压、贫血、低氧血症及高碳酸血症均会加重心肌缺血。应激或缺血引起的冠脉血管收缩都会进一步下调冠脉的血流灌注，并且冠心病患者存在的心脏收缩/舒张功能不全将在缺血及容量负荷过多时加剧，继而导致心脏失代偿及2型PMI。

## 三、心血管造影及病理学研究

在美国克利夫兰洲进行的一项临床研究中，研究人员通过在术前对冠脉重建手术的患者进行冠脉造影发现，81%出现PMI或心源性猝死的患者存在冠脉(主干及侧支)多根血管慢性梗阻，相比之下，对照组(无心脏相关并发症的患者)只有29%出现阳性发现。由此可以推断出现PMI或心源性猝死的患者，其冠脉系统存更多的病变血管，而且其病变梗阻程度更严重。

## 四、预后

PMI早期的死亡率在3.5%至25%之间，而且明显肌钙蛋白升高与更高的死亡率相关。PMI同样对远期的生存率产生影响：轻度的肌钙蛋白水平升高的患者其远期死亡率较高，而术后越高的肌钙蛋白水平将预示越差的生存率。

## 五、预防与治疗

**1.预防性药物**

（1）β-受体阻滞剂

关于围术期β-受体阻滞剂的应用目前仍存在较多的争论，其争论的焦点在于：虽然β-受体阻滞剂通过控制心率、减轻心肌氧耗并最终减少PMI的发生，但是不少的研究认为β-受体阻滞剂未能有效的降低心律，而且在术后使用β-受体阻滞剂可能会因为降低血压而加剧血流灌注的不足，同时削弱机体在感染、贫血及活动性出血时心率的代偿性上升，最终影响心排量。因此，目前较为被接受的观点是对于术前长期使用β-受体阻滞剂的患者不应中断术后的用药，而有针对性的对症(心动过速、高血压及心肌缺血)应用β-受体阻滞剂较预防性的使用更有益处。

（2）钙通道阻滞剂

尽管在胸外科手术后能减少室上性心律失常及心肌缺血，但尚未有随机对照研究显示钙通道阻滞剂在减少PMI或猝死方面有优势。而在一份对Meta分析中虽然钙通道阻滞剂的应用在降低围术期猝死及PMI方面有优势，但是进一步的组间比较发现其使用伴随有更多的低血压不良事件。

（3）$\alpha_2$-激动剂

仅有一份关于米伐折醇（Mivazerol）在大血管手术后的患者中应用的随机对照研究显示其能降低术后PMI猝死的发生，但是米伐西醇尚未在临床使用。除了一个小规模的研究提示皮下注射可乐定能降低围术期心肌缺血及2年内死亡率外，并没有预防性应用可乐定或右美托咪啶的获益报道。

（4）他汀类药物

鉴于有观点认为围术期停用他汀类药物(HMG-CoA转化酶抑制剂)可导致粥样斑块稳定性下降，目前仅在术后对于有长期服用该药的患者应在围术期间继续用药。而对于预防性用药的研究，在增加心脏并发症、减轻PMI及猝死等方面仍存在较多的争论。

（5）阿司匹林

尽管最新的研究提示在除颅内及前列腺外的手术外阿司匹林的应用并不会造成影响手术进程中出血或死亡率，但目前被广泛接受的观点仍是在术前5至7天停用阿司匹林以预防手术操作中的出血。而且，对于围术期是否继续应用阿司匹林，有报道指出仅在冠脉搭桥手术后显示出优势，而在非心脏手术中的获益并不显著。

**2. 联合抗血小板治疗**

对于冠脉支架植入术后的CAD患者，抗血小板的药物治疗存在停药后血栓形成但继续用药增高出血倾向的两难局面。现行的指南推荐：单纯金属支架植入术后应连续应用抗血小板治疗时间达至少4周；而对于接受带有缓释药物涂层支架植入术后的患者，该抗凝治疗的时间亦应维持1年以上。同时应尽量避免在上述疗程内进行的任何外科干预治疗。与之相呼应的是有部分的研究显示：接受PCI术后的患者再次接受任何手术治疗时其围术期主要的不良事件发生率与PCI术后的时间成负相关(单纯支架植入术后30天内心脏相关不良事件发生率下降10.5%，90天后降至2.8%；带药物涂层的支架植入术后1年内相应的不良事件发生率也降至3.3%)。如果手术要求中断噻吩吡啶类（thienopyridine）的应用，那么至少应继续使用阿斯匹林并应尽快地恢复使用噻吩吡啶类。但是在心肌桥支架植入的患者中，抗血栓、抗凝或糖化蛋白$II_b/IIIa$均为显示出临床获益。

**3. 冠脉血管成形术**

在8份受试者超过10000例的临床研究中(其中6份为回顾性研究)，预防性的术前行冠脉血管成形术(主要为冠脉搭桥术)显示出在一定程度上能改善远期预后。但是在另外两份来自CARP及DECREASE(预防性冠脉血管成形术及德国超声心动图应激相关心脏危险评估)的回顾性随机分析中，预防性的冠脉成形手术治疗却并未显示出上述临床益处，同时，在其所含括的以PCI为成形方式的病例(比例分别为59%、65%)中，研究者指出：在稳定型CAD患者中，预防性的术前行PCI预防治疗与较高的围术期并发症相关，而且对远期的预后改善效果也并不确定。然而，在进一步对CARP的数据进行独立分析时，研究者又发现术前先行冠脉搭桥术及其它形式的完全性血管成形术与较低的PMI发病率相关。因此，鉴于上述各种不同的实验结果，在没有明确的循证医学证据前，在一般情况下并不推荐预防性的术前冠脉血管成形治疗。

**4. 围术期管理**

最近的一份病例数达316例的随机临床研究中发现：在80例12导联心电图提示长期心肌缺血的患者中，β-受体阻滞剂及最优化心肌氧供-氧耗平衡治疗能降低术后6个月内的死亡率及术后肌钙蛋白上升的水平。

应该特别强调的是对心率的严格控制是非常重要的，同时，所有引起心动过速、高血压、低血压、贫血及疼痛的原因均应予以积极的干预。其中，对于心率快伴随血压低的治疗，应建立在充分了解患者基础的及术后的心血管系统病理改变(心肌、瓣膜及冠脉)的基础之上。在大多数情况下，应用血管活性药物维持正常血压(血流灌注)、在血容量充足的前提下应用β-受体阻滞剂控制心率、术后阵痛及呼吸支持都是很必要的。但是，除非出现ST段抬高或顽固性的心源性休克，在术后的病情变化中并不常规推荐紧急的冠脉外科干预治疗、抗凝或糖化蛋白$II_b/IIIa$激动剂的使用，同时上述治疗手段也将增加术后出血的风险。

与药物治疗降低氧耗同样重要的是保证有充足的血红蛋白为心肌提供氧。对于输血指征的界定，目前对红细胞压积(Hct)在25%-33%之间视为模糊地带，因为分别有研究提示：对于非心脏手术后的患者，当Hct<39%时予以输血干预将改善术后生存率；但是，当Hct>25%时，输血却显示出于的死亡率增高及院内获得性感染相关。因此，对于存在心肌缺血的术后血流动力学不稳定的病人，适当的纠正血红蛋白水平将有一定的临床益处。为此，为指导输血、判断血容量水平及心衰的发生，严密的血流动力学检测(如超声心动图、有创动脉血压检测、中心静脉压监测以及肺动脉压监测)是非常必要的。在此基础上，多导联的心电监护对无症状的心肌缺血亦得到广泛的认可。

## 六、小结

术后的心动过速、低血压、高血压、贫血、低氧血症及收缩性或舒张性心功能障碍是导致稳定型冠心病患者非心脏手术术后发生长期ST段压低及2型PMI的常见原因。1型PMI上未能通过现有的诊断手段明确发现，但其发生率较2型PMI低。虽然PMI大多数是无症状并伴随一过性的心电图改变，但是即便是轻微的肌钙蛋白升高也将对术后近期及远期的并发症及死亡率的预测有重要的临床意义。对于PMI围术期药物治疗相关问题仍然存在许多不确定性，但是在围术期对心肌缺血细致严密的监护、在保证血压的基础上严格的控制心率、降低心输出量及预防心脏失代偿的发生，都对PMI的预防具有积极的意义。而冠脉血管的外科干预治疗并不是推荐的预防PMI的治疗手段，同样，常规的抗血栓治疗亦可能加重围术期出血。为了更好的改善PMI患者的远期生存率及预后，仍需要更多的研究以指导临床诊治中在进行选择术后监护、药物治疗及冠脉外科干预等方面遇到的问题。

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**摘要**

Sugammadex是一种经过修饰的γ-环糊精，能够与氨基甾类非去极化肌松药形成稳定的复合物从肾脏排泄，迅速逆转肌松作用，并且对深度肌松也能够快速逆转，有助于降低术后残余肌松，是一个接近理想状态的肌松拮抗剂。

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# Sugammadex：一个新型的肌松拮抗药

## Sugammadex: A Novel Muscle Relaxant Antagonist

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**Abstract**

Sugammadex,a modified γ-cyclodextrin, can rapidly reverse neuromuscular blockade induced by aminosteroid nondepolarizing relaxants,including profound blockade. Sugammadex exerts its effect by forming very tight complexes with aminosteroid nondepolarizing relaxants and the complex is excreted completely in the urine. Thus,sugammadex is a nearly ideal antagonist of muscular relaxants and helpful to reduce the residual paralysis rate greatly.

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1942年Griffith和Johnson[1]将箭毒用于临床麻醉，让人类麻醉历史进入了一个全新的时代，彻底改变了依靠过深麻醉来达到肌松的历史。从而，为外科手术提供充分的肌松，推动外科技术的迅速发展，同时，这还大大减少了由于麻醉过深带来的众多并发症。至今，肌松已经成为现代全身麻醉的三元素（镇静、镇痛、肌松）之一。

然而，目前没有一个肌松药能够达到理想肌松药的特点[2]，没法同时满足快速起效、快速恢复、副作用小的要求。去极化肌松药琥珀胆碱和非去极化肌松药瑞库溴铵尽管能够达到快速起效、快速恢复的要求，但由于它们副作用较大，前者正逐渐淡出临床实践，后者已经彻底退出历史舞台。当前，临床上使用的肌松药主要是中、短时效非去极化肌松药，术后对肌松的拮抗主要是乙酰胆碱酯酶抑制剂。由于乙酰胆碱酯酶抑制剂存在明显的局限性：封顶效应、副作用较多，在临床上是否常规使用、如何合理使用仍存在分歧。所有这些都可能导致术后残余的肌松作用，而术后残余肌松作用是麻醉复苏室内发生严重呼吸事件的首要原因[3]，对患者术后恢复产生较大的影响。

Sugammadex能够与氨基甾类非去极化肌松药形成稳定的复合物，快速逆转肌松作用，且副作用较小，让肌松药的使用接近理想状态。目前此药已经在二十多个国家上市使用。下面对sugammadex的作用机制、临床特点、副作用及其局限性等方面作一综述。

### 一、Sugammadex的作用机制

Sugammadex是一种经过修饰的γ-环糊精。未经修饰的γ-环糊精由8个D-吡喃葡萄糖单元组成，其三维结构呈环状圆桶型，中间是疏水性内腔，外周为亲水性结构。这种特殊的结构决定了它可以结合一些亲脂性分子，使其获得水溶性。但γ-环糊精的疏水性内腔容积小于氨基甾类非去极化肌松药分子的体积，不能够将其完全包裹。需要通过修饰，加入8条带羟基的侧链加深其内腔才足以容纳氨基甾类肌松药，每条侧链的末端再加入带负电荷的羧基，以增加其与氨基甾类肌松药的静电力结合力[4]。这样，Sugammadex就能够与氨基甾类非去极化肌松药之间通过范德华力和疏水性相互作用按1∶1形成牢固的水溶性复合物而发挥拮抗作用[4]。不同氨基甾类非去极化肌松药之间由于分子大小的不同，与Sugammadex的匹配度不同，结合力存在差异，其中罗库溴铵匹配度最高，结合力最强，拮抗效果最好，维库溴铵次之，泮库溴铵最差[5]。

### 二、Sugammadex的临床特点

#### 1. Sugammadex的药代学、药效学特点

VladimirN[6]等利用模拟的药代-药效学模型证实sugammadex具有以下特点：(1)血浆中sugammadex的时间-浓度曲线与血浆中罗库溴铵的时间-浓度曲线相似；(2)sugammadex能够扩散到肌松药的效应部位与游离的肌松药分子结合从而隔绝肌松药在神经肌肉接头的作用；(3)sugammadex与肌松药的亲和力大于肌松药与神经肌肉接头后膜的亲和力；(4)使用2-4倍于肌松药剂量的sugammadex能够快速有效的逆转肌松作用，而小剂量的肌松药逆转肌松作用相对较慢。Bart A.P.等[7]在分析了既往的临床试验后也得出相似的结论。

