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

ISSN 1682-9018 02>

2012 Mar/Apr Vol.19 Issue 2

ISSN 1682-9018
CN(HK)· NR 2650/910/02

第19卷 第2期

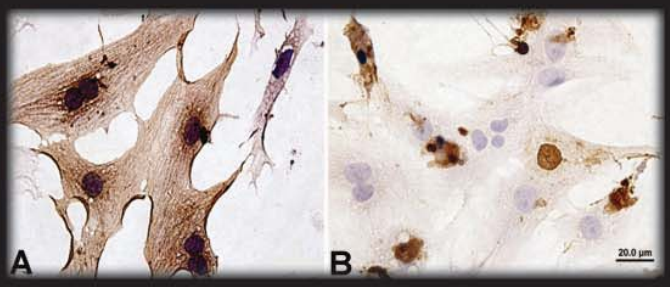


Figure 1. Apoptosis of the ventricular myocytes: (A) control, myocytes treated with (B) NE (10^{-5}mol/L), (C) NE (10^{-5}mol/L) + SP (10^{-6}mol/L) and summary of the effects of NE on apoptosis (D).

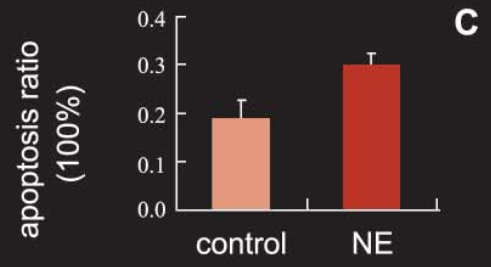
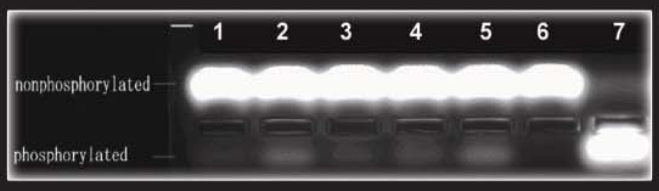
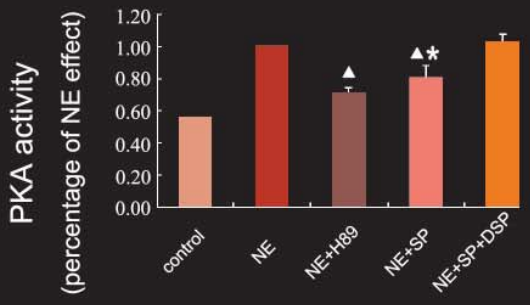


Figure 4. The activity of PKA. Upper panel shows the PKA activities in the cultured myocytes treated with (1) culture; (2) NE (10^{-5}mol/L); (3) NE (10^{-5}mol/L) + H89 ($3x10^{-6}$mol/L); (4) NE(10^{-5}mol/L)+SP(10^{-6}mol/L); (5) NE (10^{-5}mol/L) + SP (10^{-6}mol/L) + DSP (10^{-7}mol/L); (6) negative control; (7) positive control. The lower panel presents a summary of the 3 tests on PKA activities. ▲p<0.05 vs NE; ★p< 0.05 vs NE+SP+DSP.





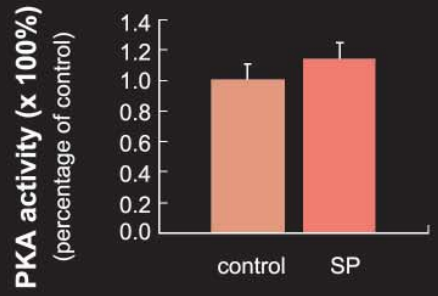
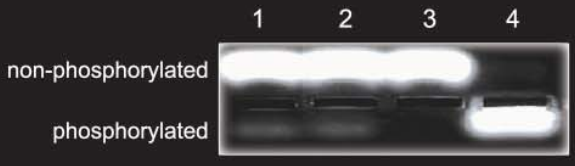


Figure 5. In the upper panel, lane 2 and lane 1 presents the activity of PKA of the ventricular myocytes, treated with SP (10^{-6}mol/L, 113% of the control, lane 2) alone was not statistically different from that of the control (treated with the culture only, lane 1). Lane 3 and lane 4 shows the negative and positive controls respectively.



Norepinephrine induced increase in apoptosis of cultured myocytes by up-regulation of PKA activity, which could be inhibited by substance P, via modulation of the activity of PKA.

Figure related to "Substance P Inhibits Norepinephrine Induced Apoptosis in Cultured Rat Cardiomyocytes Via Modulation of PKA" by Peng-fei Wang, Fu-ping Zhao, Zheng Guo, pp.92.

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出版者：香港醫療信息有限公司
主　辦：中華醫學會麻醉學分會、香港醫療信息有限公司
编　輯：《麻醉與監護論壇》編委會、編輯部

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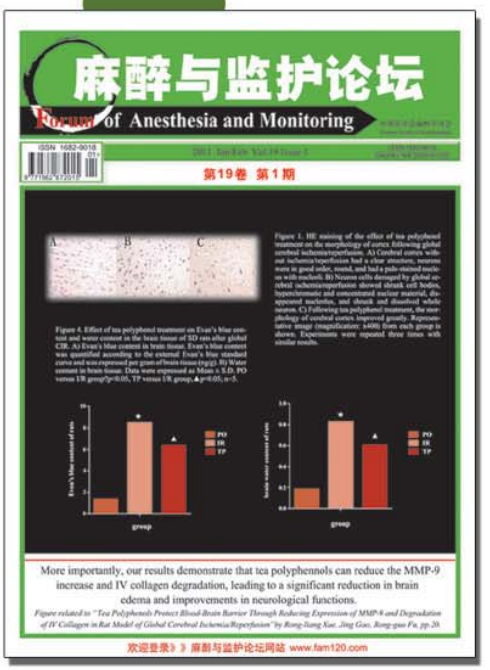
2012 Mar/Apr Vol.19 Issue 2 第19卷 第2期 创刊于1993年

《麻醉与监护论坛》有奖征文！



本刊自改版以来，在众多作者的大力支持下，在编委专家的潜心奉献下，在编辑部员工的辛勤努力下，最终得到了广大读者的热心鼓励和积极的评价，使我们更坚定了办一本国际化的专科刊物的信心。我与众多编委和编辑部全体成员都充满激情，希望能在较短的时间内，将本刊打造成一本以英文为主、走国际化开放路线的专业刊物，成为中外麻醉、重症监护、疼痛领域学科交流的桥梁与纽带。近两年来，刊物在大家的支持下，迈着坚实的脚步，一步一步向我们的目标接近。

当然，作为中国人自己主办的英文刊物，要真正办成一本能为以英语为母语国家的专业人员所接受的专科期刊，我们还面临很多的困难，还需要我们继续付出不懈的努力。

因此，为了鼓励业内同仁们踊跃投稿，《麻醉与监护论坛》自2012年起特设有奖征文活动，希望有更多的专家、学者参与进来，为我国麻醉、重症监护、疼痛领域学科的发展齐心协力，实现我们共同的理想和目标。

于布为
中华医学会麻醉学分会第十届委员会主任委员
《麻醉与监护论坛》主编

在此次征文活动中，《麻醉与监护论坛》杂志所收录文章的作者均有奖品赠送。其中获奖文章作者将在“2012年全国麻醉学术年会”上参加《麻醉与监护论坛》获奖文章颁奖典礼。

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《麻醉与监护论坛》，原《麻醉学论坛》，创刊于1993年，由中华医学会麻醉学分会主办并编辑，由于布为教授担任主编，**是中华医学会麻醉学分会的机关刊物。**《麻醉与监护论坛》以致力于创建国际性学术期刊为宗旨。

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6. 临床经验
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FORUM OF ANESTHESIA AND MONITORING

Publisher: Medical Information Limited
Sponsors: Chinese Society of Anesthesiology, Medical Information Limited
Editing: Editorial Board and Editorial Office of Forum of Anesthesia and Monitoring

Editorial Board Office Address:
Department of Anesthesiology,Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Address: Room 1411，Shanghai Ruijin Building，No.205 Maoming South Road，200025
Tel: 021-64737666 Fax: 021-64737002
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Singarpore(Representative Office)
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Printer: Network Telecom Information Limited, Printing Division, Hong kong
Address: Rm,2104,21/F,Admiralty Center Tower 1, NO.18 Harcourt Rd., Hong kong

Pricing:HK$50
International Standard Serial Number: ISSN 1682-9018
Periodical(Hong kong)Number Registered: CN(HK)-NR 2650/910/02
Forum of Anesthesia and Monitoring magazine had been registered to Hong Kong Special Admin-istrative Region Government,People's Republic of China,in accordance with the Registration of Local Newspapers(Periodical) Ordinance, Cap.268 and its subsidiary legislation.
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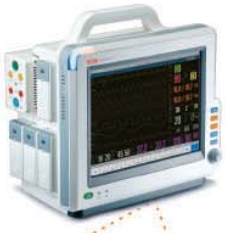
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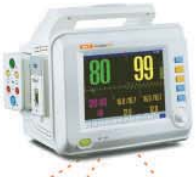
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Forum of Anesthesia and Monitoring

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

ISSN 1682-9018 02>

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Publisher: Medical Information Limited
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2012 Mar/Apr Vol.19 Issue 2

ISSN 1682-9018
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Contents

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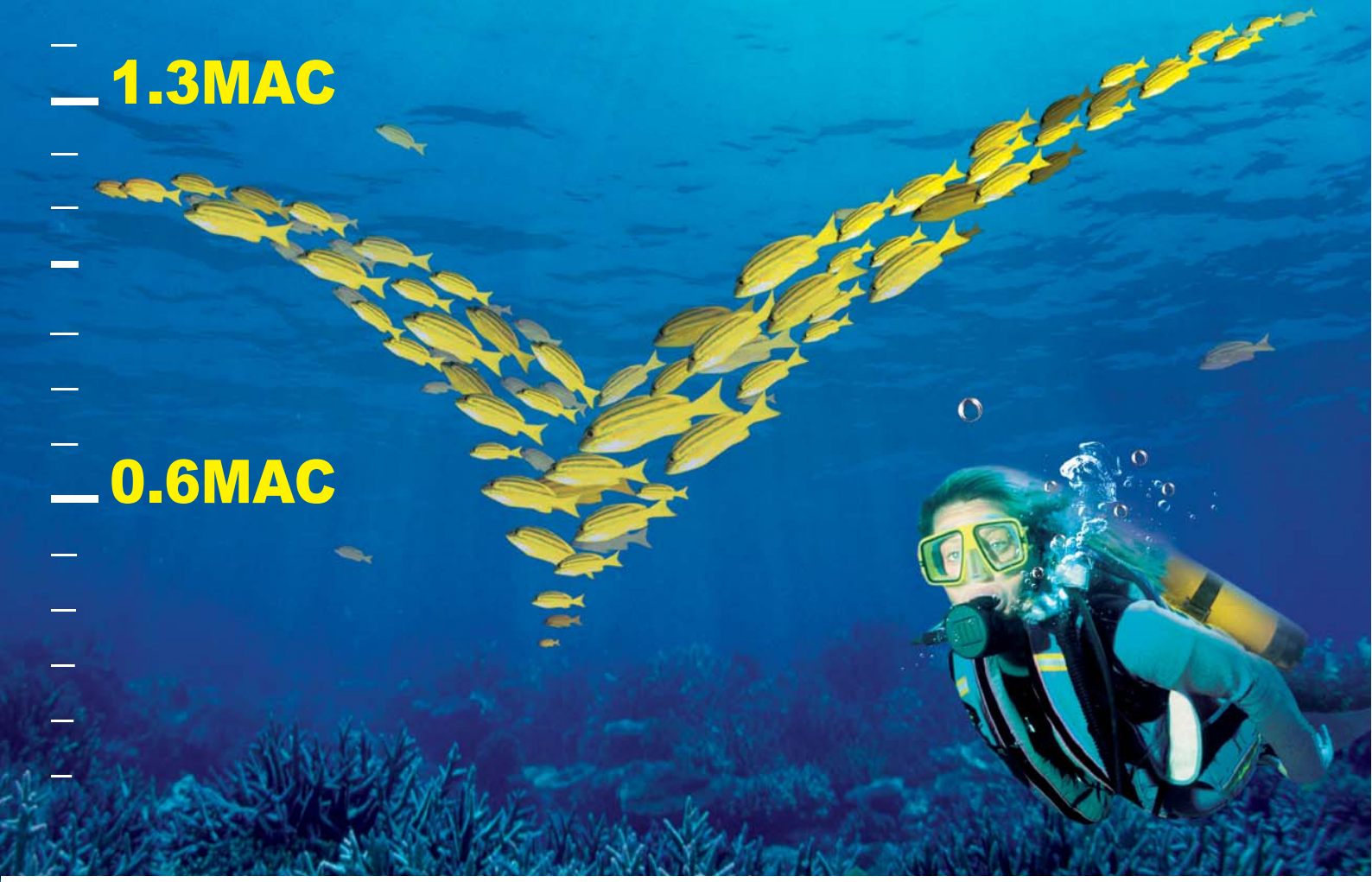

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1.Clinical Investigations

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

5.Technical Communications: 1500 words

6.Special Articles: 2000 words

7.Letters to the editors: 200 words

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.).

3.Mailing address, phone, fax numbers, e-mail address, the department, institution, city, state and country of the corresponding author.

4.Individuals or organizations to be acknowledged. Provide complete name, degrees, academic rank, department, institution, city, state and country.

5.Abstract and Key Words (new page). Abstract contains for paragraphs of Background, Methods, Results and Conclusions, with the words less than 250 (except for Review Articles and Case Reports).

Text. The body of the manuscript should typically be divided into four parts (except for Case Reports):

1.Introduction (new page). This should rarely exceed one paragraph in length

2.Materials and Methods (new page). A subsection entitled “Statistical Analysis” should appear at the end of the section when appropriate.