#### 2. 剂量依赖特点

Sugammadex在拮抗罗库溴铵肌松作用时，存在明显的剂量依赖性。动物实验和临床研究都证明了这一特点。Hans等[8]给猕猴静脉注射0.5mg/kg罗库溴铵（5倍ED90）后1分钟，静脉注射生理盐水、1mg/kg的sugammadex或者2.5mg/kg的sugammadex，发现TOF达到90%所需时间分别为28分钟、26分钟和8分钟，随着sugammadex剂量的增加，肌松的恢复显著加快。Scott B等[9]在Ⅱ期临床试验中也发现sugammadex存在明显的剂量依赖性，给予患者静脉注射0.6mg/kg罗库溴铵或者1.2mg/kg罗库溴铵，当PTC(强直刺激后单次刺激计数)达到1或2时，分别静脉注射sugammadex0.5mg/kg、1.0mg/kg、2.0mg/kg、4.0mg/kg或8.0mg/kg，0.6mg/kg罗库溴铵组TOF达到90%的时间分别为44.2分钟、19.1分钟、5.4分钟、3.3分钟和1.5分钟，1.2mg/kg罗库溴铵组TOF达到90%的时间分别为20.6分钟、11.5分钟、4.3分钟、1.9分钟和1.0分钟。Shields[10]在多次追加罗库溴铵的长时间手术中发现sugammadex的剂量依赖性也十分明显，当$T_2$重现时，静脉注射sugammadex0.5mg/kg、1.0mg/kg、2.0mg/kg、4.0mg/kg或6.0mg/kg，TOF达到90%的时间分别为6:49、2:43、1:46、1:22和2:37。因此，要快速逆转肌松作用，需要根据当时肌松状态，选择sugammadex的合适剂量。当$T_2$重现时，给予2.0mg/kg的sugammadex已经足以快速逆转肌松；当达到PTC 1-2时，需要4.0mg/kg的sugammadex来快速拮抗肌松；若是诱导剂量（2-4倍ED95）罗库溴铵使用后5分钟内，则需要8mg/kg的sugammadex才能达到快速逆转肌松。

### 3. 快速逆转深度肌松

只要sugammadex的剂量足够，就能够在较短时间内逆转罗库溴铵的肌松作用，这也是sugammadex相对于胆碱酯酶抑制剂的一大优点。R.Kevin Jones[11]等在sugammadex的III期临床研究发现，当罗库溴铵的肌松作用恢复到PTC1-2时给予4mg/kg sugammadex或者0.07mg/kg新斯的明+0.014mg/kg格隆溴铵，sugammadex组TOF比值达到90%的平均时间为2.9分钟，而新斯的明组为50.4分钟，差异十分显著。Hans等[12]和Friedrich等[13]进行的多中心临床研究均发现，1.2mg/kg罗库溴铵静脉注射后3分钟或5分钟，静脉注射8mg/kg的sugammadex能够使TOF值在5分钟内达到90%以上。Harald等[14]的临床实验也发现，0.6mg/kg罗库溴铵静脉注射后3分钟或5分钟，静脉注射4mg/kg的sugammadex能够使TOF值在5分钟内达到90%以上。Chingmuh等[15]还进行了sugammadex与琥珀胆碱的临床对照研究，sugammadex组在1.2mg/kg罗库溴铵诱导后3分钟静脉注射16mg/kg的sugammadex进行拮抗，琥珀胆碱组静脉注射琥珀胆碱1mg/kg后让其自然恢复，结果发现罗库溴铵组从开始注射罗库溴铵到TOF值达到10%和90%的时间分别为4.4分钟和6.2分钟，而琥珀胆碱组从开始注射琥珀胆碱到TOF值达到10%和90%的时间分别为7.1分钟和10.9分钟，罗库溴铵组肌松恢复较快。

Sugammadex的这一特点意义重大。首先，在麻醉诱导期遇到气管插管失败且面罩加压通气困难时，sugammadex可以作为抢救药物使患者快速恢复自主呼吸，挽救患者的生命；其次，对于一些短小手术，完全可以用全量的罗库溴铵，为手术提供充分的肌松，而不必顾忌术后肌松恢复延迟。再次，可以让琥珀胆碱逐渐退出临床，因为，琥珀胆碱可能带来的严重不良反应，而罗库溴铵与sugammadex的结合，已完全能够达到琥珀胆碱快速肌松、快速恢复的效果。

### 4. 肝肾功能的影响

Sugammadex不在体内代谢，它以原形或结合罗库溴铵的复合物从肾脏排泄。临床研究发现sugammadex从肾脏的排泄能够增加被其包裹的罗库溴铵从肾脏的排泄[16]。当肾功能受损时，sugammadex及其结合罗库溴铵复合物的排泄是否会产生影响，对其逆转肌松作用是否会产生影响，一些动物和临床实验对此做了研究。在双侧肾动脉结扎造成肾功能不全模型的猫实验中发现sugammadex能够快速而完全地逆转罗库溴铵的肌松作用，不受肾功能损害的影响[17]。Staals L等[18]进行的一项临床小样本研究也发现，当罗库溴铵的肌松作用恢复到$T_2$重现时静脉注射2mg/kgsugammadex，肾功能损伤组TOF值恢复到90%的时间为2.0分钟，肾功能正常组为1.65分钟，两者没有明显差异。最近，L.M.Staals等[19]作了肾功能不全患者和肾功能正常患者对sugammadex和罗库溴铵药代动力学的临床对照研究，结果发现，sugammadex总的血浆清除率在肾衰患者为5.5ml/min，而正常患者为95.2ml/min，罗库溴铵总的血浆清除率在肾衰患者为41.8ml/min，而正常患者为167ml/min；正常患者24小时后sugammadex和罗库溴铵尿中平均排泄量分别73%和42%，而肾衰患者72小时后sugammadex和罗库溴铵尿中平均排泄量分别只有29%和4%。由此可见，尽管肾功能正常与否对sugammadex逆转罗库溴铵的肌松作用无明显影响，但药代学研究结果提示肾衰患者对sugammadex和罗库溴铵的清除要显著慢于肾功能正常患者，sugammadex和sugammadex-罗库溴铵复合物在肾衰患者体内有较长时间的无症状存留，这是否会对肾衰患者的机体产生影响目前还缺少更深入的研究。

至今，尚没有肝功能不全对sugammadex作用影响的动物和临床研究，然而，一个的药代-药效学互动模型已经被用于模拟sugammadex逆转肝功能不全患者罗库溴铵肌松的肌松作用[17]。利用此模型，可以计算出严重肝功能不全患者使用1.2mg/kg罗库溴铵15分钟后给予4mg/kg sugammadex肌松恢复比肝功正常患者慢4.12分钟；而当$T_2$重现时给予2mg/kg sugammadex，肝功能严重受损患者肌松恢复比肝功正常患者慢2.55分钟。因此，尽管肝功能衰竭患者中sugammadex逆转肌松作用较肝功正常患者稍慢，但其逆转速度还是远快于新斯的明。

## 三、副作用

Sugammadex在体内不进行代谢，无内在生物学活性，不

与血浆蛋白结合，以原形或结合甾体类肌松药形成复合物从尿中排泄，具有良好的安全性。既往研究报道sugammadex可能的副作用有：恶心、呕吐、口干、味觉异常、低血压、心电图QT间期延长等[13,11,20,12,21]。目前对于sugammadex引起QT间期延长还存在争论，因为在安慰剂组患者也同样出现QT间期延长[13]，Bernard F.Vanacker等[22]的研究则认为许多麻醉药物（如七氟醚）本身会导致QT间期延长。最近Abrishami等[23]对2008年以前有关sugammadex的临床随机对照研究进行了循证分析，共有18项研究、1321名成年患者被纳入，sugammadex的拮抗剂量包括2mg/kg、4mg/kg或16mg/kg，拮抗时机包括$T_2$重现、PTC1-2或诱导剂量罗库溴铵使用后3-5分钟，结果发现，sugammadex组的不良反应与安慰剂组、新斯的明组没有明显差异。

## 四、局限性

Sugammadex的使用存在一定的局限性。Sugammadex特殊的空间结构和作用机制决定其只能对少数氨基甾类肌松药有拮抗作用，不能逆转卞异喹啉类肌松药如阿曲库铵、顺式阿曲库胺的肌松作用，这些肌松药的拮抗仍然需要胆碱酯酶抑制剂，因此，sugammadex还不能完全取代胆碱酯酶抑制剂[24]。此外，sugammadex高昂的价格可能也是其使用受限的一大因素。

## 五、小结

Sugammadex能够快速逆转氨基甾类肌松药产生的不同程度肌松作用，不留残余肌松，无严重的副作用，是一个接近理想要求的肌松拮抗药。它在临床上广泛应用将能够大大推动快通道麻醉技术的发展，有助于患者术后早期恢复，减少平均住院日。

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## 2010年全国神经外科麻醉年会

时　　间：2010年8月6日至8月9日

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许凤丽 章蔚 方才

安徽医科大学附属省立医院麻醉科 合肥 230001

**摘要**

围手术期地塞米松常应用于抗过敏治疗，近年来关于地塞米松引起的过敏反应的报道也越来越多。这些反应主要包括IgE介导的过敏反应和药物直接刺激释放组胺引起的类过敏反应。地塞米松引起的过敏反应是一种全身性或系统性反应，症状可从局部至全身。围手术期过敏原检测起着重要的作用，这些检测方法包括皮肤过敏试验，血清中组胺、类胰蛋白酶和IgE抗体浓度检测等。另外过敏反应发生后及时供氧、扩容和肾上腺素的应用是抢救患者的关键。

关键词：地塞米松；围手术期；过敏反应

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# 围手术期地塞米松过敏的研究进展

## Research of Perioperative Dexamethasone Allergy

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**Abstract**

Dexamethasone is frequently used to treat allergic reactions in the perioperative period.Immediate hypersensitivety reactions to dexamethasone during the perioperative period have been reported more and more recently. Most reactions induced by IgE mediated(anaphylaxis) or by histamine directly(anaphylactoid reactions).The severity level of the reaction can vary from a rash to anaphylaxis.Any suspected anaphylactic reaction must be investigated to confirm the allergen by skin test,plasma histamine,tryptase or specific IgE concentration.Immediate treatment with oxygen,fluid and adrenaline may be important for survival.

**Key Words**：dexamethasone;perioperative period;allergic;anaphylactic reactions

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地塞米松又名德沙美松、氟甲强的松龙、氟甲去氢化可的松，为长效糖皮质激素，具有抗炎、抑制免疫、抗休克及增强应激反应等药理作用，广泛应用于治疗多种疾病，如自身免疫性疾病、过敏、炎症、哮喘及皮肤、眼科疾病等。近几年更多的麻醉医生将地塞米松用于围手术期，但随着该药使用频率的增加，其本身引起的过敏反应报道日益增多，本文着重就围手术期地塞米松的过敏反应机制、高危因素、临床症状和防治进行探讨。

### 一、主要机制

围手术期的过敏性反应是麻醉医师关注的重点，因为这些反应通常难以预测且反应剧烈。Reisacher[1]等指出围手术期过敏反应机制主要有IgE介导、非IgE介导的过敏反应和非免疫因素过敏反应。

#### 1. IgE介导的过敏反应

超敏反应是机体再次接受相同抗原刺激时，出现的生理功能紊乱或组织细胞损伤的异常适应性免疫应答所致。超敏反应可分为四型：I型即速发型过敏反应，又称过敏反应；Ⅱ型称细胞毒型或细胞溶解型超敏反应；Ⅲ型称免疫复合物型或血管炎型超敏反应；Ⅳ型即迟发型过敏反应。1960年King首次对皮质醇激素全身过敏反应进行了报道研究，地塞米松作为一种抗原物质可引起多型变态反应。

1966年Ishizaka等首次证实速发型过敏反应主要由特异性IgE抗体介导产生，且Burgdorffd[2]等指出不同皮质醇阳性针刺试验均显示其过敏反应主要由IgE介导。其发生消退快，有明显个体差异和遗传背景的特点。其发生过程为抗原进入机体后，诱导变应原特异性B细胞产生IgE类抗体应答，IgE类抗体以其Fc段与肥大细胞或嗜碱性细胞表面相应的Fc ε RI结合，使机体处于致敏状态，当机体再次接触地塞米松时，其与致敏的肥大细胞或嗜碱性粒细胞的IgE抗体特异性结合，使细胞活化释放生物学物质，包括组胺、激肽原酶、白三烯、前列腺素多种细胞因子，引起平滑肌收缩，毛细血管扩张、通透性增加，腺体分泌增多，从而产生变态反应。近来研究表明，人和小鼠超敏反应所致的死亡也与IgG类抗体有关，肥大细胞或IgE缺陷小鼠也能被抗原诱导产生过敏性休克甚至死亡。

过敏主要是接触过敏原与其特异性IgE抗体发生的过敏反应，IgE抗体主要存在于过敏个体的血清、肥大细胞和嗜碱性粒细胞中[3]。类胰蛋白酶是一种中性蛋白酶，主要存在于肥大细胞中，和组胺都是肥大细胞活化的标志。研究表明过敏反应患者血清中类胰蛋白酶浓度和对照组相比有明显增加，成为过敏反应高度敏感指标，血清中高浓度的类胰蛋白酶也成为IgE介导的过敏反应另一个机制[4]。

#### 2. 类过敏反应

围手术期常应用地塞米松抗过敏，且常为患者首次用药，即出现过敏反应。美国权威机构[5]指出这种非IgE介导的，临床表现与过敏反应相似，首次用药即发生，称为类过敏反应或过敏样反应。它无需免疫系统参与，由化学性或药

理性介质介导，组胺是其主要介质。研究表明类过敏反应机制主要有：(1)药物直接作用于肥大细胞和嗜碱性粒细胞而释放组胺，且研究表明快速注射或大剂量给药更易激起肥大细胞和嗜碱性粒细胞脱颗粒释放组胺；(2)旁路途径补体激活而释放血管活性物质；(3)快速给药或药物混合可使蛋白质与循环中某些免疫球蛋白发生聚集，轻者出现水泡、荨麻疹，重者可出现支气管痉挛或休克。

### 3. 赋形剂

皮质醇类固醇激素类水溶性及差，但加上酯类如琥珀酸酯、磷酸酯等便可以成为水溶性药物。临床上常用地塞米松为其磷酸钠注射液，由于磷酸酯类为低分子量类，故地塞米松可能只是作为一种半抗原来参与过敏反应，当其进入机体后与体内载体蛋白结合为完全抗原引起过敏反应[6]。Gayle[7]指出磷酸盐也可与钙离子直接络合直接影响心肌完整性。另有学者认为溶剂中含有杂志、污染物、添加剂、特殊代谢产物也可形成抗原导致过敏反应的发生。同时由于地塞米松磷酸钠在生成、分装过程中的各个环节的条件控制不严格，造成不同批号的产品杂质含量不同，因此未必每个患者每次应用地塞米松都能引起过敏反应。

### 4. 交叉反应

另有少数研究已发现不同类固醇激素之间有交叉反应发生[6]。目前关于激素类之间交叉过敏反应的机制并未得到明确的证实，故现在关于这方面的报道并不多见[8]。临床上各种类固醇激素之间有着相似的结构，只是个别基团或含的酯类不同，曾使用过激素治疗的患者在围手术期予以地塞米松治疗时，可能发生交叉过敏反应。

## 二、高危因素

在手术麻醉期间，尤其是全身麻醉时患者要使用多种药物，在这种情况下，中等敏感的IgE抗体就有可能激活肥大细胞和嗜碱性粒细胞而释放组胺等活性物质[9]。另有研究指出患者自身疾病也可增加过敏风险，原因可能是任何药物都有一定的副作用，而患者体内血液动力学不稳定可减少其对激素的耐受性，增加了用药的风险性[7]。

患者的易过敏体质也会增加过敏风险。从免疫学角度看，过敏体质的人常有以下特征：(1)血清IgE明显比正常人高；(2)Th2细胞比Th1细胞相对于正常人占优势，Th2细胞能分泌IL-4，它能诱使IgE的合成，使血清IgE水平升高；(3)与遗传性分泌型IgA缺乏有关，胃肠道、呼吸道等的外分泌液中分泌型IgA缺乏或减少，使肠道细菌在粘膜表面造成炎症，从而加速了肠粘膜对异种蛋白吸收，诱发胃肠道过敏反应[10]；(4)缺乏组织胺酶，对引发过敏反应的组胺不能破坏，而表现为明显的过敏症状。

## 三、临床表现

地塞米松过敏反应可发生在麻醉的任何时间，多表现为用药后几分钟内，但也可发生于手术后几天内，症状和体征也多种多样，轻重不一，范围可从局部至全身。其临床症候群包括：全身性的过敏性休克；呼吸系统的喉头或支气管水肿及痉挛；消化道的呃逆以及皮肤的荨麻疹等，严重者可导致休克甚至死亡。

### 1. 皮肤过敏反应

最常见，可以表现为局部反应，也可出现全身反应。如皮肤瘙痒、潮红、荨麻疹、胸闷、面色苍白、皮疹加重、双眼浮肿及皮下水肿等，孕妇有可能会出现会阴针刺及瘙痒感。目前认为皮肤改变是由于肥大细胞释放血管活性物质引起的血管扩张及通透性增高致。

### 2. 呃逆

呃逆是由于某种原因刺激迷走神经、膈神经时，反射性引起横隔不自主、间歇性痉挛，同时伴吸气时声门闭合产生声音所致。地塞米松引起呃逆的机制尚未确定，可能是由于地塞米松引起胃肠功能紊乱，刺激迷走神经、膈神经所致，多为一过性，停药后可缓解。

### 3. 呼吸系统症状

呼吸系统改变主要为喉头或气管水肿与痉挛引起的呼吸道症状，表现为过敏性鼻炎、胸闷气短、哮喘加重、呼吸困难、发绀，伴有头晕、口干、眼花等。如全麻气管插管病人则表现为气道阻力增加，通气不好，血氧不能维持，肺部听诊哮鸣音[10]。另外呼末$CO_2$分压减少也具有重要诊断价值[11]。一般来讲过敏反应很少引起死亡，但顽固性支气管痉挛或伴喉头水肿所引起的严重低氧，进一步导致循环障碍，甚至危及生命，是围手术期的危象之一。

### 4. 过敏性休克

过敏性休克主要表现为全身症状，呕吐、面色苍白、唇周发紫、四肢厥冷、脉细弱、呼吸困难、心动过速、血压下降等，发病急骤，如未及时发现和治疗，可导致死亡。它的发生主要与休克的两个始动环节有关：血管活性物质引起毛细血管通透性增加，血浆外渗造成血容量减少；同时引起的血管扩张也导致血管床容量增大，造成血管内容量的相对不足，回心血量急剧减少，动脉血压迅速下降，形成过敏性休克特殊的血流动力学变化特点。

### 5. 其他

一些并不常见过敏反应，如烦躁不安、晕厥、昏迷、腹痛、低钾血症、肌无力、心肌缺血等症状发生，麻醉医生应提高警惕。

## 四、过敏反应的诊断研究

任何在围手术期发生过敏反应的患者都应进行随访检查，否则很难准确找出过敏原[12]。患者的病史是重要的诊断依据，随着免疫学和分子生物学技术的迅速发展，现已建立了多种过敏反应的诊断方法。Caimmi[13]等指出激素过敏的诊断检查方法可有皮肤过敏试验，RAST法血清IgE测定，嗜碱性

粒细胞释放组胺试验（BAT）等。

皮肤过敏试验(皮试)主要是检测机体是否对某种过敏原处于致敏状态，测试点通常选在前臂，包括皮肤点刺试验和皮肤过敏试验。基本原理为过敏反应与皮下组织中肥大细胞上的IgE结合后释放多种活性物质，引起毛细血管扩张、渗出增加，而出现红晕、风团等。皮肤点刺试验现为欧美国家公认最方便、经济、有效的诊断方法，安全性及灵敏度高。皮内注射法比针刺试验更敏感，可用来检测针刺试验阴性者[6]，但难以解释全身过敏反应。这两种皮肤过敏试验均得到广泛的应用，尽管皮肤过敏试验存在假阴性和假阳性，但仍有一定参考价值。

放射过敏原吸附试验（radioallergosorbent test，RAST）是将过敏原吸附到固相载体上而测定血清中相应特异性IgE浓度的一种体外试验方法，可以提供重要的依据，还可以确定过敏药物并帮助诊断皮肤试验阴性者。有许多病例通过RAST检测方法都成功的证实了血清IgE抗体为激素过敏的病因[14]。研究表明RAST的特异性及敏感性受抗原载体影响，适当的载体将增加特异性诊断的机率，是一项敏感、特异性高的方法。

另外还有许多其他方法可以间接诊断过敏反应，如白细胞组胺释放试验，流式细胞仪或血清监测嗜碱性粒细胞活化研究，嗜酸性粒细胞阳离子或LTC4释放试验等，但这些方法现并未广泛应用于临床。另外有研究表明血清组胺水平升高证实了过敏反应中组胺的释放，而血清中类胰蛋白酶浓度>25ug/L更加有力的证实了过敏反应的机制[11]。

## 五、地塞米松过敏反应的防治

预防为主是避免过敏反应首要措施。我们在麻醉访视时，应详细询问患者过敏史。如患者有过敏史或哮喘史等，应在手术前作针刺或皮内试验。对可疑过敏的患者，用药时应小心谨慎，严格掌握用药适应证，以减少过敏反应的发生，同时作好抢救准备。

如在麻醉期一旦确诊过敏反应发生，应严密监测患者生命体征，并给予相应措施。一般过敏反应轻微者，无需特殊治疗。若患者过敏反应症状严重，有休克危险，要及时采取措施。有人提出及时应用肾上腺素，快速补液和充分供氧是缓解症状的关键所在，并很少留下后遗症[15]。目前AAGBI(The Association of Anaesthetists of Great Britain and Ireland)提出了ABC(Airway，Breathing，Circulation)方法，即同时关注气道，呼吸，循环三方面[16]。具体措施如下：保持气道通畅，充分供氧，全麻病人应予以呼吸支持，延长拔管，对于非全麻患者，必要时可行气管插管或气管切开；充分补液，由于毛细血管大量渗出造成有效循环血量减少，应在短时间内快速补液；应用肾上腺素，Currie[17]等指出，麻醉师应根据患者的生命体征及临床表现迅速作出判断，及早给予肾上腺素，即使是全身严重多系统反应，给予保守剂量静脉滴注也可缓解症状。肾上腺素主要是激动α1受体，收缩血管，纠正低血压，减少水肿；同时兴奋β2受体，使支气管扩张，增强心肌收缩，肥大细胞和嗜碱性粒细胞cAMP释放增加，抑制组胺、白介素释放。成人首剂量可给50ug(1:10000溶液的0.5ml)，如严重的低血压或支气管痉挛可继续追加几个剂量，若血压仍不能维持，可静脉滴注肾上腺素或根据麻醉师经验改用收缩血管药物如间羟胺；若患者发生支气管痉挛，可用沙丁胺醇雾化吸入或氨茶碱6mg/kg缓慢静注；H1、H2受体阻断剂如苯海拉明50～100mg静脉给药，可与组胺竞争细胞膜受体，减轻临床症状。

## 六、结论

在围手术期，地塞米松是常用的抗过敏、抗休克药物，其过敏反应不常见。但麻醉期间用药多，患者耐受差，增加了发生过敏反应的危险性。麻醉医生在麻醉期间应时刻保持警惕性，尤其对有过敏史的患者应谨慎用药，必要时可在麻醉前作皮肤过敏试验确定对地塞米松有无过敏反应。过敏反应一旦发生并确诊，应迅速在稳定生命体征的基础上予以相应的处理措施，减少不良事件的发生。

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## 摘要

脓毒症具有患病率高、病死率高、治疗费用高等特点，迄今为止仍是危重症亟需解决的重大难题。其病理生理特点也未完全阐明。尽管如此，但近年来在改善脓毒症休克和多脏器衰竭的生存率方面仍取得了一些新进展。ATP敏感的钾通道（$K_{ATP}$）就是其中之一。$K_{ATP}$是心血管应激反应中起关键作用的离子通道，在脓毒症的发生发展中至关重要。目前认为，过度激活血管$K_{ATP}$会导致脓毒症休克时的低血压和血管对儿茶酚胺的低反应性。据此，有许多研究者提倡通过阻断血管上的$K_{ATP}$来治疗脓毒症。然而，在脉管系统外，该通道开放又可减轻细胞损伤。因此，在总体上如何把握$K_{ATP}$在脓毒症中的作用，仍有待探讨。本文拟对$K_{ATP}$通道在脓毒症中的作用作一综述。

关键词：ATP敏感钾通道；脓毒症；血管低反应性；钾通道开放剂

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# ATP敏感钾通道在脓毒症中的作用

## Function of ATP-sensitive Potassium Channel in Sepsis

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## Abstract

Sepsis and septic shock present the leading challenges in intensive care units, characterized by high morbidity, mortality, and costs. The pathophysiological mechanisms remain to be fully elucidated. Nevertheless, new discoveries have made great improvements in the high mortality conditions of shock and multi-organ failure. ATP-sensitive potassium channel ($K_{ATP}$) is an ion channel critical to the cardiovascular stress response. Excessive activation of $K_{ATP}$ is now recognized as a major cause of hypotension and vascular hypo-responsiveness to catecholamine in septic shock. Some researchers found that inhibition of these channels remains an attractive option to treat excessive vasodilation during systemic inflammation. However, channel opening may protect cells from damage outside the vasculature. Therefore, future studies are warranted to clarify the role of $K_{ATP}$ in sepsis. In this review, we summarize the role of the $K_{ATP}$ in sepsis.