3.Results (new page)

4.Discussion (new page)

References (new page). Number references in sequence if they appear in the text. Original articles should rarely have more than 25 items. For a review article, up to 35 items are acceptable. Case Reports rarely need more than 10 items. Using the following reference formats:

1.Journal: Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P: Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: Results of a randomized trial. ANESTHESIOLOGY 2002; 97: 540-9

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

3.Chapter: Blitt C: Monitoring the anesthetized patient, Clinical Anesthesia, 3rd edition. Edited by Barash PG. Cullen BF, Stoelting RK. Philadelphia, Lippincot t-Raven, 1997, pp563-85

Tables. Number tables consecutively in order of appearance (Table 1, etc.). Each Table should be submitted as a separate file. Each Table must have a title and a caption.

Figures and Figure Legends.

1.Each figure should be submitted as a separate file.

2.Figures must be clearly labeled and cited in the consecutive numeric order

3.Scan precision≥300dpi, size≥6×8cm.

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3.The units for pressers are mmHg or cmH_2O.

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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Substance P Inhibits Norepinephrine Induced Apoptosis in Cultured Rat Cardiomyocytes Via Modulation of PKA

Peng-fei Wang[1], Fu-ping Zhao[1], Zheng Guo[1,2]

1.Department of Anesthesiology, Shanxi Medical University and Second Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi, PR China

2.Key Laboratory of Cellular Physiology (Shanxi Medical University), Ministry of Education of China

Abstract

Cardiac sensory afferent nerves play important role in cardioprotection against myocytes apoptosis in acute myocardial infarction. However the molecular mechanism underlying the protection is still elusive. We designed this study to test the effect of substance P, one of the main agonist of neurokinin 1 receptor, on norepinephrine induced apoptosis in cultured ventricular myocytes of rats. Cultured neonatal rat cardiomyocytes were exposed to norepinephrine (10^{-5} mol/L) alone, norepinephrine + substance P (10^{-8} mol/L, 10^{-7} mol/L and 10^{-6} mol/L) for 15minutes, respectively, to investigate a potential anti-apoptotic effect of substance P on norepinephrine induced apoptosis of myocytes. Apoptosis was assessed by terminal deoxynucleotidyl transferase-mediated nick end-labeling. Activity of cAMP-dependent protein kinase A (PKA) was measured and analyzed to investigate the mechanism of the effect of substance P. It was observed that substance P (10^{-6} mol/L) reduced norepinephrine induced apoptosis rate, from 29 ± 4% to 20% ± 4%, and reduced the PKA activity, by 38% ± 8%. The effects of substance P could be antagonized by D-SP, a specific neurokinin-1 receptor blocker. A specific PKA inhibitor, H89, produced a similar anti-apoptosis to that produced by substance P. Norepinephrine induced increase in apoptosis of cultured myocytes by up-regulation of PKA activity, which could be inhibited by substance P, via modulation of the activity of PKA. The anti-apoptotic effect of substance P was mediated by neurokinin-1 receptor.

Key Words:Apoptosis; Cardiomyocytes; Substance P; Norepinephrine; Protein kinase A (PKA)

Corresponding Author: Prof. Guo Z., Chairman of the Departments of Anesthesiology, Shanxi Medical University and Second Hospital of Shanxi Medical University, 56 Xinjian Nan Road, Taiyuan 030001, Shanxi, PR China,Tel: +86 351 3365790 , Fax: +86 351 2024239 , E-mail:guozheng713@yahoo.com

Introduction

The activities of sympathetic nervous system and cardiac sensory afferent nerves are actively involved in the pathology of acute myocardial ischemia and infarction [1-5]. The catecholamines could reach such a high level as 100-1000 times of normal concentration1 and such a high concentration of catecholamines could induce apoptosis in myocytes [6], which is associated with over activation of PKA [7]. In a recent study, we demonstrated that cardiac sensory nerves play an important role in cardioprotection in acute myocardial infarction [8]. However, the molecular profiles of the mechanism underlying the protective effects remain elusive.

Substance P (SP), a main neurotransmitter of sensory afferent nerves, belongs to the family of neurokinins (NKs), which are widely distributed in the central and peripheral nervous systems. It was found that SP was significantly up-regulated in the cardiac sensory neurons [5,9] and myocardium [10] during acute myocardial infarction. The cardiac effects of SP have been reported indicating that the peptide may participate in the pathology of acute myocardial infarction [11-13]. It was demonstrated that denervation of sensory afferent nerves resulted in exacerbation of myocardial injury, including myocardial apoptosis, and down-regulation of SP in myocardium [8] during acute myocardial infarction, implied that SP may play a role in the cardioprotection. In this study, we investigated the potential anti-apoptotic effect of substance P in cultured rat cardiomyocytes.

Materials and Methods

Protocol

The experiments were conformed to the guidelines for the care and use of experimental animals (National Institute of Health Guide for the Care and Use of Laboratory Animals, NIH Publications No. 80-23, revised 1996)

and approved by the Institutional Animal Care and Use Committee of Shanxi Medical University. The experiment was carried out using cultured ventricular myocytes of neonatal Sprague-Dawley rats of either sex. The effects of SP on the norepinephrine induced apoptosis and the changes in the activity of the cAMP-dependent protein kinase A (PKA) of the cultured myocytes were examined.

Myocyte Isolation and Culture

Primary myocyte cultures were prepared according to the previous report [14,15]. Briefly, the hearts were removed from 1 day old neonates under ether anesthesia and processed in chilled phosphate buffered solution (PBS, pH 7.4), containing (in mmol/L) NaCl 137, KCI 2.7, Na_2HPO_4 10 and K_2HPO_4 2. The ventricles were washed three times with chilled PBS and then were cut into 1 mm^3 pieces in PBS. The myocardium were digested by collagenase (1 mg/ml, Type II, Invitrogen Corporation, California, USA) for 3 minutes at room temperature with gentle pipetting. The primal supernatant was discarded. The procedure was repeated 4-5 times till all tissues were digested. The free-floating cardiomyocytes were centrifuged in cold culture medium contain fetal bovine serum at 800 rpm for 3 minutes. The cells were re-suspended in 12 ml of DMEM (Dulbecco's modified eagle medium) in a 90 mm culture dish and incubated for 60 minutes at 37°C in a carbon dioxide incubator with a gas phase of 5% CO_2 in humidified air. The floating cardiomyocytes were collected and cell numbers were adjusted to 5 x 10^5 cells/ml in DMEM supplemented with 10% fetal bovine serum and 0.1 μM 5-Bromo-2`-deoxyuridine (Sigma-Aldrich, Missouri, USA) to prevent NMCs proliferation, while the non-myocardial mesenchymal cells (NMCs) attached to the bottom of the culture dishes after 60 min of incubation. Three milliliters of the cell suspension were loaded and inoculated in each well of a six-well cell culture cluster (Corning Gilbert Inc, Arizona, USA), with coverslips (pretreated with Poly-L-Lysine) for TUNEL assay and without coverslips for PKA assay. After 48 hours of incubation, more than 70% of the cells adhered to the culture dish or to the coverslip.

TUNEL Assay

The apoptosis of ventricular myocytes was assessed using terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL), using an in situ cell death detection kit (Roche, Germany) according to the manufacturer's instructions. The cells were exposed to one of the test agents or the combination of agents for 15 min in separate wells: (1) control vehicle solution, (2) norepinephrine (NE, 10^{-5}mol/L), (3) NE (10^{-5}mol/L) + SP (at 10^{-8}mol/L, 10^{-7}mol/L and 10^{-6}mol/L), (4)NE(10^{-5}mol/L)+a PKA inhibitor, H89(3×10^{-6}mol/L)and(5)NE(10^{-5}mol/L)+SP (10^{-6}mol/L) + D-SP (10^{-7}mol/L), a blocker of neurokinin-1 receptor. Then the cells were washed with PBS and fixed in 4% paraformaldehyde for 60 minutes. After washout with PBS, the cells were incubated in penetrating solution (0.1% Triton X-100, 0.1% sodium citrate) for 2 minutes. The cells were then rinsed with PBS and incubated with the TUNEL reaction mixture for 1 hour at 37°C, in a humidified chamber. After washout with PBS, the cells were incubated with Converter-POD for 30 minutes at 37°C and then rinsed with PBS. DAB (3,3N-diaminobenzidine tertrahydrochloride) was added substrate for about 1 minute before counterstaining with hematoxylin. The cells were washed with PBS then rinsed in 75% ethanol, 85% ethanol, 95% ethanol and 100% ethanol then in xylene, consecutively. The coverslips were mounted with slides and analyzed under light microscope. The percentage of apoptosis myocytes was measured by counting the cells exhibiting brown nucleus in 10 randomly chosen fields (40x) in triplicate plates. The ratio of apoptotic myocytes was calculated using the formula:

$$RA = \frac{NpA}{Nt} \times 100\%$$

In the formula, RA stands for ratio of apoptosis; NpA, the number of positively stained apoptotic myocytes; Nt, the total number of myocytes counted.

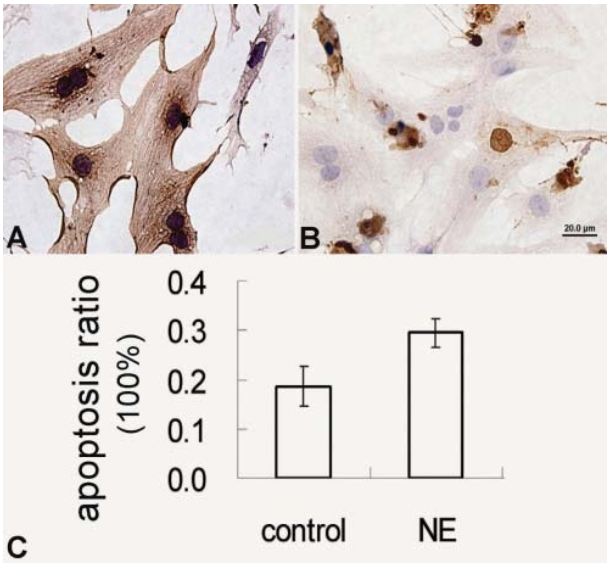
The doses of NE, H89 and D-SP were determined by the pilot studies of our research group.

Array of PKA Activity

The PKA activity was determined according to the reports [15,16]. The cultured myocytes were re-fed with culture medium without fetal bovine serum for one hour before being exposed to the test agents for 15 min in separate wells: (1) control vehicle solution, (2) NE (10^{-5} mol/L), (3) NE (10^{-5}mol/L)+SP(10^{-6}mol/L), NE(10^{-5}mol/L)+H89(3×10^{-6}mol/L) and NE (10^{-5} mol/L) + SP (10^{-6} mol/L) + D-SP (10^{-7}

mol/L). The dose of SP was determined according to the results of the TUNEL assay. Then cells were scraped off the culture cluster with a plastic lifter (Corning Incorporated, New York, USA) and removed into 1.5 ml centrifuge tubes, separately. The suspension containing about 5×10^6 cells were incubated in the PBS for 30 min at room temperature then 25 µl of cold PKA extraction buffer containing: 25 mM Tris-HCl (pH 7.4), 0.5 mM EDTA, 0.5 mM EGTA, 10 mM β-mercaptoethanol, 1 µg/ml leupeptin, 1 µg/ml aprotinin, 0.5 mM PMSF (Phenylmethanesulfonyl fluoride) were added and then the cells were lysed and homogenized on ice. The homogenate was centrifuged at 14,000 × g for 5 minutes at 4°C. The resulting supernatant was assayed for PKA activity using the PepTag non-radioactive PKA assay kit (Promega, Madison, Wisconsin, USA) as described in the Promega Technical Bulletin. The assay was based on changes in the net charge of the fluorescent PKA substrates before and after phosphorylation. The phosphorylated substrate migrated toward the positive electrode, while the nonphosphorylated substrate migrated toward the negative electrode, when electrophoresed. The results were normalized with the quantity of the protein in each respective supernatant.

Figure 1: Apoptosis of the ventricular myocytes: (A) control, myocytes treated with (B) NE (10^{-5}mol/L), (C) NE (10^{-5}mol/L) + SP (10^{-6}mol/L) and summary of the effects of NE on apoptosis (D).



Statistical Analysis

The values were presented as mean ± S.D. One-way ANOVA followed by a post hoc Bonferroni's test was performed to analyze the changes of the parameters. Statistical significance was defined as $p < 0.05$.

Results

Apoptosis

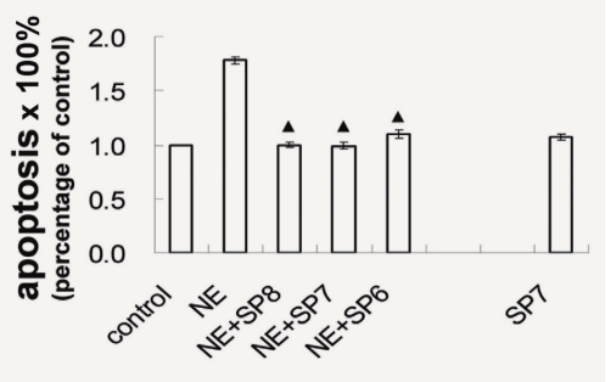
An apoptotic ratio of 29% ± 4% was observed in the NE treated cells, which was statistically higher than that in the control group (19% ± 5%, $p < 0.05$, Fig. 1). SP (at 10^{-8} mol/L, 10^{-7} mol/L and 10^{-6} mol/L) significantly attenuated the NE induced apoptosis of the cardiomyocytes ($p < 0.05$, Fig. 2), when the SP and the NE were co-administrated. The anti-apoptosis effect of SP could be reversed by D-SP, resulting in an apoptotic ratio of 27% ± 4% when the NE (10^{-5} mol/L), SP (10^{-6} mol/L) and D-SP (10^{-7} mol/L) were given simultaneously, indicating the anti apoptosis effect of SP was mediated by specific neurokinin-1 receptor (Fig. 3).

A similar anti-apoptotic effect (21% ± 2% of the apoptotic ratio) on the NE induced apoptosis was induced by H89, a specific inhibitor of PKA, at a similar dose to SP (Fig. 3).

PKA activity

NE, at a concentration of 10^{-5} mol/L, induced significant increase in the activity of PKA in the cultured myocytes, by 44% ($p < 0.05$), compared with the control.

Figure 2: Effects of a range of concentrictions of substance P (10^{-8}mol/L, 10^{-7}mol/L, 10^{-6}mol/L labeled as SP8, SP7 and SP6 respectively) on NE induced apoptosis. And SP7 showed the effect SP (10^{-7}mol/L) alone on the apoptosis. ▲p <,0.05 vs NE.



Co-treatment of the myocytes with NE (10^{-5} mol/L) plus SP (10^{-6} mol/L) resulted in a reduction of PKA activity by 36%, which was similar to that induced by the same concentration (10^{-6} mol/L) of H89.

(38% reduction of PKA activity, Fig. 4), when compared with the PKA activity induced by NE alone. And the effect of SP could be antagonized by co-administration of D-SP (Fig. 4), indicating that SP inhibited PKA activity through the mediation of neurokinin-1 receptor. SP(10^{-6} mol/L) given alone failed to cause any obvious change in the PKA activity (Fig. 5).

Discussion

Apoptosis may play important roles in a variety of cardiovascular diseases, including ischemic heart disease [17-19]. Excessive apoptosis of cardiomyocytes may cause the loss of the contractile cells and the strength for a functioning heart. Among the conventional medical therapy strategies, preservation of contractile mass based on the number of myocytes is a major goal in a multimodal therapeutic approach for cardiac disease. Therefore one of the aims of cardioprotection is preserving myocytes in acute myocardial infarction.

Over activation of sympathetic nervous system in acute myocardial ischemia and infarction is associated with myocardial injury, including apoptosis of cardiomyocytes [1,6,7]. We observed in previous research that substance P was up-regulated in the myocardium in acute myocardial infarction in experimental animals [4] and reduction of SP in the sensory nerve denervated animals was accompanied by severer myocardial injury after coronary artery occlusion, which raises the possibility of a protective role for SP in the pathology of ischemic myocardial injury. In this study, we established a set of experiments, inducing apoptosis of the cultured myocytes by a high dose of norepinephrine and then the difference in the apoptotic ratio of myocytes, in the presence and the absence of the treatment with exogenous SP and H89 was analyzed. In this study a baseline apoptosis ratio of 19% ± 5% of the cultured ventricular myocytes was obtained, which was reproducible and constant. The results of current study showed a significant increase in the apoptotic ratio in the myocytes when norepinephrine was introduced in the culture, which was in accord with previous study [6]. However, a significantly lower apoptotic ratio of the myocytes was observed when SP was co-administrated, at a range of concentrations of 10-8mol/L, 10^{-7}mol/L and 10-6mol/L, with NE, indicating a protective effect of SP on the NE induced apoptosis of myocytes,

Figure 3: The anti-apoptotic effect of SP on NE induced apoptosis in myocytes. Cultured myocytes grown on coverslips were exposed to the culture (control), NE (10^{-5}mol/L), NE (10^{-5}mol/L) + H89 (3x 10^{-6}mol/L), NE (10^{-5}mol/L) + SP (10^{-6}mol/L) and NE (10^{-5}mol/L) + SP (10^{-6}mol/L) + DSP (10^{-7}mol/L) for 15minutes and subjected to TUNEL staining as described in Methods. △p < 0.05 vs control; ▲p <,0.05 vs NE; ★ p < 0.05 vs NE + SP + DSP.

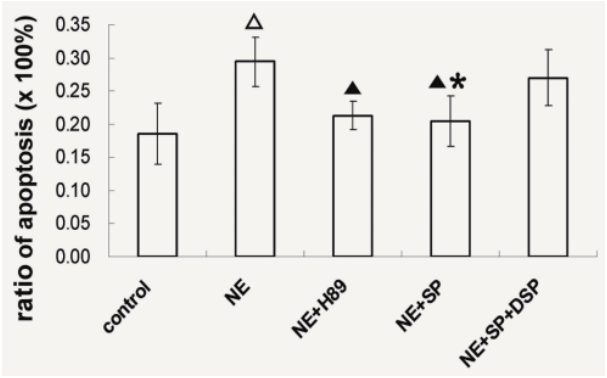
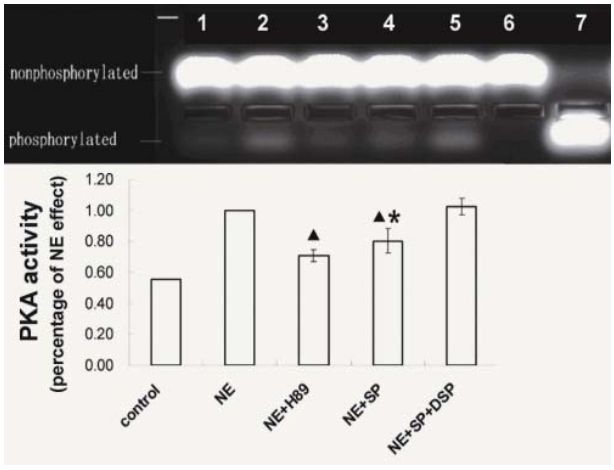


Figure 4: The activity of PKA. Upper panel shows the PKA activities in the cultured myocytes treated with (1) culture; (2) NE (10^{-5}mol/L); (3) NE (10^{-5}mol/L) + H89 (3x 10^{-6}mol/L); (4) NE (10^{-5}mol/L) + SP (10^{-6}mol/L); (5)NE(10^{-5}mol/L)+SP(10^{-6}mol/L) + DSP (10^{-7}mol/L); (6) negative control; (7) positive control. The lower panel presents a summary of the 3 tests on PKA activities. ▲p <,0.05 vs NE; ★ p < 0.05 vs NE + SP + DSP.



while the substance P alone did not produce any obvious effect on apoptosis (Fig. 2). The anti-apoptotic effect of SP could be blocked by D-SP, a specific antagonist of neurokinin-1 receptor, indicating an involvement of a specific neurokinin-1 receptor in mediation of the effect of SP. Although a dose response pattern was not induced by the range of doses of SP in this study, an inhibitory effect of SP was observed with all the doses, which may indicate that lower doses might be effective in the anti-apoptosis.

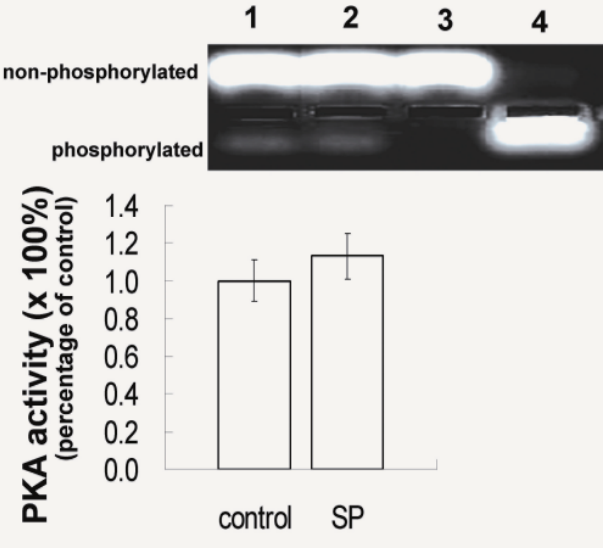
Activation of PKA was observed when norepinephrine was administrated in this study, which is shown to be critically associated with myocardial apoptosis.7 The results of current study showed a close association of NE-induced increase in the apoptosis with an increase in the PKA activity in the myocytes, which in agreement with previous reports [6,7]. Substance P shown anti-apoptotic property when it was co-administrated with NE, resulted in reduction of PKA activity, which were reversed by D-SP, suggesting SP suppresses the NE induced increase in PKA activity and apoptosis via the specific neurokinin-1 receptor. The specific PKA inhibitor, H89, produced anti-apoptotic effect on NE induced apoptosis of the myocytes, served as a control supporting the notion that SP exerts anti-apoptotic effects on NE induced apoptosis of myocytes via modulation of the activity of PKA. However, opposite observations were reported demonstrating an anti-apoptotic effects of adrenergic stimulation [20] and up-regulation of PKA [20,21]. Taken together, the findings may suggest that adrenergic activity and PKA may play different roles when the adrenergic and PKA activity were at different stage.

The findings of this study demonstrate an anti-apoptosis effect of substance P via modulation of PKA activity, which may indicate that NK-1 activity may be benefit for the myocardium insulted by acute myocardial infarction.

Acknowledgements

The research work has been supported by National Natural Science Foundation of China (30772083 and 30972860 to Dr. Guo).

Figure 5: In the upper panel, lane 2 and lane 1 presents the activity of PKA of the ventricular myocytes, treated with SP (10^{-6}mol/L, 113% of the control, lane 2) alone was not statistically different from that of the control (treated with the culture only, lane 1). Lane 3 and lane 4 shows the negative and positive controls respectively.



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Ubiquitin Reduces Expression of Intercellular Adhesion Molecules and Tumor Necrosis Factor-α in Lung Tissue of Experimental Acute Lung Injury

Zhen-yang He, Juan Xing

Department of Critical Care Medicine, Hainan Provincial Hospital, Haikou, 570311, China

Scientific Research Project Subject of Hainan Provincial Health Brueau（Number：Qiong Wei 2007-25）

Abstract

Background: Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are two important cytokines in inflammatory response, which may induce rolling and adhesion of both leukocytes and lymphocytes, while modulating vascular permeability at the same time. These adhesion molecules usually serve as surrogate markers of activation and injury of vascular endothelial cells. Tumor necrosis factor–α (TNF-α) is a key factor to induce the expression and production of the above cell adhesion molecules. However, it remains to be elucidated whether exogenous ubiquitin exerts any effect on the cytokines in sepsis-induced ALI.

Methods: Sixty mice were devided randomly into five groups with twelve mice in each group, ie. CLP group, SHAM group, UB1 group (10mg/kg), UB2 group (5mg/kg) and UB3 group(1mg/kg). Mice of SHAM group underwent sham operation, and other four groups underwent CLP. Six hours after surgery, mice of three UB groups received ubiquitin by caudal vein injection while CLP and SHAM group received vehicle. Seven hours after surgery, blood and lungs of all mice were collected. ICAM-1, VCAM-1 and TNF-α level of 9% lung homogenate and serum TNF-α level were measured by ELISA.

Results: Pulmonary ICAM-1, VCAM-1 and TNF-α level of three UB groups were lower than CLP and SHAM group, and there were several comparisons with a statistically significant difference. Serum TNF-α level of three UB groups were slightly lower than CLP group, but far higher than SHAM group. Pulmonary ICAM-1 level, VCAM-1 level and serum TNF-α level of UB3 group were lower than UB1 and UB2 group, and there was a significant difference in VCAM-1 between UB3 and UB1 group. Pulmonary TNF-α level of UB3 group was slightly higher than UB1 and UB2 group.

Key Words: Ubiquitin; Acute lung injury; Intercellular cell adhesion molecule-1; Vascular cell adhesion molecule-1; Tumor necrosis factor-α

Corresponding Author: Zhen-yang He，E-mail:hezy118@yahoo.com.cn

Introduction

Ubiquitin is a peptide of 76 amino acids found in all eukaryotic cells. Because of its participation in one selective protein degeneration pathway, the intracellular and extracellular role of ubiquitin has been the subject of laboratory investigations for decades. Recent studies have demonstrated that extracellular ubiquitin may modulate inflammatory response [1]. Furthermore, exogenous ubiquitin also exerts both anti-inflammatory effect by inhibiting septic or non-septic inflammation and immunodepression by inhibiting immune responses as well as prolonging survival of grafts [1-3].

Experiments with swine models of septic or hemorrhagic shock demonstrate that exogenous ubiquitin significantly decrease the fluid requirement for volume resuscitation, and improve ventilation and oxygenation [1]. In our preliminary study in septic mice model induced by cecal ligation and perforation (CLP), exogenous ubiquitin prevents sepsis-induced acute lung injury (ALI), by inhibiting formation of pulmonary edema and inflammatory infiltrates [2].

Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are two important cytokines in inflammatory response, which may induce rolling and adhesion of both leukocytes and lymphocytes, while modulating vascular permeability at the same time. These adhesion molecules usually serve as surrogate markers of activation and injury of vascular endothelial cells. However, it remains to be elucidated whether exogenous ubiquitin exerts any effect on the adhesion molecules in sepsis-induced ALI.

The objective of our study is to demonstrate the effect of exogenous ubiquitin on pulmonary cell adhesion molecules in mice model of CLP-induced ALI. Moreover, pulmonary and serum levels of tumor necrosis factor–α (TNF-α) are measured, due to the fact that TNF-α is a key factor to induce the expression and production of the above cell adhesion molecules [4, 5]. Potential dose-effect relationship of ubiquitin is also investigated.

Materials and Methods

Animal Protocol

All procedures were performed in accordance with the National Institutes of Health Guidelines for Use of Laboratory Animals and approved by the Institutional Ethics Committee.

Sixty male Kunming mice, weighing 18 to 23 g, age 8 weeks, were allocated randomly into 5 groups (n = 12

in each group). In CLP group, mice were subjected to CLP (14-gauge needle) as previously described[2]. A sham operation (laparotomy and cecal exposure without any more manipulation) was performed in SHAM group as negative control.

Six hours after CLP in three intervention groups, mice received a normal saline solution containing ubiquitin (LSA14199, Bioworld, USA) at the dose of 10 mg/kg body weight (UB1 group), 5 mg/kg body weight (UB2 group), and 1 mg/kg body weight (UB3 group), respectively, through caudal vein, while mice in CLP and SHAM groups received vehicle injection of the same volume.

Seven hours after the operation, a midline incision from the pubis to the neck was performed to gain access to the heart-lung block. A blood sample was drawn from the left ventricle for determination of serum level of TNF-α . Subsequently, the mice were sacrificed by exsanguination. The heart-lung block was rapidly excised, and the pulmonary circulation was flushed via the right ventricle with 20 ml of normal saline. The serum and separated lung specimens were stored at -80°C until further analysis.