**Key Words**：ATP-sensitive potassium channel; sepsis; vascular hyporesponsiveness; $K^+$ channel opener

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脓毒症是创伤、休克、感染、大手术等临床危重患者的严重并发症之一，也是诱发脓毒症休克和多器官功能衰竭（MOF）的重要原因。其发病机制复杂，对机体组织器官的损伤明显、治疗也很困难，因而成为世界性的难题。

### 一、脓毒症休克和多脏器衰竭的病理生理变化

疾病相关的基因和细胞因素使得感染在某些特定人群中可引发过度的炎症反应。微生物组分通过结合至血浆中可溶性的膜结合蛋白而激活白细胞、内皮细胞、血小板和凝血通路[1]。病原相关分子模式（细胞壁组分、毒素、超抗原和细菌DNA）通过结合至Toll样受体和其它识别受体，进而激活核转录因子，如NF-κB[2]。转录因子使促炎因子的基因表达上调，包括细胞因子，如肿瘤坏死因子（TNF）α、白介素（IL）-1和IL-6；以及酶，如诱导性一氧化氮合酶（iNOS）以及环氧化酶-2（COX-2）[3]。这些病原因素通过刺激内皮细胞内的花生四烯酸产生前列腺素、血栓烷和白三烯；活化的中性粒细胞产生和释放大量蛋白酶、过氧化氢和活性氧物质[2]。其最终结果导致血管通透性增加，渗出到血管外的液体、血浆蛋白和活化的中性粒细胞增加，产生微凝血病并使微血管张力改变。促炎介质以及继发于低血容量、间质水肿和血流的重新分布的组织低氧之间的协同作用会进一步减少线粒体能量的产生并降低代谢；在临床上则表现为各器官的功能异常[1]。

脓毒症所导致的机体重要脏器的功能衰竭，在心血管方面的表现就是脓毒症休克，其特征为组织灌注不良和对足量液体复苏无反应的严重低血压。低血压源自血管过度扩张、

血管低反应性（如对儿茶酚胺反应性降低）和不同程度的心肌抑制[1,2]。血管低反应性的发生机制包括一氧化氮（NO）通路、钾通道的过度激活以及循环内血管加压素减少[3]。在给予一氧化氮合酶（NOS）抑制剂[4]或血管加压素[3,5]后儿茶酚胺的用量常可减少，而这些作用中的部分则是由血管平滑肌$K_{ATP}$关闭所介导的。

## 二、$K_{ATP}$通道的结构和功能

$K_{ATP}$通道是由Noma于1983年在心肌细胞中发现。在胰岛β细胞、骨骼肌细胞、血管与非血管平滑肌细胞和神经细胞等多种细胞中也有发现[6]，在中枢神经系统中也有广泛分布。$K_{ATP}$通道属于内向整流$K^+$通道，由两个完全不同的亚单位构成，即磺酰脲受体（SUR）和属于Kir6.0家族的通道形成亚单位[7]。该通道的化学结构包括Kir6.0亚单位四聚体，形成$K^+$选择性通道，由四个具有不同功能的SUR蛋白包绕[6,8]。Kir6.0为内向整流/ATP通道家族成员，含2个跨膜螺旋，其侧端有一个富含Gly-Phe-Gly或Gly-Tyr-Gly的序列片段，该片段为$K^+$选择性通道所共有。其第二跨膜螺旋决定内向整流程度。Kir6.0形成$K_{ATP}$通道的中心孔道，其跨膜功能区的氨基酸序列与电压门控离子通道的$H_5$或P区同源，具有ATP结合抑制点，控制$K_{ATP}$通道对$K^+$的选择性，也是ATP感受器的作用位点。SUR含有对磺脲类和$K^+$通道开放剂具有高亲和力的结合位点和核苷酸结合位点[7]，为ATP结合盒(ATP-binding Cassette,ABC)的超家族成员，可分为$SUR_1$、$SUR_{2A}$和$SUR_{2B}$三种，有三个疏水结构域$TM_0$、$TM_1$、$TM_2$，其中$TM_1$和$TM_2$为核苷结合区。现已证实，$SUR_1$是$K_{ATP}$通道对ATP、ADP等敏感的调节亚单位。在$SUR_{2A}$上有两个核苷酸结合域(nucleotide binding domains，$NBD_1$和$NBD_2$)，$NBD_2$水解ATP的速度为$NBD_1$的两倍。ATP酶的活动依赖$Mg^{2+}$参与，但对喹巴因、寡霉素、左旋咪唑均不敏感，当$NBD_2$上的K1348A和D1469N两个位点突变后，ATP酶的活性减弱，使通道对ATP的敏感性增强。一定浓度的与SUR偶联的$K_{ATP}$开放剂可增加ATP酶的活性，但高浓度反而会使酶活性下降。这些结果表明，$K_{ATP}$通道也是内生性ATP酶活性调节的酶依赖性核苷调节通道（通过SUR亚基）。该类通道通过形成亚单位，再通过此通道调控$K^+$内流，当ATP结合于此位点时可抑制该通道。值得一提的是，血管平滑肌$K_{ATP}$通道（亦KNDP通道）和常规的$K_{ATP}$通道不同，对ATP并不敏感。然而，此通道仍可被NDPs活化且被硫脲类（如格列本脲）抑制[8]。其关键的代谢活性蛋白包括参与ATP合成的糖分解酶，存在于$K_{ATP}$通道的巨分子复合物中，且在通道附近维持高ATP/ADP的比率中起关键作用[9]。

表1

| 激活$K_{ATP}$通道的因素 | 抑制$K_{ATP}$通道的因素 |
|---|---|
| $[Mg^{2+}ADP]_i$ | $[ATP_i]$ |
| 钾通道开放剂 | 磺脲类 |
| 酸中毒、缺氧 | 钙调磷酸酶 |
| 磷脂酰肌醇4，5二磷酸（$PIP_2$） | 血管紧张素II |
| 蛋白激酶A（PKA） | 血管加压素 |
| 胰岛素 | 内皮素 |

$K_{ATP}$通道激活或抑制的因素归纳于表1中。

## 三、$K_{ATP}$通道的激素调节

已知血管活性药物可以调节$K_{ATP}$通道的活性。血管扩张药增加cAMP（包括降钙素基因相关多肽（CGRP）、腺苷和前列环素）、激活$K_{ATP}$电流、产生格列本脲敏感的开放和低血压。通道激活包括PKA和位于$SUR_{2B}$和Kir6.1的位点的同时磷酸化。增加cGMP的药物也能激活血管平滑肌和心肌细胞的$K_{ATP}$通道，这个过程可能涉及cGMP依赖的激酶或Ras和丝裂源活化蛋白激酶激酶。然而，在生理条件下，这些药物很少通过NO介导血管舒张。相反，血管收缩剂例如血管加压素、内皮素和血管紧张素II通过激活蛋白激酶C和增加ATP合成而抑制离体心肌细胞的$K_{ATP}$电流。

## 四、钾通道在脓毒症中的作用

$K^+$通道对动脉平滑肌细胞的膜电位和动脉血管张力起重要的调节作用。$K^+$离子外流的增加和细胞膜的超极化可激活$K^+$通道，接着引起电压门控钙（$Ca^{2+}$）通道关闭增加并降低$Ca^{2+}$内流。细胞内$Ca^{2+}$浓度的降低引起血管平滑肌细胞收缩功能的降低和反应性降低。目前，已经发现四种血管$K^+$通道，亦即电压依赖的$K^+$通道、$Ca^{2+}$激活的$K^+$通道、内向整流$K^+$通道和$K_{ATP}$通道。血管舒张休克状态中$K_{ATP}$通道的作用已被阐明[6]。血管平滑肌中$K_{ATP}$通道对细胞代谢变化起反应。在低氧状态下（例如，收缩性酸中毒、细胞ATP浓度降低和血浆乳酸水平增加），该通道活化增加，随之发生血管舒张且引起低氧状态下的血流增加[6]。脓毒症和脓毒性休克的特征是无氧代谢和全身酸中毒[10]。因此，如果血管平滑肌中的$K_{ATP}$通道被广泛活化，即可引起血管舒张和血管反应性降低[3]。$K_{ATP}$通道的激动剂包括血管活性物质，例如NO、CGRP、前列环素和腺苷[6,11]。据报道，内毒素引起$K_{ATP}$通道活化，接着通过iNOS通路使大鼠肠系膜动脉的血管反应性降低[12]。在内毒素大鼠中，阻断$K_{ATP}$通道会抑制iNOS的表达。磺脲类为口服降糖药，且已知其可抑制$K_{ATP}$通道。因此推测给予硫脲类，如格列本脲和格列吡嗪可拮抗脓毒症引起的全身性低血压[13]。

## 五、脓毒症的$K_{ATP}$通道活化的机制

### 1. 一氧化氮/环鸟苷酸（cGMP）通路

内毒素引起的低血压和血管低反应性大部分可归因于血管壁内源自iNOS的NO的过度产生。脓毒症患者中NO的含量增加，且与平均动脉压和全身血管抵抗成负相关[14]。iNOS的活化仅限于人类，且主要发生于感染时的血管内或是中性粒细胞中。源自iNOS的NO并不是人类脓毒症时的唯一的NO来源[14]。脓毒症时患者对NO的敏感性增加[4]，NO可激活可溶性鸟

苷酸环化酶并且可增加cGMP，或者可与超氧化物起反应形成过氧亚硝酸物，此物质的活性强于NO，可以使酪氨酸残基硝基化且可与巯基和含铁蛋白起反应。

短期内（<6小时）NO/cGMP通路的活化可激活$K_{ATP}$通道。据观察，NOS或鸟苷酸环化酶抑制剂可完全逆转内毒素引起的低反应性或膜超极化，且$K_{ATP}$通道具有类似的效应[15,16]。外源性NO不能使通道持续活化，表明iNOS通路可产生其它的或是更稳定的与NO共同起作用的因子。同样的，NO介导的KATP通道的开放需要先进行内毒素干预[15]或是形成过氧亚硝酸物。此外，NO和/或超氧化物产生增加会抑制神经钙蛋白的活性[16]，导致KATP通道的过磷酸化并引起正常ATP水平下$K_{ATP}$通道的开放。

### 2. 降钙素基因相关多肽（CGRP）

CGRP为含37个氨基酸的多肽，存在于感觉神经末端中，散在存在于大部分动脉血管床的血管舒张神经中，并以神经递质的形式起作用。CGRP与脓毒性休克的病理生理过程相关，在休克患者和动物的血浆中含量增加，并与疾病的严重性相关[17]。此外，给予受体拮抗剂（hCGRP）可瞬间逆转内毒素血症大鼠的心动过速和低血压。CGRP通过PKA介导的磷酸化激活血管KATP通道[8]。格列本脲可部分逆转体内和体外大部分暴露于CGRP的血管的舒张[11]。$K_{ATP}$通道的其它神经激素激活剂，包括心房尿钠肽和腺苷，在脓毒症时亦有增加，同样可逆转血管舒张[18]。

### 3. 肌动蛋白骨架

肌动蛋白骨架以多聚（F）和非多聚（G）的球形肌动蛋白形式组成，代表了细胞内约50%的总蛋白含量。F和G肌动蛋白以动态的能量依赖的形式流动，并可控制血管收缩性、细胞运动和包含KATP通道在内的多种离子通道[19]。在血管平滑肌中，由GTP酶形成肌动蛋白骨架，RhoA为维持血管收缩的主要的通路。因为cGMP抑制RhoA，在脓毒症时该通路被下调，并引起不可逆的血管低收缩性。

肌动蛋白解聚可增加心肌中的$K_{ATP}$通道的开放，削弱硫脲类的抑制作用，且可削弱血管平滑肌中格列本脲结合至SUR的高亲和力[20]。同样地，代谢应激可能通过$Mg^{2+}$ADP抑制SUR结合[6]，该特征与体内体外脓毒症发生时SUR抑制剂格列本脲引起的效应类似[12,15]，但与特定的通道阻断剂PNU37883A引起的效应不同。该机制有助于解释具有不同作用位点的$K_{ATP}$通道抑制剂之间的差异。因为肌动蛋白骨架的正常装备和维持有赖于ATP依赖的多聚反应，脓毒症时因能量降低而发生骨架断裂[21]。NO可抑制线粒体呼吸，使包括肾脏、肝脏和小肠集合淋巴结在内的不同细胞类型的肌动蛋白骨架断裂[22]。牛主动脉和肺血管内皮细胞经过内毒素或TNFα处理后，肌动蛋白骨架亦发生断裂[23]。

### 4. 线粒体$K_{ATP}$通道和器官功能异常

在脓毒症患者和动物中，线粒体发生肿胀和扭曲，且基质碎裂，这些改变与细胞氧化能力降低相关[24]。基质含量是线粒体代谢的重要调节因素[25]。在生理条件下，持续的$K^+$内流伴随着阴离子和水的跨膜运动。为维持线粒体的完整性，$K^+$通过$K^+/H^+$交换转运至基质外。线粒体$K_{ATP}$通道有助于线粒体$K^+$内流[26]。KCOs以$K^+$依赖的方式增加基质含量，然而，格列本脲和ATP抑制线粒体水肿。基质含量的增加可通过保留膜间空间的结构和功能和保持外膜对ADP和ATP的低通透性使线粒体免受缺血性损害[25]。然而，线粒体$K_{ATP}$通道过度的开放会显著引起去极化、外膜破裂、线粒体通透性转换孔开放、细胞色素C丢失等，并触发细胞的死亡通路[25]。然而，细胞膜较低程度的去极化可通过降低ROS的含量而使细胞免受损害和死亡，因此阻止了线粒体$Ca^{2+}$超载和转换孔的开放[26]。线粒体$K_{ATP}$通道可能通过上游p53拮抗剂使细胞免受凋亡[26,27]。脓毒症时线粒体$K_{ATP}$通道相关的机制在整个病理生理过程中所起的作用程度尚不清楚。