Preparation of Lung Homogenates

Immediately before analysis, tissues were homogenized 1:5 by volume in ice-cold 10 mmol/L Tris/HCl pH 7.4, 100 mmol/L NaCl, 1 mmol/L ethylenediaminetetraacetic acid, 1 mmol/L NaF, 0.1% sodium dodecyl sulphate, 1% trition, 10% glycerol, 0.5% deoxycholate, 1 mmol/L dithiothreitol, NaVO4, NaPO3, 0.2 mg/mL phenylmethylsulphonyl fluoride, and aprotinin using a Brinkmann-Polytron homogenizer (Best-Lab-Deals, Raleigh, NC). Homogenates were centrifuged (20,000 g, 5°C, 30 mins), and supernatants (or homogenates) were aliquoted.

Cytokine Assays

The concentrations of ICAM-1, VCAM-1, and TNF-α in lung homogenates and TNF-α in serum were measured by ELISA (EK0538, EK0371, EK0527, Boster, China).

Statistical Analysis

All data are presented as mean ± standard deviation (SD). Data were compared by one-way analysis of variance with either LSD test or Tamhane's test (α = 0.05). Correlation between cell adhesion molecules and TNF- was analyzed with Pearson correlation efficient. A p value of < 0.05 was considered to be statistically significant.

Results

Compared with SHAM group, serum TNF-α level significantly increased in CLP group (6803 ± 1375 pg/ml vs. 5596 ± 1257 pg/ml, p = 0.012), while ICAM-1, VCAM-1, and TNF-α levels in lung homogenates did not differ significantly (table 1).

Ubiquitin treatment at 6 hours after CLP procedure significantly decreased VCAM-1 level in lung homogenates, when compared with those of SHAM group and CLP group. Moreover, VCAM-1 level was lower in UB3 group than UB1 group (p = 0.031). ICAM-1 levels in lung homogenates demonstrated a similar profile, although statistically insignificant (table 1).

Treatment of ubiquitin also decreased TNF-α level in lung homogenates, while the difference only reached statistical significance with higher doses of ubiquitin, ie. 5 and 10 mg/kg body weight (table 1). In contrast, ubiquitin did not exert any effect on the CLP-induced increase in serum TNF-α level.

Correlation between pulmonary cell adhesion molecules and TNF-α was shown in table 2.

Discussion

ICAM-1 and VCAM-1 are two members of immunoglobin supergene family. Normally, ICAM-1 is only expressed at a low level in endothelial cells and epithelial cells, or constitutively on the surface of alveolar cells [4]; while VCAM-1 is constitutively expressed on a number of

Table 1 Effect of CLP and ubiquitin treatment on pICAM-1, pVCAM-1, pTNF-α and sTNF-α level of each group

	SHAM	CLP	UB1	UB2	UB3
pICAM-1 (ng/ml)	244.3	293.9	209.1	217.9	179.9
	±77.5	±96.6	±36.2	±46.6	±33.2*
pVCAM-1 (ng/ml)	43.19	57.08	35.80	30.79	29.63
	±6.41	±15.72	±3.85*^	±6.78*^	±5.08*^
pTNF-α (pg/ml)	2797	3170	2483	2563	2732
	±508	±906	±375*	±382*	±606
sTNF-α (pg/ml)	5596	6803	6550	6420	6373
	±1257*	±1375	±832^	±895	±1201

CLP, cecal ligation and perforation; pICAM-1, intercellular adhesion molecule-1 in lung homogenates; pVCAM-1, vascular cell adhesion molecule-1 in lung homogenates; pTNF-α, tumor necrosis factor–α in lung homogenates; sTNF-α, serum tumor necrosis factor–α level.
* compared with CLP group, P<0.05; ^ compared with SHAM group, P<0.05.

cell types other than vascular cells, such as chondrocytes and tissue macrophages, and is not appreciably expressed on resting vascular endothelium [5]. High-level expression of ICAM-1 and VCAM-1 could be induced by TNF-α, IL-1 and IL-6, which probably is due to activation of the transcription factors such as nuclear factor kappa B (NF-kappaB) [4, 5]. Unlike VCAM-1, expression of ICAM-1 is also increased on bronchial and alveolar epithelial cells under such circumstances [6, 7].

In our study, ICAM-1 and VCAM-1 level in murine lung homogenates significantly increased at seven hours after CLP, which was inhibited by intravenous ubiquitin, to a level similar to or even lower than that of SHAM group. This suggests that exogenous ubiquitin could prevent ALI secondary to not only sepsis but also other non-septic etiologies, including surgery and trauma. Moreover, ubiquitin exerts dose-dependent inhibition of ICAM-1 and VCAM-1, with the most significant inhibition at the dose of 1 mg/kg. This probably indicates that ubiquitin at the dose higher than 1 mg/kg might provide no further benefits.

TNF-α, produced mainly by mononuclear cells in vivo, is the core of interactive regulation of cytokine network. TNF-α regulates the release and activation of different cytokines within inflammatory cascade. In our study, ubiquitin inhibited the sepsis-induced production of TNF-α in lung homogenates, which might in turn lead to decreased pulmonary ICAM-1 and VCAM-1 levels. The possible mechanism is that exogenous ubiquitin, when transferred into cells, may inhibit the activation of NF-kappa B which reduces subsequent production of ICAM-1, VCAM-1 and TNF-α. Similar to ICAM-1 and VCAM-1, pulmonary TNF-α level is also affected by ubiquitin. However, unlike ICAM-1 or VCAM-1, the production of TNF-α is more significantly inhibited with higher dose of ubiquitin. The non-parallel changes of TNF-α, ICAM-1 and VCAM-1 in lung homogenates suggest that TNF-α is not the major modulator of expression of cell adhesion molecules.

Table 2 Correlation between ICAM-1, VCAM-1, TNF-α in lung homogenates, and serum TNF-α level

	pICAM-1	pVCAM-1	pTNF-α	sTNF-α
pICAM-1	1	0.492**	0.280*	0.299*
pVCAM-1		1	0.338**	0.270*
pTNF-α			1	0.218
sTNF-α				1

pICAM-1, intercellular adhesion molecule-1 in lung homogenates; pVCAM-1, vascular cell adhesion molecule-1 in lung homogenates; pTNF-α, tumor necrosis factor–α in lung homogenates; sTNF-α, serum tumor necrosis factor–α level.
*p < 0.05, **p < 0.01

Similar to the study by Majetschak and his colleagues in lethal sepsis model of swine [8], we found that exogenous ubiquitin did not affect serum TNF-α level significantly. It seems that ubiquitin does not show any inhibition of TNF-α overproduction in sepsis, therefore its effect can not be predicted by serum TNF-α level.

Overwhelming systemic inflammatory response in sepsis leads to tissue and organ damages. ALI, characterized by pulmonary edema and parenchymal infiltrates, represents pulmonary manifestation of the above inflammatory response [9]. Therefore, functional changes of endothelial cells in sepsis and ALI are extensively investigated. Although pulmonary endothelial cell is only one source of ICAM-1 production, our results suggest that exogenous ubiquitin play a protective role in sepsis-induced ALI, which might be supported if function of endothelial cells is tested with in-situ technology, or with circulating endothelial cells. At last, we believe that further investigation on dose-effect relationship is needed since we only observe a significant difference of pulmonary VCAM-1 levels between ubiquitin 1 mg/kg and 10 mg/kg group.

Conclusion

Exogenous ubiquitin not only significantly inhibits the increases of pulmonary ICAM-1, VCAM-1 and TNF-α level in acute lung injury of mice induced by CLP, but also lowers the increases elicited by operation and stress. But ubiquitin doesn't effect serum TNF-α obviously. With a decline in doses, ubiquitin's inhibition of pulmonary ICAM-1 and VCAM-1 level gradually increases while inhibition of pulmonary TNF-α level decreases.

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Stable Fetal Heart Rate after Phenylephrine Infusion during Spinal Anesthesia for Cesarean Delivery

*X.G. Guo[1], M. Wang[2], C.B Han[1], Y.N.Qian[1]**

1.Department of Anesthesiology, First Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China
2.Department of Anesthesiology, Maternal and Child Health Care Hospital in Wuxi, Jiangsu Province, China
* Corresponding Author at: Department of Anesthesiology, the First Affiliated Hospital to Nanjing Medical University, No. 300, Guangzhou Road, Nanjing210029, China.

Abstract

Background: Use of phenylephrine for prevention of hypotension following spinal anesthesia in women undergoing caesarean delivery can improve the fetal oxygen supply and demand balance. The authors hypothesized whether the mechanism underlying this is the stable fetal heart rate and metabolism in the fetus compared with ephedrine.

Methods: Sixty women having elective cesarean delivery under spinal anesthesia randomly received ephedrine 4 mg/ml (Group Ⅰ) or phenylephrine 50 μg /ml (Group Ⅱ) titrated to maintain the systolic blood pressure near baseline. The fetal heart rate, maternal heart rate and maternal blood pressure were measured at various time points after medicine infusion. At delivery, maternal arterial, umbilical arterial, and umbilical venous blood samples were taken for measurement of blood gases and plasma concentrations of lactate and glucose.

Results: Compared with baselines, fetal heart rate after ephedrine infusion in group Ⅰ was significantly increased ($P < 0.05$), and fetal heart rate after phenylephrine infusion in group Ⅱ did not significantly change ($P > 0.05$). Umbilical arterial and venous pH and base excess were lower in group Ⅰ than in group Ⅱ ($P<0.05$). Compared with group Ⅱ, umbilical arterial plasma concentrations of lactate (median 4.23 [interquartile range 2.28-6.18] vs 2.23 [1.57-2.89] $mmol.l^{-1}$, $P<0.05$), umbilical venous concentration of lactate (median and interquartile 3.12 [1.80-4.44] vs 1.78 [1.45-2.11] $mmol.l^{-1}$, $P < 0.05$), umbilical arterial PCO_2 and plasma concentrations of glucose were higher in group Ⅰ ($P < 0.05$).

Conclusions: Compared with ephedrine, the fetal heart rate after phenylephrine infusion maintains stable, which may be one of mechanisms that phenylephrine can improve fetal acid-based status.

Key Words: Ephedrine; Phenylephrine; Spinal Anesthesia; Hypotension; Cesarean Delivery; Fetal heart rate

Corresponding Author: **Y.N.Qian**, E-mail:yanning_qian@yahoo.com.cn

Introduction

Spinal anesthesia is widely used for cesarean delivery, but hypotension, a frequent complication, may result in cerebral hypoperfusion, gut hypoperfusion on the mother and decreased uteroplacental bloodflow on the fetus.[1,2,3] Ephedrine was historically recommended as a choice of vasopressor for prevention of hypotension following spinal anesthesia in women undergoing caesarean delivery, as it can preserve the uteroplacental circulation better.[4,5] Some studies have suggested that phenylephrine may, in fact, be safe alternatives to ephedrine in management of arterial blood pressure during cesarean delivery under spinal anesthesia, for ephedrine crosses the placenta to a greater extent and has a propensity to decrease fetal pH and base excess.[6-10] Recently, moreover, Ngan et al[11] reported that phenylephrine had similar efficacy in the treatment of parturient hypotension following spinal anesthesia for cesarean delivery while improving the fetal oxygen supply and demand balance by increasing fetal pH and base excess without causing fetal academia when compared with ephedrine. He supposed that maybe the β receptor could not be excited by phenylephrine in the fetus so that the fetal metabolism dropped.

We know the fetal heart rate which is regulated by β receptor in the heart, as a vital factor of fetal haemodynamics, has not been included when comparing

between ephedrine and phenylephrine before. Thus, we designed this study to compare the effects of ephedrine and phenylephrine on fetal heart rate (FHR) and fetal acid-based status during spinal anesthesia in women undergoing cesarean delivery in order to explore whether the fetal heart rate is stable in this situation.

Methods

After institutional ethics committee approval and written informed consent were obtained, 60 parturient women with singleton, ASA physical status Ⅰ and Ⅱ, aged 18 to 35 years, scheduled for elective cesarean delivery under spinal anesthesia were included in this study. The maternal prenatal care and preoperative liver and kidney function of all selected puerperants were within normal range. All parturient women had no history of cardiopulmonary diseases and fetal screening showed no abnormality. Exclusion criteria were hypertension (systolic blood pressure (SBP) greater than 140 mmHg or diastolic blood pressure greater than 90mmHg), cardiovascular or cerebrovascular diseases, known fetal abnormality, contraindications to spinal anesthesia, diabetes and other endocrine disorders and intraoperative supine hypotension syndrome.

Based on computerized random numbers, all parturient women were randomly divided into two groups: group Ⅰ was intravenously infused ephedrine 4 mg/ml and group Ⅱ infused phenylephrine 50 μg/ml. As previously described, the potency ratio between ephedrine and phenylephrine was 1:80 (ephedrine 8 mg = phenylephrine 100 μg) [12].

All parturient women preoperative fasted for more than 10h, with no premedication. On arrival in the operating room, patients were positioned in the left-tilted supine position for 5 minutes, and noninvasive monitoring (BSM-2301 bedside monitor, Nihon Kohden Kogyo Co., Ltd) was applied to measure systolic blood pressure, maternal heart rate (MHR) and FHR for 3 minutes. The mean of three successive measurements was calculated as the baseline of MAP, MHR and FHR. During the study period, no oxygen was administered in all patients.

After an intravenous catheter was inserted into the forearm superficial vein and compound sodium lactate solution 10 ml /kg was pre-infused, patient was placed in a left lateral position and needle was inserted at $L_{3\sim4}$ space. On discovering the cerebrospinal fluid, 0.5% hyperbaric bupivacaine 2.0 ml was injected, with a speed of 0.2 ml/s. Then, the patient was returned to a left-tilted supine position and vasoconstrictor drug selected for each group was infused with a speed of 60 ml/h, using a micro-infusion pump (TCI-Ⅲ type of thinking high injection pump, high-tech Development Co., Ltd. Beijing idea), until uterine incision. One minute after stopping drug infusion, maternal MAP, MHR and FHR were measured every 2 min. If SBP was lower than baseline, delivery vasoconstrictor was sustained. If SBP was higher than the baseline, then delivery vasoconstrictor was stopped. If SBP was less than 80% of baseline, 1-ml vasoconstrictor was intravenously injected; If HR was less than 50 beats /min, atropine 0.5 mg was intravenously administered. When the SpO_2 was less than 95%, 100 % oxygen was supplemented via a facemask.