## 六、$K_{ATP}$通道和脓毒症有关的研究

### 1. 体内实验

关于脓毒症时$K_{ATP}$通道研究的体内证据主要来自麻醉的内毒素血症大鼠、狗和猪。格列本脲可迅速恢复血压，主要由于全身血管阻力的增加而非心输出量的效应[28]。在短期（3小时）和长期（24小时）暴露于内毒素后，格列本脲亦可增加血管加压素对$\alpha_1$-肾上腺激动剂的反应[29]。格列本脲对对照组动物没有作用，表明脓毒症时$K_{ATP}$通道首先开放，且为低血压和血管低反应性的潜在原因。这可解释内毒素处理后对药物性通道激活剂的反应性增加[30]。用皮质激素如地塞米松预处理可抑制$K_{ATP}$通道功能的增强、血管低反应性和格列本脲的加压反应[30]。这可能与地塞米松抑制通道亚单位表达和/或调节表达的介质合成有关。事实上，在内毒素处理的大鼠的横膈中Kir6.1的mRNA和蛋白表达增加，在24-48小时达到最高值。类似地，Kir6.1基因表达在实验性结肠炎中上调22倍[31]。因此，$K_{ATP}$通道表达增加是代谢性应激的共同特征，脓毒症时此效应有益或有害尚需测定。据动物研究推测，通道表达降低为脓毒症患者应用糖皮质激素的基础[32]。

由于近来对脓毒性休克患者的安慰剂对照研究发现格列本脲对血压没有作用且不需要去甲肾上腺素，$K_{ATP}$通道参与脓毒症的相关血管障碍的机制已遭到质疑。

### 2. 体外研究

使用体外器官浸浴模型发现存在血管低反应性[15]。实验所用动脉环取自脓毒症/内毒素血症动物或浸浴于内毒素的健康对照动物的血管。血管收缩性降低表现为对儿茶酚胺类血管收缩剂的剂量-反应曲线变得平坦，张力的强度和最大值降低。由于内毒素血症时iNOS表达于血管的全层，内毒素诱导体外无内皮的静脉的血管低反应性的持续能力并不足为奇[33]。

$K_{ATP}$通道和较少程度上的大电导钙激活钾（$BK_{Ca}$）通道的异常开放可引起取自暴露于内毒素6小时之久的大鼠的肠系膜

动脉和主动脉的膜超极化增加[34]。同时若不通过抑制孔关闭$K_{ATP}$通道的药物（PNU-37883A和钡）几乎可完全恢复对α1-肾上腺激动剂（苯肾上腺素）的张力[12]。到20小时时，逆转低血压的效应降低，表明额外的机制引起低反应性和/或对收缩性器官的不可逆损伤。同样地，在内毒素诱导的低反应性的体内和体外模型中，KCOs引起的舒张效应亦被加强，表明血管平滑肌中$K_{ATP}$通道的功能上调[15]。

脓毒症的死亡率很高，但其病理生理机制尚未完全阐明。在实验动物中阐明的机制亦需进一步在人类进行验证。脓毒症时许多机制与$K_{ATP}$通道的过度激活有关，包括血管低反应性。然而，通道的开放还可提供一定的细胞保护作用。这使$K_{ATP}$通道的作用更加扑朔迷离。用通道抑制剂进行治疗干预仍为一有前途的选择，但用特定的通道抑制剂而非SUR抑制剂靶定脉管系统在脓毒症的治疗时更为合适。脓毒症时$K_{ATP}$通道究竟是起保护作用还是有害作用尚需进一步实验来更好地阐明。通过这方面的研究可开发出组织特异性的、具有靶定调节通道功能的作用的药物。这不仅对脓毒症患者有益，对其他病理状态可能亦有一定作用。

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## 中华医学会第十二次全国物理医学与康复学学术会议

中华医学会第十二次全国物理医学与康复学学术会议定于2010年8月19-23日在安徽省歙县岩寺华商山庄召开。本次会议的主题是 “继往开来，共谋全国康复医学事业发展”， 重点学习和交流物理医学与康复学专业的新理论、新知识、新技术，邀请国内外著名专家就康复医学领域的热点问题作专题讲座，进行中英文学术交流并评选优秀论文，届时将举办康复设备展览。欢迎广大物理医学与康复科、康复医学科、理疗科、骨科、神经内科、神经外科、老年医学科、儿科、中医科、针灸推拿科及其他相关学科的医师、治疗师、护士投稿并参加此次盛会。

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**摘要**

随着对脑功能研究的深入和对疼痛机理认识的不断提高，雌激素在疼痛中的作用日益受到关注。G蛋白作为众多膜受体的重要组成部分，在人体各项机能中发挥着广泛的作用。本文主要从雌激素膜受体GPR30,阿片样受体，G蛋白偶联的内向整流型钾通，瞬时受体电位通道四个方面介绍了G蛋白在雌激素调节疼痛中的作用。

关键词：G蛋白；雌激素；疼痛

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# G蛋白在雌激素调节疼痛中的作用

## Role of G Protein in the Regulation of Pain by Estrogen

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**Abstract**

The role of estrogen in pain follows with interest recent years, for the studies about the functions of brain and the mechanism of pain go deeper. As a super-family of membrane receptor, G protein play various functions in the body. Here we induced the role of G protein in the regulation of pain by estrogen in four part. Those are GPR30, opioid receptor, G protein gated inwardly rectifying $K^+$ channels,transient receptor potential channel.

**Key Words**: G protein; estrogen; pain

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随着对脑功能研究的深入和对疼痛机理认识的不断提高，雌激素在痛觉传递调制中的作用日益受到关注[1-3]。许多动物实验表明，体内雌激素水平与疼痛的行为学表现及镇痛药物的作用效果密切相关，通过性腺切除或外源补充的方法改变雌激素水平，能明显改变动物对伤害性刺激的反应[6-10]。很长一段时间里，雌激素受体(ER)一直作为经典的核受体（ERα和ERβ）参与了雌激素的基因组效应，即雌激素与ER结合后受体发生空间构象改变而形成二聚体，从而暴露DNA结合区，使特异DNA序列与之结合，即靶基因调节区的雌激素反应元件(ERE)与ER结合，并募集辅助因子，形成转录启始复合物而启动基因转录，从而发挥其生物效应。

与传统的基因组效应相对，雌激素的快速反应也被称为雌激素的非基因组效应，由雌激素与膜受体直接作用影响蛋白质的磷酸化或去磷酸化所致[11]。研究发现[12]，17β-雌二醇($E_2$)可在缺乏ER的细胞发生快速效应。

G蛋白作为众多膜受体的重要组成部分，在人体各项机能中发挥着广泛的作用。很多激素类物质作用于相应的靶细胞时，都是先同膜表面的特异受体相结合，再引起膜内侧胞浆中cAMP含量的增加，实现激素对细胞内功能的影响。近年来，人们发现了雌激素的快速反应[13]，并提出了雌激素膜受体这一概念。此外，G蛋白还通过其他受体来参与了雌激素对疼痛的调节。

### 一、G蛋白偶联受体30（G Protein-Coupled Receptor 30，GPR30）

G蛋白偶联受体30（G protein-coupled receptor 30，GPR30）1997年由斯坦福大学医学院Carmeci等人发现[14]，是介导雌激素快速反应的一种新型雌激素受体（estrogen receptor，ER），它与传统雌激素核受体a、b无同源性，而且其作用模式和效应与二者也有差异。GPR30广泛表达于神经系统及其他系统，通过激活表皮生长因子受体（epidermal growth factor receptor，EGFR）及第二信使等介导雌激素样物质快速反应和转录调节，从而参与了疼痛调节以及多种疾病的发生发展[15]。GPR30的信号调节途径主要为细胞外信号调节激酶（ERK）/丝裂原活化蛋白激酶（MAPK）途径，环腺苷酸-蛋白激酶A-丝裂原活化蛋白激酶（cAMP-PKA-MAPK）途径，三磷酸磷脂酰肌醇-抗凋亡激酶-一氧化氮（PI3-Akt-NO）途径。

已有研究发现生理剂量的雌二醇（$E_2$）可通过跨膜信号转导迅速引起MAPK磷酸化，该通路是神经元活动、基因转录以及神经保护作用的关键，MAPK的激活是$E_2$对神经元与大脑部分活动的潜在调节介质。大量研究已经证实GPR30是雌激素膜受体，而且能够独立介导雌激素的诸多生理作用 。近期一项关于女性三叉神经痛的相关因素的研究中[16]，探讨了雌激素受体GPR30和雌激素核受体α在外周神经敏化中的作用，该研究认为GPR30和雌激素间接参与了三叉神经痛的调节。

### 二、阿片样受体

痛敏肽(FQ，孤啡肽）是一种近些年发现的阿片样受体-1受体的酶底物，是内源性十七烷肽[17]。该受体是与阿片受体有着显著同源序列的一种G蛋白耦联受体，是内源性阿片样受

体-1激动剂。

研究显示：在大鼠中，鞘内注射痛敏肽对电休克反应性的基础阈值没有影响。然而，在妊娠晚期或者模拟给予此时激素水平时，痛敏的阈值则降至基础阈值的70%左右，鞘内给药实际上减弱了阈值上调的剂量依赖作用，而且痛敏肽的痛觉脱敏作用并不受限于妊娠或性激素介导的痛敏。这一结果强调了激素环境下痛敏肽痛觉脱敏敏感性的重要性，但对妊娠中的额外疼痛，可以忽略痛敏肽作为脊髓伤害性疼痛通路的潜在影响。

## 三、G蛋白偶联的内向整流型钾通道

G蛋白门控内向整流钾离子通道（G protein gated inwardly rectifying $K^+$ channels,GIRK）是内向整流钾通道家族（inwardly rectifying $K^+$ channels，Kir）中的一员，存在5种亚单位（GIRK1-5），它们与神经兴奋性和心率的调节有关，特别在维持神经元的静息电位及慢突触后抑制中起重要作用[18]。GIRK通道的分子组成已经得到鉴定，是3.x钾通道家族的成员。G蛋白亚单位2（G-protein-activated inwardly rectifying potassium channel 2, GIRK2）是GIRK的亚型。

曾有研究指出GIRK2介导的痛觉感知和镇痛疗效因性别而存在显著性差异[19]。2002年Kelly MJ等人研究中枢神经系统中雌激素通过G蛋白耦联受体激活钾离子通道的快速调节作用时[20]，并观察到雌激素直接介导的促性腺激素释放激素神经元的超极化，这些发现证明了GIRK在下丘脑神经元中参与调节调自稳态功能的作用。

## 四、瞬时受体电位通道（transient receptor potential channel，TRP）

外周感觉神经广泛分布于心、肺等内脏器官，其神经元位于节状和颈神经节内，对辣椒素、酸、热和内源性炎症介质敏感。据研究提示这些刺激主要通过辣椒素受体(vaniloid1,TRPV1)而产生生物学效应。辣椒素受体是TRP的亚型之一，存在于感觉神经末梢和胞体。

在一项关于在成年大鼠伤害性感受器神经元的研究中[21]，发现在背根神经节感受器神经元上，TRPV1可以由非经典雌激素信号系统通路激活。另一项关于在急慢性宫颈痛的研究中指出[22]，雌激在大鼠的急慢性宫颈痛模型中可以介导痛敏的发生，而且给予TRPV1拮抗剂时可以减轻这一作用。

雌激素因受体在体内分布广泛，且存在组织差异性，其在机体内的调节作用益受到重视。G蛋白耦联受体作为体内广泛存在的膜受体家族的重要组成，在人体中发挥着广泛的作用。因此探讨G蛋白偶联受体对雌激素在疼痛中的调节作用，可能有助于我们进一步了解疼痛信号传导通路，甚至可能在疼痛的治疗新药的开发中给予启迪。

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## 第七届东西方国际疼痛会议

为加强国内外疼痛届的学术交流与合作，促进我国疼痛医学的进一步发展，国际疼痛学会中国分会(CASP)、中华医学会疼痛学分会、中国疼痛医学联盟和北京大学神经科学研究所将于2010年10月9日～11日在北京国际会议中心共同举办“第七届东西方国际疼痛会议”。

中国科学院院士韩济生教授和国际疼痛学会主席G..F. Gebhart教授担任大会共同主席，麻醉、肿瘤、康复、口腔、骨科等多学科领域领衔的国际国内知名疼痛专家共聚一堂。此次盛会将为与会代表搭建展示最新研究进展和临床成果的平台，提供与著名学者面对面讨论和交流的机会，共同探讨疼痛学前沿理论和治疗进展，推动疼痛学科的发展。

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**摘要**

植物人状态的定义是什么？植物人与植物人状态的区别何在？植物人状态可以被唤醒吗？怎样才有可能把植物人唤醒？

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# 拨雾工程——把植物人唤醒

## The Project of Dispelling the Clouds——To Awaken Patients in Persistent Vegetative State

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**Abstract**

A PVS patient is lying lonely on a bed in a quiet ICU ward, but his or her function of sensory organs is normal unless they are harmed. So all of nerve signals which caused by the environment stimulus can be surely transmitted to downwards or upwards the injured site of brain. Regretly that a PVS patient's sensory organs received too less and disproportional of stimulus usually because his or her families and doctors thought that the PVS patient cannot hear and see, etc, have not any communication with him or her. The patient will be in persistent vegetative state unavoidably. In fact, many of PVS patients may awaken some years later after their being injured. Here I initiate "the project of dispelling the clouds——To awaken patients in persistent vegetative state".