After disinfecting the operative field, the probe of the foetus ECG monitor was inserted into the sterile cover of the laparoscope, and applied below the surgery paster for FHR monitoring.

After infusion of vasoconstrictor, MAP, MHR and FHR were recorded at the following time points: 1min, 3min, 5min, 10min, skin incision and uterine incision. Time from the intrathecal drug infusion to the fetus delivery (I-D interval) and time from uterine incision to the fetus delivery (U-D interval) were recorded. Before the baby was delivered, 2 ml blood were drawn from the maternal dorsal artery to analyze the arterial blood gases with the GEM Premier 3000 automatic blood gas analyzer (Instrumentation Laboratory, USA). After the baby was delivered, the selected umbilical

Table1 General information of the parturients in two groups

	Group Ⅰ	Group Ⅱ
Age, yr	27.2±2.8	27.6±3.1
Height, cm	161.1±4.0	160.7±4.7
Weight, kg	71.1±9.5	70.1±7.3
Block height, dermatome	5.3±0.8	5.3±0.9
Total intravenous fluid, ml	1675.0±166.7	1700.3±75.4
Induction-to-delivery interval, min	19.1±2.2	19.0±3.4
Incision-to-delivery interval, min	4.1±1.7	3.8±1.6
Uterine incision-to delivery interval,s	86.0±48.7	90.7±55.6

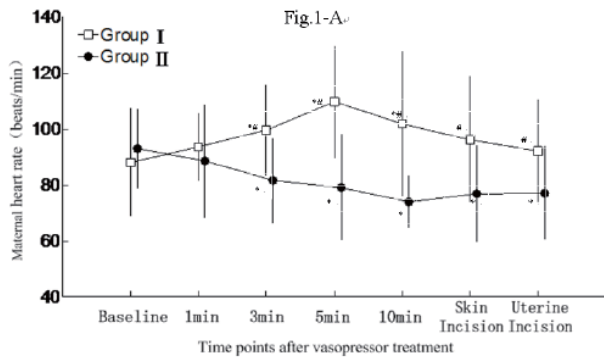
cord was closed immediately with two vascular clamps, and 1 ml collect umbilical artery (UA) blood and 1 ml umbilical vein (UV) blood were collected for blood gas analysis. The glucose and lactate concentrations were also measured. The Apgar scores of the fetus and heart rates at 1 min and 5 min after delivery were recorded.

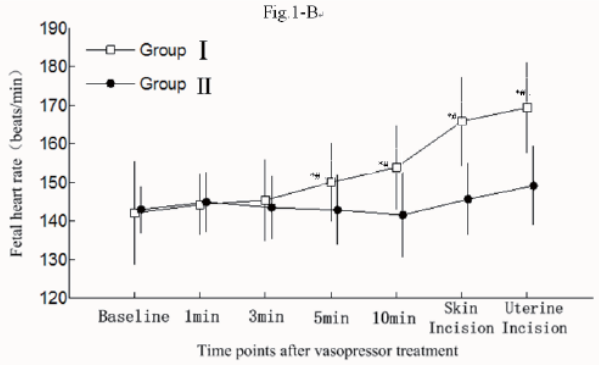
The total doses of ephedrine and phenylephrine were calculated. Furthermore, the incidents of nausea, vomiting and other maternal side effects were noted.

Statistical analysis

Descriptive statistics were calculated for continuous variables as mean ± standard deviation and as frequency distribution and percentage (n [%]). The datas in one group were compared with variance for repeated measurement data and the comparison between the two groups used covariance analysis. The count datas were compared with c2 test. $P < 0.05$ was regarded as statistically significant. SPSS 13.0 for Windows statistical software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

Fig.1 The changes of maternal (A) and fetal (B) heart rates during the observed period in two groups.





Data are expressed as the mean ± SD. Compare with baseline; *P <0.05; Compare with group 2, # P <0.05

Results

There were no significant differences in the maternal age, weight, height, anesthesia methord, operative time, intraoperative fluid volume, bleeding volume and infants' weight between the two groups (Table 1). In group 1, MHR and FHR were significantly increased after infusion of ephedrine ($P < 0.05$). In group 2, the MHR after the infusion of phenylephrine was significantly slower ($P < 0.05$) (Fig.1 A), but the FHR did not evidently change ($P > 0.05$) (Fig. 1B).

The umbilical artery and vein pH and base excess were lower in group 1 than those in group 2 ($P < 0.05$). The PCO_2 and concentrations of blood lactic acid and glucose were higher in the group 1 than in the group 2 ($P < 0.05$) (Table 2).

There was no significant difference between the 1 min and 5 min Apgar scores and the 1 min and 5 min HR of the newborns between the two groups. The incidence of maternal hypotension, nausea and vomiting as well as the highest SBP in group Ⅰ were higher than those in group Ⅱ ($P < 0.05$). There was no significant difference in the lowest SBP and the dose of vasoconstrictor of the two groups.

Discussion

Hypotension after spinal anesthesia for cesarean delivery has an incidence up to 70%, which may cause intrauterine death of the fetus. Currently, various clinical measures were taken to prevent maternal hypotension, including postural adjustments, pre-anesthetic pre-expansion, stretched bar leg veins, reducing the amount of

Table2 Blood gas of umbilical arteries and umbilical venous in two groups (x± s)

		pH	PCO_2	PO_2	Glucose	Lactic acid	HCO_3-	BEecf
UV	Ⅰ	7.29±0.09[a]	49.6±8.5[a]	24.5±4.5	4.2±0.7[a]	3.1±1.3[a]	23.4±2.0	-3.3±2.9[a]
	Ⅱ	7.34±0.03	46.6±5.3	24.9±5.2	3.7±0.4	1.8±0.3	24.9±1.7	-0.9±1.5
UA	Ⅰ	7.20±0.10[a]	66.8±13.9[a]	12.3±4.8	3.3±0.6[a]	4.2±2.0[a]	25.1±1.9	-3.1±3.1[a]
	Ⅱ	7.28±0.03	56.2±5.6	14.4±3.5	3.0±0.4	2.2±0.7	26.4±1.7	-0.3±1.7

Umbilical artery (UA); Umbilical vein (UV); Compared with group Ⅱ, a P <0.05

local anesthetic and slowing the speed of injection of local anesthetic. However, these can not effectively eliminate the incidence of hypotension, and the vasoconstrictor drugs were often needed.[13]

As asympathomimetic drug, ephedrrine not only directly excited the β 1 receptors in the heart to raise blood pressure by accelerating HR and increasing cardiac output, but also indirectly stimulated the sympathetic nerve endings releasing norepinephrine to contract blood vessels. Since the lack of direct sympathetic intervation in placental circulation, ephedrrine had a lesser propensity to cause vasoconstriction of the uteroplacental circulation.[14] Previous animal experiments [4] have shown that, compared with α -agonists, ephedrine can better maintain the uteroplacental blood flow. So ephedrine used to be the preferred vasopressor agent in obstetrics.

Early studies have shown that the declination of fetal pH and base excess were associated with the application of ephedrine in obstetric anesthesia with a dose-dependent manner. [7, 10, 11, 16] Lee et al [17] reported that ephedrine was a major factor for the reduction of the umbilical artery pH and base excess; Cooper et al [7] confirmed that ephedrine-induced acidosis was associated with the difference between the umbilical arterial and venous blood PCO_2, which suggested that acidosis may result from the increased CO_2 production. Studies also confirmed that ephedrine could more easily cross the placenta to activate β -adrenergic receptor of the fetus.[7, 17] Animal experiments also showed that activation of β -adrenergic receptor could increase oxygen consumption and blood lactate concentration, causing decreased blood pH.[18] Past studies of ephedrine focused mainly on the link between ephedrine and fetal acid-based status, but the mechanisms remained elusive. Recently Ngan et al[11] reported that the mechanism underlying the ephedrine-induced fetal acidosis is transfer of the drug across the placenta and stimulation of metabolic processes in the fetus. And the β receptor could not be excited by phenylephrine in the fetus, causing no fetal metabolism excitation.

In our study, the umbilical artery and umbilical vein pH and base excess of group Ⅰ were less than those in group Ⅱ, but umbilical artery and umbilical venous PCO_2, concentrations of lactic acid and blood glucose of group Ⅰ were higher than those of the group Ⅱ. This result showed that use of ephedrine was related to lower values for fetal pH and base excess compared with phenylephrine, which was in accordance with those of previous studies. In group Ⅱ umbilical arterial pH and base excess had no significant decline, and the concentration of PCO_2, lactic acid and blood glucose of group Ⅱ was lower than those of group Ⅰ, and neonatal 1min and 5min Apgar scores had no significant difference. This result suggested that phenylephrine could treat maternal hypotension without affecting the fetal oxygen supply. Recently no evidence has found that the right amount of phenylephrine would adversely affect the fetus. [22] Phenylephrine can effectively maintain maternal blood pressure, reducing the incidence of nausea and vomiting without causing fetal acidosis. [9.10.11.21]

Early studies of effects of ephedrine and phenylephrine focused on MBP, MHR, blood gases of UA and UV blood and Apgar scores, with fewer reports on the changes of FHR. In our study we monitored both MHR and FHR. After infusing ephedrine, MHR and FHR in group Ⅰ were significantly faster, while in group Ⅱ MHR after the infusion of phenylephrine was slower and the FHR had no evident change. The results suggested that the increased FHR following the infusion was associated with use of ephedrine. Compared with phenylephrine, ephedrine had a greater extent to cross the placenta to agonist of β 1 receptors of the fetus, which raised the FHR. The faster FHR increased oxygen consumption and enhanced organization metabolism, leading to more production of CO_2 and lactic acid. This mechanism may also explain that the UA and UV pH and base excess in group Ⅰ were lower than those in group Ⅱ, while the PCO_2 and the concentration of lactic acid and blood glucose of group Ⅰ were higher than group Ⅱ.

Hypotension in spinal anesthesia mainly results from wide sympathetic block, leading to the arteriovenous expansion. Direct pressor effect of ephedrine is related to agonist of β 1 receptors on the heart, [23] which is insufficient in uterine placenta cycle; While phenylephrine can directly contract blood vessels, which is more targeted for the prevention of hypotension. This study showed that the fetus in ephedrine group had high metabolism and increased acid products. In addition, ephedrine had slow onset and needed a relatively long maintain time, and its accuracy of blood pressure control was lower with some

overcompensation. Phenylephrine had rapid onset, short duration and timely and accurate control of the blood pressure changes. The highest value of SBP in group Ⅰ was higher than the highest of group Ⅱ, which suggested that the two drugs were different in the onset time and duration.

Our study has a number of limitations. First, objects of this study were healthy women undergoing elective caesarean delivery, so it may be not valid to extrapolate this result to fetus with compromise or emergency caesarean delivery. Second, the effect of phenylephrine combined with ephedrine on the fetal heart rate is still unknown. Futher study is needed in this field.

In summary, we have found that, compared with ephedrine, use of the phenylephrine can maintain stable fetal heart rate, with no increased oxygen consumption and metabolism excitation, which may be one of metabolisms of phenylephrine.

Acknowledgement: All authors have no financial support and potential conflicts of interest for this work.

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The Improvement of Ventilator:The Manufacture of Expiratory Oscillatory System and Cough Simulation Assembly ——Summary

Qiang Wang, M.D
Department of ICU, Beijing TianTan Hospital, 100050

1.Brief contents and significance

1) Specific contents

We are going to manufacture active expiratory oscillatory assembly with adjustable frequency, and at certain frequency the assembly can resonate with respiratory system; concurrently the cough simulation assembly can simulate the process of cough reflex. Equipments of different kinds will be produced, such as manual, mechanic, even electric one. The equipment can send and draw out gas in fix pressure （volume）directly, then produce high-speed oscillatory airflow, which will help to remove secretion from airway more effectively if combined with postural drainage. If we integrate the assemblies with ventilator, then the modern breathing machine can manage respiratory tracts (Respiration Therapy) besides the function of ventilation. Finally a series of experiments will be designed to evaluate its practical value after the samples are manufactured .

2) Main problems to be resolved

Many patients after neurosurgical operations, also including other critically severe patients, will have pulmonary infection because of the declining autonomic clearance of sputum and the retention of secretion. It has been recognized that the effective clearance of sputum is the key point of therapy of pulmonary infection. However, the effect of common measures of manual secretion-clearance tend to be limited. The research's objective is to resolve the problems of secretion-clearance better, thus to reduce the incidence and the total mortality rate of pulmonary infection. And it also is the significance of the study.

3) Anticipatory results

If the research can get through successfully, it will resolve the clinical problems of the prevention and therapy of pulmonary infection effectively. Also the assembly will become a new type of breathing therapy apparatus, and be commercialized later. The assembly can be separately used, or be integrated into breathing machine, which will consummate the therapy function of breathing apparatus and produce a new-type machine.

2.The general situation of the domestic and foreign research and the basic of study

The declining autonomic clearance of sputum and the retention of secretion can directly result in a series of serious aftermath such as pneumonia. Clinically many patients will have injured competence of removing secretion, which brings difficulties to therapy. The present manual sputum- clearance only can draw out secretion from bigger airway, but be helpless to the secretion from deep part. Patients after neurosurgical operations, ones in coma, or patients in sub-hypothermia needed to be sedated and relaxed fully are prone to have pulmonary infection because of the declining, even lost, autonomic clearance of sputum. This condition seriously affects the therapeutic efficacy.

For many years, many measures have been taken to resolve patients' clearance of secretion, including Forced Expiration Technique (FET), Postural Drainage (PD, combined with clapping, oscillatory massage and pouting breath), Auto-Drainage (AD). However, these physical therapies cost much time, and professional breathing therapeutists or medical staffs are necessary. Some techniques, such as Postural Drainage, can result in occupational diseases. What is more important is that many serious patients are not permitted to turn the body over that frequent. Also based on present medical conditions, a real Postural Drainage is difficult to realize.

CoughAssist manufactured by EMERSON company (USA) has been applied in cough-assistance for many years, which takes the mode of sending and drawing gas in a fix pressure. Since the 90s, based on the theory of Controlled Oscillatory System(COS), a new product—FLUTTER has been manufactured. FLUTTER has been proved to be effective by large numbers of experiments. However, FLUTTER is just a simple assembly applied in conscious patients. Our Expiration Oscillatory System may just base on the theory. Functional Electric Stimulation (FES) was proposed to be another way, which enhances cough strength by stimulate abdominal wall muscles. This technique also can be applied to our research of cough assembly. Its feature lies in simulating the process of cough reflex in vivo directly, changing expiratory phase into a initiative process, increasing maximal expiration speed, and turning traditional oscillation in vitro into one in the airway. The assembly will be applied in all kinds of severe patients whose cough reflex have been destroyed partly or completely. Most techniques taken are mature and effective art in modern breathing machines. We need to bring some new ideas to gas-suction equipment and concert and integrate all functions. Now we have had initial ideas, and clinical effects are estimated to be obvious. Also the system will have some extending value and marketing prospect.

3.Foundations and conditions

The initial designing ideas have been shaped. Most techniques to be taken have been utilized in modern respiratory apparatus. Fund and cooperation with corresponding professional enterprise are the next plans. Then the work will set about. The applier has been devoting to respiratory therapy, and is familiar with the related knowledge. By now, I myself have achieved three state patents, one of which is a new respiratory healer—moisture, and other two of which are new-type infusion sets. So I know the manufacturing process of new products well. The patients with declining initiative clearance of secretion are easily available in ICU. They will become adequate resources of research subjects during later clinical study stage.

4.Chief contents, study design and key points

The study mainly is designed to deal with the clearance of secretion, to simulate normal process of cough reflex, and to manufacture mechanic orelectric secretion-clearance assembly. The chief design plans include:

1) Expiratory Oscillatory System

The system drives expiratory phase airflow to chatter, then to resonate with respiratory system because of the same intrinsic frequency. The effectual frequency ranges from 8 to 16Hz. We can have two ideas about specific structures. One is the pure-mechanic structure, such as an oscillatory piston with changeable angle (frequency). The other structure can chatter at expiratory phase, such as electric controlled valve with adjustable frequency, some chattering structure based on the theory of high frequency oscillatory respiratory apparatus. The structure can be integrated to breathing machine as a simple part and switch on at a settled time. But its influence on trigger system must be resolved. Flow trigger system will be the solution. Sampling frequency and time interval should be adjusted. The conversion between inspiration and expiration can be achieved through the switch of volume or speed. After deep inspiration, the pressure of expiratory phase will be reduced to negative by drawing gas in negative pressure. Also we can combine it with FES to stimulate expiratory muscle, raise the maximal expiratory pressure and increase expiratory speed. But the expiratory volume must be controlled and we must be sure that it will not exceed inspiratory volume, and the airway pressure will return to the baseline at end-

expiration. In clinical research of FLUTTER, the oscillatory theory of secretion-clearance has been proved. If matching with postural drainage, it will enhance the efficacy of secretion-clearance greatly.

2) Gas-Sending/Drawing Systems

For the safe of patients, the mode of definite-volume can be taken. It would not be so difficult to add gas-suction equipment to gas-sending system of respiratory apparatus. The parameters will be set according to the pneodynamic characteristic of normal cough reflex. The key point is to assure adequate expiratory speed and the less volume of gas-suction than that of inspiration. The switch between inspiration and expiration can be achieved easily. And sputum-collecting equipment must be available, which can be used in cooperation with common suction.

3) Expiratory Stimulus System

Electric stimulation synchronized with expiration can drive abdominal and other relating muscles to contract. The expiratory pressure and speed will be raised; the crushing action on lung can be enhanced. Finally the efficacy of sputum-clearance is reinforced greatly. The system must synchronize with expiratory trigger system of breathing machine.

4) Safeguard System

The main danger comes from the sharp alteration of airway pressure. Now the pressure-protecting system has been mature. We just need to add some adjustment to the protection of negative pressure. Through safeguard system and volume-trigger synchronizing switch system, airway pressure and expiratory speed should be limited in the physical range of normal cough reflex.

If the above functions can be integrated to breathing machine, it will really have the function of managing respiratory tracts. These will consummate respiratory apparatus.

5.Year plan and schedule

After manufacturing samples, clinical experiments can be carried out.With enough fund support and cooperation with proper enterprise, it will be completed within(less than) two years in china.

6.Anticipatory financial efficacy and social benefit

According to present information, the same-kind products haven't emerged. If we can carry it out successfully, it will be a new assembly of respiratory therapy. More new-type respiratory apparatuses will be manufactured. Patients will benefit more. If patent is obtained, it will bring economic efficacy after spread.

7.Budgetary estimate

The cost mainly depends on the manufacture and improvement of samples. It would not take much to perform clinical observation. Referring to the price of a top grade respiratory apparatus, it might cost 40,000$. But specific expend has been difficult to estimate accurately.

8.Division of labor

Dr. Wang Qiang will take charge of manufacture and clinical experiment.

高沈平 罗艳

上海交通大学医学院，瑞金医院麻醉科，上海 200025

摘要

目的：睡眠呼吸暂停综合征是以反复发作的部分或完全性的上呼吸道梗阻为特征的综合征，它可导致睡眠暂停，低氧血症，伴有潜在严重的后果。右美托咪定托咪定是一种α2肾上腺素受体激动剂，具有良好的镇痛镇静效果，且呼吸抑制的副作用有限，因而对睡眠呼吸暂停综合征患者围手术期有积极作用。文章就这一药物及其对睡眠呼吸暂停综合征患者的围术期应用作一综述。

关键词：右美托咪定托咪定；睡眠呼吸暂停综合征；疼痛；血流动力学

右旋美托嘧啶在睡眠呼吸暂停综合症患者全麻中的应用

The Application of Dexmidetomidine in Patients with Obstructive Sleep Apnea During General Anesthesia

Shen-ping Gao, Yan Luo

Department of Anesthesiology,Ruijin Hospital,Shanghai Jiao Tong University,School of Medicine,Shanghai 200025,China

Abstract

Obstructive sleep apnea syndrome(OSAS) is a syndrome characterized by periodic, partial or complete upper airway obstruction resulting in the disruption of sleep and hypoxemia with potentially serious physiologic consequences.It is identified as a major health problem during general anesthesia. Dexmedetomidine is an α2-adrenoreceptor agonist, with beneficial analgesic and sedative properties and limited respiratory depressant side effects. Thus it may be useful in the postoperative period for patients with OSA.The aim of the review is to describe dexmidetomidine and its clinical application in patients with OSA.

Key Words: Dexmedetomidine; Obstructive sleep apnea; Pain;Hemodynamics

引言

睡眠呼吸暂停综合症（obstructive sleep apnea syndrome，OSAS）是最常见的与睡眠有关的呼吸障碍疾病，可引起反复发作性的部分或完全性的上呼吸道梗阻。它的定义是患者在睡眠期间发生持续10秒以上的呼吸暂停。Schwab[1]等所在的一所睡眠研究实验室调查报道，睡眠障碍性呼吸的发生率在男性中为24%，在女性中为9%，而症状明显的OSA的患病率在男性中为4%，女性中为2%。中等程度的OSA在男性中发生率为11.4%，女性中为4.7%。在OSA患者的咽喉壁外侧常有脂肪沉积在上呼吸道，导致咽喉管径狭窄，上呼吸道阻力及胸内压相应增加[2]。诸多因素结合往往造成OSA患者在睡眠和麻醉中发生上呼吸道塌陷[3]。到目前为止，多项研究均表明OSA患者术后并发症的发生率高于正常对照组。Gupta[4]等发现在髋关节和膝关节置换手术中，术后并发症的发生率OSA患者（24%）显著高于非OSA患者（9%）。而在择期手术中术后出现显著的氧饱和度降低事件的发生率OSA患者（17%）高于非OSA患者（8%）[5]。在围手术期间对OSA患者予以镇静，麻醉和镇痛都会加剧喉部的梗阻。OSA患者在全身麻醉下，其上呼吸道肌肉所受到的负压大于膈肌的压力。在吸气时由于上呼吸道塌陷，尽管呼吸机在做功，但上呼吸道的肌肉活性明显下降[6]。这不仅是因为全麻下呼吸中枢对上呼吸道反射的抑制，还因为麻醉本身可以阻碍喉部机械性感受器的调节，从而抑制呼吸反射冲动的传递[7]。随着当今社会肥胖症患者数量的增加以及OSA患病率的逐年上升，麻醉医师需要通过临床数据进一步完善OSA患者围术期管理标准，最大程度减少麻醉所致的副作用。美国麻醉学家学会最新公布的OSA患者手术期间麻醉管理指南，要求对诊断为OSA的入院手术病人和门诊手术病人，手术期间施行麻醉镇静处理[8]。

一、右美托咪定托咪定

1. 药理学研究

右美托咪定托咪定刺激α2肾上腺素受体，以一种抑制结构偶联L型钙离子通道。通过作用于脊髓处受体发挥镇痛作用，作用于蓝斑发挥镇静和抗焦虑作用，并且在降低应激反应的同时不会引起明显的呼吸抑制[9]。右美托咪定托咪定对α2：α1受体的激动具有较高的选择性（1620:1相对于可乐定220:1），这说明在发挥有效镇静作用的同时不会因为兴奋α1受体而产生不必要的心血管反应[10]。但是大剂量使用时就会出现一过性的高血压和心动过缓，这是由于药物激动位于阻力血管平滑肌细胞上的α2B肾上腺素受体并抑制心肌交感神经传递[11]。右美托咪定托咪定可产生自然非动眼睡眠，在一定剂量范围内机体的唤醒系统功能仍然存在。接受右美托咪定托咪定患者Ramsay≥3分或OAA/S≤4分受到刺激时可观察到觉醒反应。右美托咪定托咪定分布半衰期（t1/2α）6min，消除半衰期（t1/2β）约2h，持续输注半衰期（t1/2CS）随输注时间增加显著延长。若持续输注 10min，t1/2CS为4min；若持续输注8h，t1/2CS为250min。静脉泵注负荷剂量1μg/kg（10min），右美托咪定的起效时间 为10-15min；如果没有给予负荷剂量，那么其起效时间和达峰时间均会延长。负荷剂量为1μg/kg（10min），以0.3μg/kg/h维持，Ramsay评分达4-5分，约需20-25min；以0.2μg/kg/h维持，Ramsay评分达4-5分，约需25-33min[12]。

2. 临床人体试验结果

到目前为止已有多项临床试验证明了右美托咪定托咪定的镇静作用。Gurbet[13]及其同事比较了右美托咪定组与安慰剂组对全子宫切除术后镇静作用的效果。结果发现两组的疼痛评分相似，但是右美托咪定组在术后48小时内所需的吗啡累计量更低。在另一项对100例全麻下行全子宫切除术患者的调查显示，右美托咪定组的术后吗啡使用量比空白对照组少29%，且术后2小时及48小时的疼痛评分显著降低[14]。Arain[15]等研究了34例择期手术患者，随机予以右美托咪定（初始计量为10ug/kg，输注10分钟后以0.4mg/kg/h维持至手术结束）或硫酸吗啡（0.08mg/kg，手术结束前30分钟给予），结果发现两组患者的疼痛评分相似，但吗啡组术后需要的吗啡剂量比右美托咪定托咪定组多66%。

3. 动物实验结果

以往的动物实验表明α2肾上腺素受体激动剂在全身用药的情况下所表现的镇痛与镇静作用呈剂量依赖关系[16]，而人体的临床数据结果显示在镇静效果上呈现明显的剂量相关性，但在镇痛效果上未发现有相关性[17]。对于动物实验和人体实验结果的不同，一种可能的解释是在动物实验中使用的药物剂量比人体实验要高出数个数量级[18]。

二、右美托咪定托咪定在OSA患者手术中的应用

1. 成人临床试验结果

Hofer[19]等报道了一例体重433kg，伴有OSA和肺动脉高压的病态肥胖患者，在全麻下行R-Y胃空肠吻合术。在第一次手术日采用连续静脉泵注右美托咪定（0.7ug/kg/h）替代阿片类镇痛药物，术后患者对阿片类药物的需求较低（苏醒室吗啡使用量为48mg），然而在第二次手术日仍持续予以右美托咪定，术后患者对阿片类药物的需求却未下降（苏醒室吗啡使用量为148mg）。四篇对OSA患者手术的病历报道显示右美托咪定可以有效降低呼吸道意外事件的发生。大部分结果认可术前应该先静脉输注右美托咪定的初始计量（0.1mg/kg），再以0.1-0.7mg/kg/h维持[20-23]。其中一例OSA患者行气管切开术采用大剂量右美托咪定（10mg/kg/h）辅助麻醉，术中患者的氧饱和度能够维持在95%以上，未有呼吸困难发生[22]。对OSA患者术中持续输注右美托咪定可以减少围术期麻醉药物、镇痛药物及抗高血压药物的量，降低术后疼痛评分，缓解麻醉中的应激反应。在一项对268例全麻下行气道重建术OSA患者的回顾性研究发现术中使用右美托咪定有效减少了抗高血压药物的使用，术后对吗啡的使用量也比未使用右美托咪定的患者有所减少[24]。对一例清醒甲状腺切除手术的病历报道也支持右美托咪定可以有效减少术中阿片类药物的使用[20]。在BIS监测下术中使用右美托咪定与安慰剂相比，能够减少丙泊酚和吗啡的用量，减少80%咪达唑仑和50%吗啡的用量[25]。有研究显示右美托咪定对OSA患者术中血流动力学具有稳定作用，对22例OSA患者行腹腔镜肥胖症治疗手术的回顾性研究证明该结论[26]。但是也有病历报道右美托咪定可能会造成术中短暂的低血压[22]。