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作为一个医生，你有病人是植物人吗？如果有，你一定尝试过很多办法让病人苏醒。经过一段时间后，也许这些办法都没有效果，于是医生、病人家属只好放弃了。面对昏睡不醒的病人，日益增长的医药费，亲人伤心欲绝，医生束手无策。

事实上，如果植物人状态（permanent vegetate state PVS）的病因是大脑实质广泛损毁，如脑结核、脓肿等原因引起，要唤醒他（她）们当然是很困难的，但有些PVS病人是可以被唤醒的。在此，本人拟发起把植物人唤醒——拨雾工程，根据自己临床上的一些经历，以及有关文献的复习，对植物人可被唤醒作一前瞻性探讨，希望能抛砖引玉，引起有识之士的共鸣。

### 一、植物人的定义

植物人在国际医学界通行的定义是持续性植物状态，简称PVS。所谓植物状态是因颅脑外伤或其他原因(如溺水、中风、窒息等)导致大脑缺血缺氧、神经元退行性改变等引起的长期意识障碍，病人表现为对环境毫无反应，完全丧失对自身和周围的认知能力；病人虽能吞咽食物、入睡和觉醒，但无黑夜白天之分，不能随意移动肢体，完全失去生活自理能力；只能保留躯体生存的基本功能，如新陈代谢、生长发育。患者有自主呼吸，脉搏、血压，体温可以正常，但无任何语言、意识、思维能力。他们的这种植物状态，其实是一种特殊的昏迷状态。因病人有时能睁眼环视，貌似清醒，故又有“清醒昏迷”之称。

### 二、人的意识和觉醒

人每时每刻都存在对环境的感知，包括意识、痛觉、温觉、触觉、视觉、味觉、嗅觉、本体感觉等。意识是机体对自身和环境的感知，包括意识内容和觉醒状态两个组成部分。意识内容包括语言、思维、学习、记忆、定向与情感，其中语言和思维是意识内容的核心。解剖学上大脑皮层是形成意识内容的器官。觉醒是由脑干网状结构上行激活系统自动发出神经冲动到大脑皮层使其维持一定的兴奋性。人依靠感觉器官与环境时时刻刻保持联系。视觉、听觉、嗅觉、味觉、温觉、痛觉、粗触觉、本体感觉、平衡觉、内脏感觉等通过相应的感受器将对环境的感知通过神经冲动传入大脑。觉醒状态可分为意识觉醒和无意识觉醒，前者是大脑皮层与上行投射系统相互作用下产生的，又称为皮层觉醒，人对外界刺激反应时具有清晰的意识内容和高度机敏力，包括经典感觉传导通路的上行投射系统和由脊髓上行的感觉传导束到达脑干后发出的侧枝与网状结构联系换元后再到大脑皮层的非特异性传导通路；后者是下丘脑生物钟在脑干网状上行激活系统作用下产生的，又称为皮层下觉醒，是指觉醒、睡眠交替周期以及情绪、自主神经和内分泌功能的本能行为，它的维持依靠下丘脑的生物钟、脑干网状结构上行投射系统和下丘脑的行为觉醒。

### 三、植物人的形成

各种损伤因素导致大脑不能接收环境信息或不能把所要表达的信息发出，病人就可表现为植物人。从大脑的原发性损伤到植物人的过程大致为：大脑原发性损伤急性期（数分钟）、脑水肿

期1-2周、损伤恢复期（数月或数年）、植物人状态。健康人大脑受到伤害，大脑暂时失去对环境的感知。大脑的原发性损伤、镇静药物等使恢复期的病人孤零零地躺在病床上，上述各种维持大脑兴奋的感觉刺激大幅度减少，传入中枢的冲动大量减少，大脑对环境的感觉消失、导致维持大脑皮层兴奋的基础消失。呼吸、血压、体温等生命体征仅存，即所谓植物人状态。

### 1. 植物人的病因

各种物理、化学、生物因素导致大脑损伤都可使病人表现为植物人状态。

### 2. 损伤的种类

导致病人处于植物人状态的损伤是多种多样的，如脑血管意外是大脑内某处血管破裂出血导致血肿压迫神经组织，造成的损伤是局灶性的；溺水、一氧化碳中毒导致PVS是由于大脑缺氧造成的弥漫性损伤引起的。

### 3. 损伤的位置

对于局灶性损伤来说，根据植物人的临床表现可初步确定损伤的大概位置。一般来说，病人存在的生理活动越多，说明损伤的位置越接近大脑皮层，存在的生理活动越少，损伤的部位越接近延髓。我们知道，如果病人仅仅有呼吸、血压，是完全的“植物人”，如果病人可活动眼睛，说明病人的动眼神经的整个神经调节活动正常。可以根据病人存在的生理功能断定大脑损伤的大概部位，以便在唤醒过程中采取相应的措施。

### 4. 损伤的可逆性和不可逆性

导致病人成为植物人的损伤有的是不可逆的，如脑阿米巴脓肿、结核性脑脓肿等，长期慢性纤维组织的形成，要想恢复原来的神经传导通路是十分困难的，也就是说要唤醒他（她）十分不容易。但有些损伤是可逆的。如一氧化碳中毒引起的大脑弥漫性损伤，大脑损伤恢复可能性大。一般来说，脑组织血运越丰富的部位损伤越容易恢复。

### 5. 大脑收集感觉刺激的均衡

人通过特定的感觉器官不停地收集环境信息，经过加工整理再发出相应的应对信息。这些感觉包括视觉、听觉、嗅觉、味觉、温觉、痛觉、粗触觉、本体感觉、平衡觉、内脏感觉等。之所以有这些感觉的存在，人类才能适应环境、生存下来。正常人的这些感觉冲动的上传，在不同生命过程中是不同的，但各种感觉之间存在相对均衡性。例如，睡眠时人的视觉冲动显然较觉醒时少；正在走钢丝的杂技演员的前庭神经传入冲动要比静坐时多。人通过生物钟、改变环境等调节各种感觉神经冲动传入数量的均衡。一旦这种均衡被打破，人脑的活动就会出现失调。例如一个在一个黑屋子里呆很长时间的人，出来后智力较前会有明显下降。

### 6. 植物人所收集的感觉

植物人虽然静静地躺在病床上，但他（她）的感觉器官并未受损，因此所有环境刺激可形成神经冲动传入大脑的损伤部位。但实际上植物人所能接收到的环境刺激明显太少！在宁静的监护室里，病人仰面朝天，听觉刺激和视觉刺激明显太少！医生、护士、家人以为他（她）无反应也就不和他（她）交流，导致患者接受的感觉刺激少而且不均衡，昏睡不醒在所难免。

## 四、植物人可被唤醒的依据

### 1. 损伤的恢复

各种类型的大脑损伤经过急性期、脑水肿期后，受伤的脑组织是可以恢复的。其理论根据是，虽然神经元的胞体损伤是不可再生的，但神经纤维是可以再生的。许多损伤实际上是损伤了大脑的传导、联络神经纤维，而神经元的胞体并未受到损伤。

### 2. 各种感觉刺激形成的冲动传入中枢可刺激神经纤维的再生

神经元的生物电活动，可刺激损伤了的神经纤维的再生。生理活动最多的器官（大拇指），在大脑皮层的投射面积和厚度都最多，就说明了这一点。反复给予大量的感觉刺激，感觉器官的感受器把神经冲动收集上传，神经细胞得以营养、神经纤维得以再生，新的传导通路得以建立，大脑的网状结构上行激动系统的兴奋程度增加（皮层下觉醒），进一步兴奋大脑皮层，植物人可苏醒 。

### 3. 各种媒体上报道的植物人被唤醒的病例不胜枚举

在互联网上输入“植物人苏醒”搜索，就会有许多植物人被唤醒的病例。

## 五、拨雾工程的实施

### 1. 召集合作者

所有身边有植物人的监护病房、神经科、康复科大夫，病人家属、病人的亲友都是我们的合作者。

### 2. 评估

收集病人的病史资料，作一详细的评估。

### 3. 唤醒工作

这里让我们试用一些方法把他（她）们唤醒，不需要花一分钱。具体方法是：

（1）由病人的亲人在他（她）的耳边反复呼唤，与他（她）一起回忆过去的快乐时光；或者把亲人对他（她）的呼唤录音后反复放给他（她）听；间歇给病人戴耳机听收音机，收听他平时最喜爱的节目，如相声、小品、流行歌曲等。是最重要、最有效的方法，可通过听觉刺激，使病人中枢兴奋。也许病人看上去毫无反应，这时千万别放弃，其实听觉是完全能够传入大脑中枢的。亲情可能是让植物人苏醒的“特效药”。

（2）长期按摩、给病人活动全身肌肉，防止四肢肌肉萎缩。可通过触觉刺激，使病人中枢兴奋。

（3）开灯给病人视觉刺激。酸味食品（如话梅）可刺激病人的味觉。香味可刺激病人的嗅觉。

（4）注意病人的营养状态。

（5）最重要的是，上述工作必须持之以恒、日复一日，坚持不懈，才能把植物人唤醒。

### 4. 再评估（每周一次）

对病人回应唤醒工作的反应进行评估，了解病人是否有进展。

# “精睿”让监护无处不在

## IntelliVue MMS X2 , To Care Everywhere

王鲁宁
飞利浦医疗保健事业部

在灾难救援现场或医院急诊大厅，人们经常看到这么一幕，救护人员紧张地观察着患者的心跳、脉搏，或手忙脚乱地将病人向病房转移。他们这样做无非是想尽早知晓患者当前身体状况，给予及时可靠地救护。那么，在医疗设备不断向临床需求靠拢的今天，是否可以有更方便可靠的手段，让生命体征的监护无处不在，更好地护卫患者健康呢？这就是本文要讨论的重点。

### 转运中的监护先锋

当重症患者由于各种原因必须进行转运时，不可避免的车体晃动可导致置入管路的移动或脱位，造成输液速度不稳，气道分泌物增多等问题，这些均会增加患者转运风险；因此，在运送患者途中，更要严密监测生命体征，确保患者有效的呼吸和循环。“精睿”(飞利浦模块化监护仪IntelliVue MMS X2)由于体积小巧，重量轻(1.2kg),具有贴心的床旁挂钩、绑带等配件设备，因此可被轻松绑定在运输车上。而独有的“户外显示模式”以及通过多项“抗震抗摔”国际标准，确保可在颠簸振颤的环境下正常工作，更使“精睿”模块化监护仪成为患者转运过程中的监护先锋。

### 分屏监护让麻醉更加便捷安全

转运及时只是更好救护患者的充分条件，大部分急诊患者在进入医院后要迅速进行手术治疗。而麻醉是手术时至关重要的环节，也是医疗事故的重要原因之一。据相关资料显示，在手术麻醉期间死亡的患者有25%是由于麻醉不当导致的，因此麻醉监护就显得尤为必要。

麻醉过程通常包括麻醉诱导、术中麻醉和术后苏醒恢复三阶段，这三阶段的监护往往各自独立，常需更换监护仪及重新连接导联线，该重复操作既占用大量时间，也不利于手术间的流畅运转。“精睿”集独立监护仪与测量模块为一体，则可将这三阶段的监护有机互联：诱导期，它是一台不折不扣的独立监护仪。术中，“精睿”作为测量模块，可与MP20-MP90监护仪直联构成“伴随模式”；提供“一机双屏双控”显示方式，让麻醉师、负责体外循环医师或主刀医师可分别察看、操作“精睿”和MP20-MP90监护仪，同步获得患者的各项生命体征，达到更加密切的配合，充分解决了多位相关人员同看一台小监护屏幕时的视觉观察死角问题。术后，“精睿”随同患者转至恢复室，再次独立监护生命体征。整个过程中，随着监护需求的变化，“精睿”可随时变

换角色，既减少了重复操作，又保证了监护数据的连续性，对确保手术安全起着至关重要的作用。

### 让急诊、ICU监护更加简捷方便

即使是在一台完美的手术或急救处理后，患者仍旧会出现各种复杂的并发症。因此，大多情况下要对患者全身各系统进行不间断的密切监护和调节。而从抢救室或手术室再至ICU的空间转移需求使得医护人员必须根据需要为患者更换转运监护或床边监护：更换电缆线、电极片、传感器校零……对于一个没有既定规程的处理环节，个体化的人工操作很难确保上述的每项更换调整都及时准确，病人的安全监护隐患在所难免。此外，这种设备的来回更换还会使监护数据间断、分散，一旦发生紧急状况，很难及时调阅连续时间段内的患者生命指征信息。

当采用“精睿”监护仪后，上述的复杂问题就将得到简单化解决。因为它不但可以在转运、麻醉监护中进行有效应用，作为监护模块，还可以与MP20-MP90监护仪直接互联，可将8小时数据趋势上载到主监护仪，在保证数据连续性的同时还增加了医护人员的工作效率。“精睿”甚至也可作为一台固定的床边监护使用，可外接大屏幕显示器，并具有成人、儿童及新生儿模式，还可以与IntelliVue信息中心进行有线或无线联网，实现病人监护集中管理。

作为飞利浦监护仪家族的新成员，“精睿”的出现解决了现有医疗在对患者进行全程监护过程中的监护盲点。在现今医疗发展完全围绕“以病人为中心”的服务模式中，这种无处不在的监护既是保障患者生命安全的坚实基石，也引领着监护产品发展的又一方向。