2. 小儿临床试验结果

小儿反复发生扁桃体，腺样体炎症可以表现为OSA症状，发病率大概在1%-3%[27]，所以扁桃体腺样体切除手术在儿外科中较为常见。扁桃体腺样体切除术后疼痛剧烈，临床中常规予以阿片类药物，但随之产生的问题是OSA患者特别是小儿对阿片类药物敏感性增强，并且术后低氧血症的发生率增加[28]。因此，近年来临床医生尝试了多种非阿片类药物（如酮咯酸，氯胺酮，曲马多等）评估对术后镇痛的效果，但由于各自的副作用及镇痛作用不满意，都不能被广泛接受和使用[29]。Anuradha[30]等报道了122例OSA小儿行扁桃体腺样体切除术，术中以吸入麻醉药维持，结果发现与对照组相比，右美托咪定组术中血流动力学较稳定，术后阿片类药物的使用量显著降低，并且术后严重躁动和低氧血症的发生率也明显下降。

三、结语

理论上右美托咪定对OSA患者会有很大帮助，它能通过刺激蓝斑受体产生镇静作用，刺激脊髓受体产生镇痛作用。虽然会降低降低人体每分通气量，增加肺泡二氧化碳分压，但是同阿片类药物相比右美托咪定的这些副作用非常的轻微。然而右美托咪定对OSA患者的临床作用还未有前瞻性的随机对照研究报道，大部分的研究结果都是基于一些病历报道和回顾性研究。所以尽管右美托咪定镇静镇痛的优势已经在临床使用中被人们所接受，但是针对OSA患者的药物临床研究还需要做进一步更多的努力。

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《疼痛医学华夏会议》通知

首届《疼痛医学华夏会议》将于金秋时节亮相北京，其前身是成功举办了七届的“东西方疼痛会议”。中英文网站www.jspmf.com现已开通，接受网上投稿和注册。

本届盛会大师云集，邀请到20余位来自欧美日韩的一流学者。美国疼痛学会主席Perry G. Fine教授、欧洲疼痛学会主席Robert V. Seventer教授和澳大利亚疼痛专家Philip M. Finch，将就微创介入治疗慢性腰背部疼痛、复杂性区域性疼痛综合征的病理机制和治疗、椎间盘源性疼痛的微创治疗等疼痛医学最新进展做精彩演讲，还将介绍疼痛科建设和运营的成熟模式。会议设立了同麻醉相关的疼痛医学领域分会场，围绕疼痛医学基础研究进展，麻醉与镇痛，微创介入，神经病理性疼痛，脊柱微创和神经调控，传统医药与疼痛，疼痛的康复、护理和心理治疗等问题进行深入探讨，让来自麻醉、疼痛、神经内外科、骨科以及康复等相关学科的国内外专家共同交流，分享经验，会议内容广泛，充分体现了疼痛医学的多学科特点。

欢迎麻醉、疼痛、骨科、神经内外科、肿瘤和中医、康复等相关专业的人员投稿并预约发言。

会议期间将举办“继续教育讲习班”，著名专家授课，定位于慢性疼痛诊疗的系统性培训和热点讨论，学员将免费参加本次大会并获得国家级继续教育Ⅰ类学分。

主办单位：北京济生疼痛医学基金会

支持单位：北京市科学技术协会/中华医学会疼痛学分会/中华医学会麻醉学分会/中国医师协会麻醉学医师分会/中国抗癌协会姑息治疗专业委员会/《中国疼痛医学杂志》/《实用疼痛学杂志》

大会主席：韩济生 院士

共同主席：Perry G.Fine 美国疼痛学会主席；Robet V. Seventer 世界疼痛医师协会主席

执行主席：李勇杰 樊碧发 于布为

会议地点：国家会议中心（北京奥林匹克公园中心区）

会议时间：2012年9月22-24日　　报到时间：2012年9月21日

讲习班时间：2012年9月21-24日　　报到时间：2012年9月20日

联系人：陈青 刘强 何智超 （电话：010-68483336；邮箱：forum@ jspmf.com）

安欣 马晓春
中国医科大学附属第一医院重症医学科 辽宁沈阳 110001

摘要

本文从指导临床危重病患的治疗的角度出发，总结了测定血管外肺水的几种常用临床方法、原理，安全性、有效性和影响因素，及其在治疗中的指导作用。

血管外肺水监测在危重症患者中的应用

The Application of Extravasculur Lung Water Mointor in Critical III Patients

Xin An, Xiao-chun Ma
Department of SICU, The First Affiliated Hospital of Chinese Medical University.Shenyang, Liaoning, 110001

Chinard在1954年提出应用指示剂稀释技术测量血管外肺水(extravasculur lung water，EVLW)，并指出其对于临床实践具有重要的指导意义[1]。经过多年的发展，随着血流动力学监测技术的不断改进，对于血管外肺水（EVLW）的研究已经相当深入，特别是在危重病患者，EVLW可安全有效的评估病情的严重程度、指导治疗等。EVLW由细胞内液、肺间质内液和肺泡内液组成。通常情况下，细胞内液变化较小，而肺间质内液和肺泡内液却能准确反映肺水肿的严重程度，因此，EVLW 的变化与肺水肿发展密切相关。监测EVLW，可以量化肺水肿的程度，分析急性呼吸衰竭患者的特征，从而指导临床治疗，降低病死率等。

一、测定血管外肺水EVLW的方法

目前测定EVLW 的方法包括：比重法、双指示剂稀释法、单指示剂热稀释法等。

1. 比重法

比重法测定EVLW 常应用于动物实验中，具体方法如下：动物全身肝素化，抽取动脉血称重备用。饱和氯化钾(KCL)处死动物，迅速开胸，扎闭双侧肺门，以防肺血丢失。切取两完整肺组织，称重后加入同重量的蒸馏水，搅拌器充分搅拌形成肺匀浆。取10ml匀浆，高速离心(5000r/min，5min)后放置于5℃1小时，取上清液。采用WHO推荐分光光度计比色法分别测定动脉血、肺组织匀浆和上清液血红蛋白浓度。另取动脉血、肺组织匀浆和上清液，80℃干燥72小时以上，分别计算含水百分比。根据下列公式计算可得出EVLW[2]：

肺匀浆血红蛋白浓度=上清液血红蛋白浓度×(匀浆含水百分比/上清液含水百分比)

肺血重=匀浆重×匀浆中血红蛋白浓度/血液血红蛋白浓度

肺血液中水重=肺血重×血液含水百分比

肺脏中总的水含量(TPW)=匀浆含水百分比×肺匀浆重一附加水

EVLW=TPW一血液中水重

这种方法是基于肺干湿重的对比，尽管该方法仍有一定的局限性，但仍被认为是测定EVLW技术的金标准[3]。

2. 双指示剂稀释法

Gee and Stage[4]报道应用双指示剂稀释法测定EVLW；该法在上世纪80年代开始应用于临床，第一台临床运用此法测定EVLW 的仪器是Edwards M9310肺水计算机(edwards laboratories，CA)[5]。

（1）基本装置及操作

通过颈内静脉或锁骨下静脉放置中心静脉(CV)导管，外接温度探头。自中心静脉注射两种不同的指示剂，一种为热稀释指示剂，可渗透到毛细血管外，常用5%葡萄糖或生理盐水；另一种为染料稀释指示剂，只能保留在血管内，常用与白蛋白结合的吲哚绿。股动脉放置一根尖端带有热敏电阻丝的导管，检测热稀释曲线；从股动脉导管中抽取股动脉血，分析得出染料稀释曲线。根据各自的稀释曲线分别得出稀释曲线的平均变化时间(MTt)。根据史德华一汉密尔顿法(Stewart-Hamiton equation)，通过热稀释曲线计算出心输出量(CO)。

（2）基本原理

染料稀释指示剂不能渗透至毛细血管外，因此其所流经的所有容积量为GEDV和PBV的总和，即ITBV；热稀释指示剂能渗透至毛细血管外，因此其所流经的所有容积量为EVIW 和ITBV 的总和，即胸腔内热容量(ITTV)。根据公式：CO×MTt=指示剂所流经的所有容积量，可得：

ITTV=CO×MTt(热稀释指示剂)

ITBV=CO×MTt(染料稀释指示剂)

两者之间的差值为EVLW，即EVLW =ITTV —ITBV

该方法在测定人EVLW时，与比重法的测得值有很好的相关性[6]。然而该方法耗时且费用昂贵，在临床实践过程中并不常用，然而却为单指示剂法的发展提供了基础。

3. 单指示剂热稀释法

单指示剂热稀释法是在双指示剂稀释法基础上演化而来，临床最常应用该法测定EVLW 和ITBV 的仪器是COLD Z一021系统和PiCCO仪(Pulsion，Germany)[5]。

（1）基本装置及操作

与双指示剂肺水测定法基本相同。放置中心静脉导管用以注射热稀释指示剂，股动脉放置一根尖端带有热敏电阻丝的导管，检测热稀释曲线。连接显示屏后注射热指示剂观察其热稀释曲线。

（2）基本原理

心脏和肺可看成是由一系列序贯而独立的容积腔组成，股动脉导管检测到的热稀释曲线可看成是每个容积腔稀释曲线的组合，稀释曲线中最长衰变曲线对应的是其中最大的容积腔。将热稀释曲线取对数后进行标记，可得到稀释曲线的指数波形下降时间(DSt)。由于肺血管和血管外容积腔显著大于其它容积腔，根据公式：CO×DSt=从注射位置到测量位置的最大容积腔的容积量，可得：

CO×DSt(热稀释指示剂)= PBV+EVLW ，

而CO×MTt(热稀释指示剂)=ITTV，可得：

CO×（MTt—DSt）(热稀释指示剂)=ITTV一(PBV+EVLW)=GEDV

ITBV和GEDV之差值为PBV，两者之间有着较好的相关性，通过分析可计算出ITBV，Sakka[7]等将57例患者的GEDV(由单指示剂热稀释法测得)和ITBV(由双指示剂稀释法测得)进行分析得出方程：

ITBV=1.25×GEDV一28.4ml

根据ITTV=ITBV+EVLW，得出：EVLW=ITTV—ITBV

（3）单指示剂热稀释法测定EVLW和ITBV的可靠性

由于单指示剂热稀释法测得的ITBV和EVLW均由推算得来，而未直接测得，其结果可靠性如何值得关注。Sakka[7]等进行分析得出方程ITBV=1.25×GEDV一28.4ml之后，进一步运用该方程计算出209例患者的ITBV和EVLW，并将其与由双指示剂稀释法直接测得ITBV和EVLW 进行比较，得出：ITBV（单指示剂）=1.06×ITBV（双指示剂）—124.3ml，其回归系数r=98(P<0.0001)；EVLW（单指示剂）=0.83×EVLW（双指示剂）+133.9ml，其回归系数r=0.96(P<0.0001)。

在很多动物实验中，单指示剂法测得的EVLW与应用比重法测得的EVLW显出了很好的相关性；但在不同的动物模型上，单指示剂所测得的EVLW均较比重法测得的EVLW高，最高者为5.4ml/kg。学者们解释为是由于动物心脏以及血管内的细胞内液对于热稀释剂的稀释所致，也可能是因为不同种动物GEDV与ITBV的计算公式存在差别；应用不同的公式重新校对之后，两种方法测得的EVLW的相关性明显提高。这些均说明应用单指示剂测定EVLW是比较可靠的。

二、单指示剂热稀释法测定EVLW的安全性

一般认为，单指示剂热稀释法测定EVLW有着较高的安全性。Boyle[8]等通过激光多谱勒分析仪对10例接受血管活性药物(去甲肾上腺素0.03～0.48ug/kg·min，肾上腺素0.09～0.8ug/kg·min)的患者(置有4.5F股动脉导管)足部进行扫描发现，无论是腓肠肌闭合压还是足底部的血流灌注在插管后及插管后24小时均无明显影响。由此可见，放置股动脉导管是安全的。然而，对于腹主动脉瘤患者放置股动脉导管有腹腔大出血的危险性，临床应慎用或禁用。

三、热稀释法的局限性

与其他方法一样，本方法同样具有局限性。熟悉其局限性对于合理解读数据，充分评价患者病情严重程度，无疑是非常重要的。

1. 肺灌注下降对于EVLW的影响

早期应用热稀释法测定ELVW时，学者们推测因热稀释指示剂不能充分地通过血流渗透至相应的肺组织，则不能充分地与血管外的组织进行热量交换[9]，因此肺灌注的下降可能会导致EVLW被低估。这包括肺大血管的阻塞（如急性肺栓塞等）以及毛细血管内微血栓等（例如急性肺损伤等）。早期有研究显示当被阻塞的血管直径≥500um时，ELVW会被低估近50%[10]。但这种情况在小的血管（直径≤175um）发生栓塞时明显改善，ELVW仅被低估16%左右[11]，这可能是因为水对于热量的传导速度非常快，而且比小分子弥散速度快的多，从而可以使热量从邻近的灌注良好的区域弥散至阻塞或者低灌注的区域[11,12]，进而不影响被阻塞区域的EVLW的测量。临床实践中，更多的医师关心肺血管中微血栓的形成对于EVLW的影响，而形成微血栓的血管直径一般小于175um，因此应用热稀释法测定的EVLW不会受到较大影响。

2. 呼气末正压（positive end-expiratory pressure，PEEP）对ELVW的影响

PEEP对ELVW的影响目前仍存在争议。一方面，高水平的PEEP可能直接导致肺血管破坏或闭锁，导致热指示剂不能通过进而影响测量，这可能解释了在一些实验研究中通过稀释法测得的EVLW偏低[13]；另一方面，高水平的PEEP导致肺的复张，使血流重新分布到之前没有开放的区域，从而人为的升高了EVLW水平[14]。实际上，PEEP确实可以通过降低肺毛细血管压力以减少EVLW[15]；PEEP也可以通过增高中心静脉压(CVP)影响淋巴回流而增加EVLW[16]。总体说来，PEEP可以影响EVLW的数值以及测量[17]。

3. 关于肺损伤

肺损伤的情况下，肺血流从损伤的区域重新分布到其他区域，这将导致ELVW被低估。Schuster等应用PET扫描评价肺灌注以及EVLW，发现缺氧性的肺血管收缩剧烈的减弱，而没观察到预期的灌注重新分流等[18]。因此，存在肺水肿的患者，热稀释技术的精确性似乎不太可能受到肺血流重新分布灌注的影响。