## 第十五次长江流域麻醉学学术年会暨中南六省麻醉学学术年会暨湖北省麻醉学学术年会胜利召开

由湖北省医学会、湖北省医学会麻醉学分会主办的第十五次长江流域麻醉学学术年会暨中南六省麻醉学学术年会暨湖北省麻醉学学术年会于2010年5月28-30日在武汉科技会展中心胜利召开，本次会议注册人数近700余人，共有1000余名代表参加，分别来自长江流域各省市、中南六省及特邀省份、国外知名学者和台湾同胞。既有在我国开创本专业的老一辈专家、教授，又有年富力强的年轻一代学者。大家共聚一堂，畅所欲言，共叙友情，交流经验，是难得的一次盛会。

会议得到了湖北省卫生厅领导的高度重视与支持，湖北省卫生厅党组书记杨有旺同志出席了会议并在开幕式上致辞，出席本次会议的还有：湖北省医学会党委书记、副秘书长张全炳同志；中华医学会麻醉学会主任委员于布为教授；中国医师协会麻醉医师分会会长黄宇光教授；中华医学会麻醉学会侯任主任委员刘进教授；中华麻醉学杂志总主编、麻醉医师终身成就奖获得者罗爱伦教授；比利时麻醉学会主席Vandermmersch Eugne；美国约翰霍普金斯大学医学院麻醉与危重症医学常务副主席Daniel Nyhan；美国麻省总医院麻醉科教授Zhongcong xie；台湾专家范守仁教授、汪智雄教授、皺美勇教授；中国麻醉界德高望重的老专家们；长江流域省份、中南六省及特邀省份的麻醉学会主任委员。

大会由湖北省医学会麻醉学分会副主任委员王焱林教授、刘菊英教授主持。

本次大会执行主席、湖北省医学会麻醉学会主任委员、华中科技大学同济医学院附属协和医院副院长姚尚龙教授在开幕式上致欢迎辞，对出席本次会议的卫生厅领导及全国麻醉界同仁，表示了热烈的欢迎和衷心的感谢。

大会开幕式上曾因明教授、罗爱伦教授、黄宇光教授、于布为教授依次致辞，对近年来我国麻醉学的发展成果做出了肯定，并对中青年麻醉医师提出殷切的希望。

湖北省卫生厅党组书记杨有旺同志在大会开幕式上致辞指出，本次会议的宗旨是为了推动和促进我国麻醉学学术研究及麻醉临床工作的顺利展开，总结和交流学术进展。我省医学发展迅速，麻醉学作为重要的临床学科在临床医学中发挥重要作用，麻醉科是医院医疗安全的保障学科，手术科室的枢纽，创建无痛医院的主导学科，重要的临床科室。长江流域麻醉学术会议是由我国著名的麻醉学家金士翱、李德磬、刘怀琼等共同发起，至今长江流域麻醉学术会议已经走过了20多个春秋。中南六省麻醉学术会议在中南六省前辈们的支持与关注下，也取得了骄人的业绩。这两个跨地区的学术会议在国内影响大，学术水平高，对促进地区间的学术交流与合作，进一步地提高各区域间麻醉学医疗技术水平起到积极的促进作用。

在本次会议上，共收到论文585篇，分别以大会专题报告、分会场发言、专题讨论与论文摘要汇编等形式进行了交流。其中设立了麻醉专家论坛、气道管理专场、海峡两岸麻醉学术交流专场、麻醉学新进展等九个专场及相关专题讨论。会议的学术交流气氛浓厚、代表发言踊跃，各抒己见，为日后的学术交流、共进，营造良好氛围。整个学术会议在平等、团结的氛围下进行，充分展现了麻醉学科广大同仁积极向上、勇于开拓的良好精神风貌，同时也体现了麻醉学科公正、民主作风与虚心求实的精神和学术氛围。特别值得指出的是第五分会场的困难气道管理培训专场，代表们表现出了热烈的学习热情，多位代表向主办方提出了再次举办的建议。

长江流域麻醉学学术会议创始人金士翱教授、刘怀琼教授称赞会议的成功召开，在会议总结时指出会议论文涉及面广、内容丰富，达到了广泛交流、教学相长的目的。

通过本次会议组委会的研究决定，第十六次长江流域麻醉学学术会议将在青海省举行。2011年中南六省麻醉学学术会议将在广东省举行。2011年湖北省麻醉学学术年会将在湖北省咸宁市举行。

本次会议圆满成功得到了广大厂家的大力支持，参展的厂家有46家，在此表示衷心的感谢！

本次会议通过湖北省医学会、湖北省医学会麻醉学分会的精心筹备，特别是孙铁汉秘书长、武庆平教授和王成夭教授的认真工作，在有关领导的支持和代表们的共同努力下，达到了预期目的，在全体代表的掌声中圆满结束。





## “麻醉深度监测技术亚洲培训中心”在上海瑞金医院正式成立

麻醉的深浅有了可以精确度量的“尺子”。3月29日，“麻醉深度监测技术亚洲培训中心”在上海瑞金医院正式成立。中华医学会麻醉学分会主任委员于布为教授表示，通过精确麻醉的推广实施，将有效避免病人出现术中知晓或麻醉过深引发危险，“国际先进水平是每２０万例手术中出现１例直接与麻醉相关的死亡等意外，我国目前的比例为五万分之一，推行精确麻醉时不我待。”

由中华医学会麻醉学分会、上海瑞金医院和德国汉诺威医科大学等设立的“麻醉深度监测技术亚洲培训中心”将为全亚洲培养麻醉深度监测的团队，共同提高麻醉安全水平。所谓精确麻醉，就是有明确的麻醉深度，能根据手术需要准确把握和调整麻醉深浅，并在术后能让患者及时苏醒，不出现呕吐等不良反应。

脑电信号是大脑皮层神经细胞群突触点位变化的综合反映，也是目前检测麻醉深度的最有效方法。通过脑电信号的监测，能准确地综合评价患者在麻醉过程中的状态，特别是监测脑部对手术刺激的反应。

于布为教授指出，良好有效的麻醉是手术的基础。通常的麻醉是以病人的体重、年龄粗略估计麻醉剂量，并在术中通过血压、心率来判断麻醉的深浅，而血压、心率受到手术刺激的影响，并不能准确反映麻醉的深度，因此，麻醉过程中医生的经验在很大程度上起了决定作用。麻醉过深，可能造成神经后遗症，患者术后长时间都可能有不适感，严重的甚至危及生命。麻醉过浅，病人可能对手术有记忆甚至痛觉，严重的会引起精神或睡眠障碍。“我们将致力脑电信号监测这一技术在国内乃至亚洲地区的推广，这一新技术在大大增强安全性的同时不会明显增加病人的经济负担。”

在综合评价的基础上，上海瑞金医院引进国际先进的麻醉脑电医师深度监测系统，已于近日在所有手术室配备设备并应用于临床全麻手术。据悉，这一系统曾经在2000年德国汉诺威世博会上展示推广，并已经在德国400多家医疗机构运用。设备发明人舒尔茨夫妇表示：“我们非常高兴在上海世博会前能带着这项技术来到中国。”

## 宝莱特开启麻醉新领域 继续横向扩大产品线

2010年4月，宝莱特公司正式签约为英国攀龙PRIMA SP系列麻醉机的中国区总代理。63届医博会以及第十五次长江流域暨中南六省麻醉学术年会上，宝莱特携PENLON麻醉机与A系列信息插件式监护仪的完美组合闪亮登场，也让BLT的高端监护仪产品得到了它应有的价值体现和实现安全信息一体化的麻醉临床应用解决方案。这优异化的组合倍受瞩目吸引了全球专业观众、众多客商、医师的关注，各位专家、医师，都对这安全信息一体化的麻醉临床应用解决方案表示关注和极大的兴趣。这创新的组合、领先的技术及专业化服务都给来宾留下了深刻的印象。

## 骨髓干细胞治疗重症肌无力研究取新突破

近日，应用骨髓间充质干细胞治疗自身免疫性重症肌无力研究在哈尔滨医科大学取得新突破，为临床解决重症肌无力难题提供了实验基础和理论依据。这一系列科研成果从2009年到现在，先后发表于德国《欧洲免疫学》、美国《神经免疫学》和英国《免疫学》等国际著名期刊上。

重症肌无力是神经系统自身免疫性疾病，也是临床上难治性疾病之一，迄今尚无有效、特异的治愈手段。以往较为公认的重症肌无力发病机制与Th1和Th2辅助性T细胞功能失衡有关。哈尔滨医科大学神经生物学教研室主任李呼伦教授带领学术团队在实验性自身免疫性重症肌无力的科研中，首次提出并证实Th1、Th2、Treg、Th17 4种CD4+辅助性T细胞的功能失衡是重症肌无力发病的重要因素，并以此为理论依据，以骨髓间充质干细胞移植作为手段进行了尝试性治疗观察。

该课题组以人类重症肌无力的大鼠实验动物模型为对象，通过尾静脉大剂量回输骨髓间充质干细胞，并对实验动物进行临床症状评定，发现和证实了重症肌无力的发生、发展与上述4种细胞亚群格局的改变有关。通过表现在骨髓间充质干细胞能降低AChR特异性T、B细胞的增殖活性，并降低B细胞的抗体分泌能力，特别是逆转4种Th细胞亚群及相关细胞因子的平衡状态以及恢复内环境的相对稳态。实验证实了骨髓间充质干细胞对于免疫细胞具有较强的免疫调节功能。

## 京医改12320热线开通征集新医改建议

北京市新医改方案公布后，还将制定一系列配套措施。北京市卫生局近日开通了北京市公共卫生热线“12320”，全程征集、归纳群众对于北京新医改进展的建议。

已经开通的热线电话“12320”是北京市收集、解答群众关于公共卫生问题的平台，北京市卫生局称，在医改进行过程中，这一热线电话将收集广大群众对医改进展和配套措施的意见和建议，值班人员将会做好记录和整理，以便完善医改措施，使医改更加惠民利民。

《北京市2010——2011年深化医药卫生体制改革实施方案》（以下简称《实施方案》）12日公布。北京市医改办主任韩晓芳说，此方案在公开征求群众意见的基础上，采纳了北京市民、外地在京居住人员等提出的145条意见和建议，对16个方面进行了修改。

《实施方案》征求意见稿4月22日至29日曾上网公开征求意见，共收到意见建议990条，共约11万字，主要分为三类：705条提出了具体意见，占71.2%;表示赞赏、支持医改方案的221条，占22.3%;咨询类意见64条，占6.5%。

根据群众提出的应将小孩门诊纳入医保的建议，《实施方案》增加了“将学生、学龄前儿童和无业居民人员门诊费用纳入医保范围”一条。韩晓芳说：“经测算，此项医保政策调整，一年内就可减轻群众负担约3亿元。”

根据群众意见，《实施方案》还扩大了北京市公共卫生服务项目范围：将宫颈癌、乳腺癌筛查和增补叶酸范围由农村妇女扩大到北京市全部适龄妇女，将艾滋病、病毒性肝炎纳入重大疾病防控，还决定为北京市慢性病家庭培养家庭保健员等。韩晓芳说：“还有部分具体意见将由北京市有关部门在制订与新医改方案配套的N+K方案及下一步工作中，细化落实或研究参考。”

## 北京公立医院改革启动 以分级诊疗为核心

以分级诊疗、有序就医为核心的北京市公立医院改革，昨起正式在平谷区率先试点。

试点内容主要是，农民常见病在基层医院解决，大病预约转诊到区医院，疑难重症通过绿色通道转诊到三级医院。市卫生局副局长邓小虹昨天表示，为推广分级就诊模式，本市将建立康复医院和护理医院。

■到大医院看病居民需要绿色通道转诊

邓小虹说，分级就诊的内容主要包括：由平谷区医院、康复医院和护理院以及基层社区医院组成区域医疗服务共同体，农民实现常见病、多发病在基层社区医院解决，大病预约转诊，依托平谷区医院与北京协和医院的对口协作关系，疑难重症通过绿色通道转诊到协和医院，康复期病人和需长期护理病人转诊到辖区的康复医院和护理院。同时，研究建立北京协和医院与平谷区医院之间远程病理和影像学会诊系统;在平谷区建立动态变化的社区居民电子健康档案，为家庭医生提供帮助;建立平谷区医院与辖区基层医疗卫生机构之间的双向转诊信息系统。

■新农合报销引导居民分级就医

平谷区卫生局副局长张友介绍，为引导农民分级就诊，平谷区制定了新的新农合报销政策：居民在一级卫生院看病，无起付线，医药费可报销65%;未经转诊在二级医院看病，起付线为650元，医药费可报销50%;未经转诊到三级医院看病，起付线为1300元，医药费可报销50%。

■11家大医院将帮扶区域医疗中心

邓小虹介绍，为实现分级诊疗，缓解农民看病难，今后三年城区的北京协和医院、中日友好医院、北京大学第一医院、北京大学第三医院、北京大学人民医院、北京友谊医院、北京同仁医院等11家“三甲”综合医院将对口支援10个郊区县的11个区域医疗中心，重点放在心脑血管意外、创伤和急重症抢救等有关学科和人才队伍建设方面，建立城区“三甲”医院与郊区县区域医疗中心的紧密协作机制，逐步形成农村居民小病不出乡村、大病不出区的分级有序就医格局。

■社区医院将设护理病床，康复病床

统计数字显示，躺在大医院里超过半年的患者约占住院总数的10%，为改变这一现状，北京计划在每个辖区内设立康复医院和护理医院，按每千人0.5张床位的比例配备康复病床和护理病床，并将建立统一入院标准、转院标准、收费标准等。

平谷区卫生局副局长张友介绍，目前，平谷区18个乡镇都设立了康复病床。下一步，平谷区将重新调整全区病床设置，在社区卫生服务中心增设康复病床和护理病床，让慢性病患者、术后患者从大医院转到社区医院继续接受治疗。

# 學會與征文

## 2010年中华医学会全国麻醉学术年会暨第十二届国际心胸血管麻醉学术会议征文通知（草案）

医学术便函（2009）第099号

各省、自治区、直辖市医学会：

各有关医疗单位：

中华医学会麻醉学分会定于2010年9月23—25日在北京国家会议中心召开“2010年中华医学会全国麻醉学术年会”，本次会议是中华医学会一类学术会议，是一年一度的学术盛会。另外，受国际组织委托，代表世界心胸血管麻醉最高水平的第十二届国际心胸血管麻醉学术会议（ICCVA）；也将于9月22—24日在国家会议中心举行；届时将有数百名从事心胸麻醉的国外学者来华参会；互相交流、学习。

年会仍将以知识更新讲座和学术论文报告相结合的形式进行学术交流；现将年会学术论文征文有关事项通知如下：

**一、征文内容及分类：**

1、麻醉学基础研究；

2、临床麻醉与研究；

3、疼痛治疗与研究；

4、重症监测治疗与研究；

5、麻醉相关新技术、新业务进展；

6、特殊病例报告；

7、其它。

**二、征文要求：**

**（一）、年会征文：**

1、凡报送参加年会交流的论文，均提交论文摘要一份（800--1000字以内），并请在稿件左上角按上述征文分类注明论文类别（请自留底稿，恕不退稿）。

2、格式要求：论文摘要请用Microsoft Word2000或2003编辑，页面设置请用4号字体，A4纸，文稿顺序为题目、单位、邮编、作者姓名、联系电话、摘要内容。

3、凡已在全国性学术会议上或全国公开发行的刊物上发表过的论文，不予受理。

4、本次年会将进行中青年优秀论文评选，参评条件为1965年9月1日以后出生（投稿时请将身份证复印件扫描成图片格式粘贴在文章的首页）。凡申请参加中青年优秀论文评选的论文，均需提交中、英论文摘要各一份（800--1000字以内）及中文全文一份，论文一律用word文档撰写（请网上投稿）；征文要求同上；并请在稿件右上角注明“中青年优秀论文评奖”字样。评选设一等奖1名，二等奖3名，三等奖5名（具体参评要求届时见有关会议通知）；获奖者将获得临床科研奖金。

**（注：年会还将继续进行2010年度SCI论文奖评选；获奖者将获得优秀论文奖金；具体评选办法请登录年会网址查询）。**

**（二）、ICCVA征文范围：**

心胸血管麻醉相关的药理学、监测、围术期管理新技术；围术期器官保护、血流动力学调控、内环境调控等。

**三、投稿方式：**

1、网上征文与报名：年会网址：http://www.csaol.cn/；ICCVA网址：www.iccva2010.cn；

2、书面邮寄：“北京东四西大街42号中华医学会麻醉学分会办公室白雪同志收（邮编：100710；投寄的论文请在信封上注明“2010年麻醉年会征文”字样）。联系电话：010-85158614，传真：010—85158753；邮箱：csaol@yahoo.cn）；（请尽量采用网上投稿；以保证投稿和注册的准确性；二种方式只选一种）

四、截稿日期：年会：2010年4月30日；ICCVA：3月31日。

五、欲了解第十二届国际心胸血管麻醉学术会议（ICCVA），请登陆：www.iccva2010.cn；

六、凡个人邀请外宾来参加全国年会并拟进行学术交流者，请与上海办公中心薛庆生联系（邮箱：xueqingsheng@yahoo.com.cn;电话：13611909814）。

**中华医学会学术会务部**

**中华医学会麻醉学分会**

**2009年12月15日**

# 会议讯息

2010 Information of Notification、Exhibition and Scientific Meeting 展

## 国内会议信息

第九次华东地区麻醉学术会议
第二次海峡两岸麻醉学术会议
山东省第十三次麻醉学术会议
山东省第四次疼痛学术会议
时　　间：2010年7月2日—4日
地　　点：山东青岛
主办单位：华东地区麻醉协作组
　　山东省医学会
联 系 人：徐 鑫/王添印
电　　话：0531-88591082

2010全国重症医学学术高峰论坛
时　　间：2010年7月9日—11日
地　　点：北京
主办单位：中华医学会
联 系 人：靳元振
电　　话：010-67534765-8888

2010年全国神经外科麻醉年会
时　　间：2010年8月6日-9日
地　　点：天津市
主办单位：麻醉学分会
联 系 人：王国林
电　　话：022--60362606
E-mail：medcon@126.com

2010年广东省麻醉学学术会议
时　　间：2010年8月
地　　点：广东佛山
主办单位：中华医学会广东分会麻醉学会
联 系 人：丁　红
电　　话：020-61641881

2010年中华医学会麻醉学分会疼痛医学年会暨可视化技术在麻醉镇痛与危重急救中的应用大会
时　　间：2010年8月12日—15日
地　　点：四川成都
主办单位：麻醉学分会
联 系 人：宋莉
电　　话：028-85422997

2010年浙江省麻醉学学术年会
时　　间：2010年8月20—22日
地　　点：浙江台州
主办单位：浙江省医学会麻醉学分会
联 系 人：冯智英
电　　话：13989881666

第五届产科危急重症救治学术研讨会（COCC）
时　　间：2010年9月10—12日
地　　点：山东青岛
主办单位：《现代妇产科进展》杂志社
联 系 人：顾先生，唐小姐
电　　话：021-64044507

第十二届国际心胸血管麻醉学术会议
时　　间：2010年9月21日—24日
地　　点：北京市东城区
主办单位：中华医学会
　　中华医学会麻醉学分会
联 系 人：秘书组
电　　话：010-85158124

2010年中国医学会全国麻醉学术年会
时　　间：2010年9月23日—25日
地　　点：北京国家会议中心
主办单位：中华医学会麻醉学分会
联 系 人：白雪
电　　话：010-85158614

第四次全国中毒与危重症救治学术会议
时　　间：2010年10月20日-23日
地　　点：广东省　深圳市
主办单位：中国毒理学会中毒与救治专业委员会
联 系 人：张文武
电　　话：0755-27880712

第七届东西方国际疼痛会议暨中华医学会疼痛学第八次全国年会
时　　间：2010年10月9日—11日
地　　点：北京市
主办单位：疼痛学分会
联 系 人：任莉梅/林雪琴
电　　话：010-85158138

第十四届世界临床疼痛大会暨第一届亚洲疼痛大会、第四届中国临床疼痛学术会议
时　　间：2010年10月29日至11月1日
地　　点：北京国家会议中心
主办单位：中华医学会麻醉学分会
联 系 人：董老师
电　　话：010-59046396

2010年疼痛医学年会
时　　间：2010年11月20日-22日
地　　点：西安
主办单位：麻醉学分会
联 系 人：徐建国
电　　话：13951033382

首届首都医科大学麻醉学系年会
时　　间：2010年11月5-7日
地　　点：北京国家会议中心（暂定）
主办单位：首都医科大学麻醉学系
联 系 人：袁扬
电　　话：010-59046399、010-59046022

## 国内展会信息

2010年中国·贵阳第六届医药博览会
时　　间：2010年7月28日-30日
地　　点：贵州省贵阳
主办单位：国家中医药管理局
　　国家民族事务委员会经济司
联 系 人：王建
电　　话：13522604338

2010北京国际健康生活方式博览会
时　　间：2010年9月1-3日
地　　点：北京
主办单位：中华人民共和国卫生部
联 系 人：程磊
电　　话：13764672529

2010中国（上海）国际健康产业博览会及健康产业发展论坛
时　　间：2010年9月2-4日
地　　点：上海光大会展中心
主办单位：国保健协会上海办事处
联 系 人：周先生
电　　话：86-021-56925020

2010山东国际医药.原料药.中间体.包装及制药设备（济南）展览会
时　　间：2010年9月18日-20日
地　　点：山东省济南
主办单位：济南市人民政府
联 系 人：王鑫
电　　话：15865545949
E-mail：qdhh_xiaojuqiub@163.com

2010年第20届郑州创新药交会
时　　间：2010年9月24日-25日
地　　点：河南省郑州
主办单位：中国医药保健品营销协会
联 系 人：郭丽
电　　话：0371-69131305,13073765606

2010中国（上海）国际口腔器材展览会暨学术研讨会
时　　间：2010年9月27-29日
地　　点：上海国际展览中心
主办单位：卫生部口腔科技研究发展中心
联 系 人：冯洋
电　　话：13162585768

2010上海国际传统医药与健康博览会
时　　间：2010年11月4-6日
地　　点：上海
主办单位：上海市商务委员会
联 系 人：刘辉
电　　话：021-51714666

2010中国（苏州）国际生物科技展
时　　间：2010年11月18-21日
地　　点：苏州
主办单位：苏州市人民政府
联 系 人：管铁松
电　　话：1872151420

## 国际展会信息

第五届印度支奈国际医院、医疗设备及实验室展览会
时　　间：2010年8月6日—8日
地　　点：印度支奈
主办单位：印度国际医院
联 系 人：马小姐
电　　话：010-82258800-623

2010年第二十届美国佛罗里达国际医疗展览会
时　　间：2010年8月11日—13日
地　　点：美国 迈阿密
主办单位：第二十届美国佛罗里达国际医疗展览会
联 系 人：王小姐
电　　话：010-82258800-627

2010越南（胡志明）第十届国际医药制药、医疗器材展览会
时　　间：2010年8月18日—21日
地　　点：越南·胡志明
主办单位：越南社会主义共和国卫生部
联 系 人：韦思
电　　话：0771-8043389

2010年泛非洲医疗展&南非康复医疗展览会
时　　间：2010年9月17日—19日
地　　点：南非 约翰内斯堡
主办单位：南非卫生部
联 系 人：檀先生
电　　话：010-84786869-601

2010年第十五届俄罗斯圣彼得堡国际医疗保健展
时　　间：2010年10月5日—7日
地　　点：俄罗斯圣彼得堡
主办单位：英国ITE展览集团
联 系 人：张冬华
电　　话：010-85912831

2010年第二十届俄罗斯国际医疗设备展览会
时　　间：2010年12月
地　　点：莫斯科国际展览中心Expocentre
主办单位：北京国派文化交流有限公司
　　国际会展部
联 系 人：张冬华
电　　话：86-10-85912831/61/02

# 《读者来信》

**尊敬的刘教授：**

您好！

我是湖北省枝江市人民医院麻醉科医生。我们在临床麻醉工作中，常常会遇到再次开颅手术病人，因为第一次开颅手术后，一般患者都做了气管切开术；第二次手术时若行控制呼吸必须做再次气管插管（因为没有带充气套囊的气管套管），而再次插管前不能行充分的面罩加压给氧，或者经气管套管加压给氧；因此插管时相对来讲时间比较紧，请问您有好的解决方法吗？

谢谢！

董传斌
枝江市人民医院麻醉科

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**尊敬的董医生：**

您好！

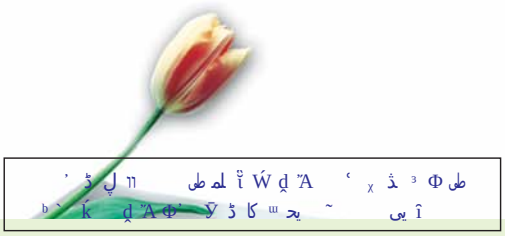
根据我院情况及本人的意见，对您提出的问题作如下解答，请参考：

1、第一次开颅手术后，一般患者应该是不做气管切开的，尤其是择期手术，如果是做了气管切开，都是比较重的病人。

2、二次开颅手术病人是病情比较重的、已行气管切开，可以用一个转换或特殊的接头，从气管套管处连接麻醉机或呼吸机给氧或控制呼吸，气管套管若不带套囊，稍漏气也不怕，潮气量大一点，吸纯氧3-5分钟，根据病人情况从静脉适量给麻醉诱导药，不给肌松药，再换带套囊的气管导管。

3、目前临床上有带套囊的气管套管，我们已在使用，因此不论行几次手术，不需要换管，直接接麻醉机或呼吸机进行给氧或控制呼吸。

刘保江
山西医科大学第一医院麻醉科




[1] ФЦ Ф ,Ф 2 Ф ! Ъ δ , и Ф0883-165,2/5

[2] Lacouments S, YeoTH,Burrin JM,et al.Fentanyl and β-endophin, ACTH and glucoregulatory hormonal response to surgery.Br J Anaesth,1987,59:713-716.

[3] ФЦ Ф ,Ф 2 Ф ! Ъ δ , и Ф0883-165,2/5

[4] Tamsen A. Comparison of patient-controlled analgesia with constant infusion and intermittent intramuscular regimes. In: Harmer M, Rose M, Vickens MD, eds. Patient-controlled analgesia .2nd eds. London: Blackwell Scientific,1985. 111-125.

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# 读者服务表

## Reader Service

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您所在的医院级别：□三甲 □三乙 □二级 □一级

您所在的科室有____人 设ICU：□是 □否

麻醉科主任：_____ ICU主任：_____

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