四、EVLW临床应用价值

1. 预测价值

Sakka等通过对373位应用双指示剂法测量EVLW的患者进行回顾性分析发现，死亡组的EVLW水平明显高于非死亡组，EVLW>15ml/kg的死亡率大于65%，而EVLW<10ml/kg的死亡率小于33%[19]，同时还发现EVLW 与简明急性生理评分SAPS II和急性生理和慢性健康评分APACHEⅡ一样，是评价危重病患者病死率的独立而可靠的因素。Martin[20]等对29例全身性感染(severe sepsis)患者进行临床研究，观察到EVLW 和氧和指数(PaO_2/FiO_2)、机械通气时间以及住院病死率均显著相关，进一步提示EVLW对判断危重病患者的病情及预后均有着重要的价值。

2. 诊断价值

（1）肺水肿

应用传统的听诊法以及胸部X线诊断肺水肿非常不精确。研究显示应用胸片评分反映肺水肿的变化，与真正的EVLW相关性很差[21]。而热稀释法能监测到EVLW的早期变化[22]，在评价肺水肿方面具有明显的优势。

（2）急性呼吸窘迫综合症（ARDS）：

有研究显示，很多急性肺损伤（ALI）/急性呼吸窘迫综合症（ARDS）患者并没有明显的肺水肿[23,24]。因此监测EVLW有助于判断患者病情的严重程度，从而指导进一步的治疗[25]。但有相当一部分（21%-35%）ALI/ARDS患者的EVLW并不升高（<10ml/kg），其原因尚不清楚[26,27,28]。Nuckton等[29]研究发现，部分ARDS患者存在较高的肺泡死腔量(可高达58%)，提示单指示剂热稀释法在测定此类患者的EVLW 时，可能有一定误差。也有学者认为，之前的研究计算EVLW时应用患者的实际体重，而患者的肺总量通常与理想体重相关，通过理想体重校正EVLW后，ALI/ARDS患者的EVLW测量值可上升[30]。这可能对于解释部分ALI/ARDS患者的EVLW并不升高方面，有一定的提示意义。

（3）鉴别高静水压性和高渗透性肺水肿：

实验发现，高渗透性肺水肿中EVLW/ITBV（胸腔内热容积）的比值明显高于高静水压性肺水肿[31]。提示EVLW/ITBV（即PVPI，肺血管通透性指数） 可用于鉴别肺水肿的主要原因。然而也有研究发现在脓毒症导致的ALI/ARDS患者中，PVPI与肺蛋白渗出的相关性很弱[32]，它的升高并不能反映毛细血管渗漏的严重程度，因此，应用PVPI进行肺水肿原因的鉴别，还有待于进一步的实验证实。

3. 治疗价值：指导液体管理

ALI/ARDS患者液体量的管理还是存在争议的。一方面，限液可能改善动脉血氧合情况以及肺机械力学，加速患者撤离呼吸机；另一方面，限液的做法可能导致血流动力学的失衡乃至器官功能损伤[33]。相对于应用肺动脉导管PAOP指导液体管理，应用EVLW进行容量管理，可以降低机械通气时间以及ICU住院时间[34]。一项大型的多中心随机研究证实，在ALI/ARDS患者中实行“保守”的液体策略，可改善肺功能、降低机械通气时间等[35]。所以，应用EVLW对患者进行个体化的滴定式的“保守”治疗可能会改善危重病患者的预后。

五、小结

测定EVLW因其准确性以及安全性已广泛应用于临床实践。但因其固有的局限性，可能导致EVLW被低估，在临床解读过程中需注意判定；在具体应用过程中，EVLW的动态变化比具体的单个数值更有意义。因此，仍需更多的临床研究来验证ELVW对于心源性肺水肿以及ALI/ARDS患者的评估价值以提高其使用价值。

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符强 蒋宗滨

广西医科大学第一附属医院，广西医科大学疼痛医学中心

摘要

臭氧疗法作为疼痛治疗的一种热门的、新型的治疗方法，近年来越来越受到高度关注和广泛应用。许多临床和实验室研究证明，臭氧的抗炎镇痛作用较强，对软组织炎性疼痛，骨关节炎疼痛、盘源性疼痛以及神经病理性疼痛有良好的治疗作用。随着癌症疼痛对患者生活质量影响的凸显，臭氧对癌症及癌痛治疗方面的探索也有所进展，然而，这方面的报道还很少且缺乏系统性。为了探讨臭氧治疗癌痛的可行性及效果，本文对臭氧治疗癌症以及癌性疼痛的基础研究与临床应用做一综述，期待可以开发出一种新的癌痛治疗方法，为备受癌痛折磨的患者带来福音。

关键词：臭氧；癌痛；治疗

臭氧治疗癌痛的研究进展

Advance in the Study of Cancer Pain Management with Ozone

Qiang Fu, Zong-bin Jiang

The First Affiliated Hospital of Guangxi Medical University, The Center of Pain Medicine of Guangxi Medical University, Nanning 530007, China.

Abstract

As one of novel and hot therapies, ozone treatment has been more and more attractive and widely practiced in recent years. Many clinical and laboratory studies have proved that ozone has a big contribution to anti-inflammation and abirritation, and be good at treatment of pain from soft tissue inflammatory, osteoarthritis, discogenic pain and neuropathic pain. Along with the influence on the quality of life from cancer pain extruding, exploration of controlling cancer and cancer pain with ozone has made a process. However it's seldom reported of these studies, and also they lack systematicness. To discuss the feasibility and effect of treating cancer pain with ozone, this article reviews the basic research and clinical practice of ozone treating cancer and cancer pain regarding it, expecting to explore a new therapy for cancer and bring a good news for patients suffering from it.

Key Words: Ozone; Cancer Pain; Therapy

臭氧最初被人类有意识的加以应用是用来保存肉类等食品，真正用于医学始于20世纪。第一次世界大战后，德国医生将臭氧用于治疗坏疽，此后，其杀灭病原微生物的作用逐渐被应用直到今天。目前研究已经证实，臭氧具有灭菌、消毒、抗炎，镇痛等医疗作用，近年来，利用臭氧的抗炎镇痛作用，其在疼痛性疾病中的治疗作用如火如荼，许多疼痛性疾病，如软组织炎性疼痛，骨关节炎疼痛、盘源性疼痛以及神经病理性疼痛，臭氧均有良好的治疗作用。然而，臭氧在癌症以及癌痛治疗中的作用与疗效却鲜有报道，事实上，臭氧在癌痛中的治疗已经逐渐进入相关专业人员的研究领域并有初步的结论。本文对臭氧治疗癌症以及癌性疼痛的研究与临床应用做一综述，期待能开发出一种新的癌痛治疗方法，为备受癌痛折磨的患者带来福音。

一．臭氧镇痛的临床应用

近年来，臭氧被越来越多的国内外疼痛科医生用于治疗各种疼痛性疾病，主要治疗机制也是利用其抗炎镇痛和强氧化作用。

1. 利用其抗炎作用，国内外学者多用臭氧治疗肩周炎[1,2]、膝关节骨性关节炎[3,4,5]、梨状肌综合征[6]、腰椎间盘突出症[7,8]、腰背肌筋膜炎[9]等。

2. 利用其镇痛作用，如用臭氧进行神经阻滞，治疗颈源性头痛[10]、三叉神经痛、面神经痛、坐骨神经痛、带状疱疹后神经痛[11]等。

3. 利用其氧化作用，如骶髂关节内注射臭氧治疗强直性脊柱炎[12]等，其强氧化作用能中和、抑制多种炎性介质以及致痛物质的合成、释放，扩张局部血管，改善局部血液循环。

4. 利用其综合作用，目前的治疗应用大多属于此类。如治疗腰椎间盘突出症[7]，机制包括上述臭氧注射治疗软组织炎性疼痛，骨关节炎疼痛，强直性脊柱炎疼痛等。

二．臭氧治疗癌痛的研究现状

1. 臭氧的认识历史

早在20世纪70年代，就有学者注意到臭氧和癌症之间的关系。那时候学者们的注意力无不例外是放在大气层中的臭氧空洞导致皮肤癌等癌症发病率增高这一点上。直到20世纪80年代初，国际医学界开始有了新的发现。1980年的《Science》刊文介绍说臭氧有助于治疗癌症，从那时大家的目光才开始有所转变。

首先需要明确的是，肿瘤的治疗，是肿瘤性疼痛的病因治疗。

最早对臭氧的医疗作用有比较系统的研究并且总结成书出版的可能要数意大利生理学家Velio Bocci了，他写的《Ozone A New Medical Drug》一书全面介绍了臭氧的各个方面，其中就写到了臭氧在肿瘤治疗中的作用。他认为，臭氧作为一种强氧化剂，可以和生理性体液中的很多分子迅速

发生反应，如抗氧化剂，蛋白质，碳水化合物，不饱和脂肪酸等。而作为这些反应的两个基本过程，脂质过氧化物（lipid oxidation products,LOPs）和活性氧（reactive oxygen species,ROS）构成了全身所有不同种类细胞所发生的生物反应。臭氧疗法有着不可思议的潜力，假如我们能够很精确的控制LOPs，则我们只用一种药物就可以达到许多理想的生物效应，因此，肿瘤也在臭氧可治疾病的范围内。

Siegfried Schulz1等人做动物实验[13]，将肿瘤细胞移植到兔子的腹腔里，然后每天给兔子腹腔注射臭氧（80ml/kg体重，O_3含量50μg/ml混合气，O_2与O_3体积比为97.5%：2.5%），两周后有一小部分兔子没发展成恶性肿瘤，因此得出结论，臭氧可以治愈恶性肿瘤。Velio Bocci则发文质疑，臭氧没有对兔子自身的免疫系统进行抑制，有可能是其本身的免疫力杀死了肿瘤细胞；再者，仅两周的暴露时间未免太短，也可能是肿瘤细胞未能成活的一个原因[14]。

不过臭氧作为癌症治疗药物更多是作为辅助药物出现，用以降低恶性肿瘤的放化疗的副作用，如膀胱炎等。也有对其直接作用于癌细胞的研究，如有临床试验表明其能直接升高肿瘤组织的含氧量从而抑制肿瘤细胞的增长，降低前列腺抗原等传统的肿瘤标志物等，但其机制仍不甚明了。某些实验结果则表明，臭氧对于那些缺氧较严重的肿瘤组织才有明显的抑制生长作用，而对于那些缺氧状况较轻的肿瘤组织则抑制生长的效果并不明显[15]。

最近的研究比较有代表性的也是将臭氧作为放化疗的一项辅助治疗，但比较倾向于分子生物医学方面的研究。这项研究认为臭氧可对肿瘤形成的复杂过程中的某些环节产生影响，并通过动物实验和临床试验得出了一些新的成果，如发现臭氧可通过操纵ROS的反应量来调节某些细胞凋亡基因（如Bax）或抑制凋亡基因(如Bcl-2)的表达；臭氧还有抑制肿瘤细胞转移的作用；通过增加氧供和改善微循环可以减缓肿瘤细胞的生长和抑制其代谢[16]，这些发现的相当一部分机制同样有待进一步的深入研究。

通过多年的共同研究，研究者达成了一些共识，探明了臭氧治疗癌症的一些机制。比如，臭氧可以通过增加肿瘤组织的氧供而减缓其生长；臭氧可以和体内很多细胞中的活性分子发生作用进而影响内环境，产生或消灭某些肿瘤相关分子，从而达到治疗恶性肿瘤的作用[11]。此外，根据这些研究，一些学者不约而同的将臭氧在治疗肿瘤中的作用放在了从属的地位。

2. 臭氧的应用现状

目前处于应用中的臭氧相关制剂有臭氧化水，臭氧化油，O_2-O_3混合气体，用法则根据病情而多种多样，有静脉内，动脉内，肌肉内，皮下，腹膜内，胸膜内，关节腔内，椎间盘内，病灶内，表面或局部途径，等等。但是动静脉内的O_2-O_3混合气体注射因为有造成气栓而引发严重不良反应的危险，所以现已被禁止应用。臭氧化水和臭氧化油常常被用于皮肤粘膜来治疗局部感染和烧伤，其强有力的杀菌效应甚至能杀死耐药菌和厌氧菌[11]。

臭氧具体应用于肿瘤的治疗，可能的作用机理主要有如下5个[11]：（1）O_2-O_3混合气在体内和体外对癌症细胞的直接效应。（2）改善氧合作用和新陈代谢。（3）随着细胞氧化还原电位的改善，抗氧化酶系统可能上调。（4）对免疫系统的影响。（5）对中枢神经系统和内分泌系统的影响，以及与癌症相关的疲劳治疗。这里主要的依据是臭氧作用于血液后将改善肿瘤微环境，从而抑制肿瘤生长。肿瘤组织生长的理想微环境与正常组织的显著差别是氧分压，前者为1mmHg～10mmHg，后者为40mmHg～50mmHg。当臭氧混合气作用于血液，通过直接作用及诱导生成“超级红细胞”，会有效持续的提高氧利用度，极大的改变肿瘤的微环境，导致肿瘤细胞休眠或处于非常脆弱的状态，从而抑制其生长或转移。这些已经分别被独立的研究所证实。显然，当肿瘤的进展得到有效抑制时，有肿瘤带来的疼痛必然随之得到有效的控制。

三．臭氧治疗癌痛的展望

关于臭氧治疗癌痛的有效性，因为缺乏系统的基础及临床研究，现在仍未有肯定的定论，也没有可以使人信服的循证证据。不过，臭氧在治疗感染，缺血，溃疡等方面均已被大量事实证明是确切有效的；同时，从目前的一些实验研究和理论探索可以看出，臭氧治疗癌痛也是有效的。

回顾臭氧治疗癌痛的发展史，各学派之间开始有了初步的共识，这说明关于臭氧在癌症治疗中所起作用的一些可能是正确的事实，正在为医学界所发现，所认可。相信循着这一条条相关的线索，可能会发现臭氧所蕴藏的更大的潜能。与其他治疗方法相比，臭氧最为安全、有效、无害，因此这些作用也是值得进一步证实的。应该会找到一个切实可行的方法，使臭氧为治疗癌痛贡献其应有的力量，为不幸的肿瘤以及癌痛患者送去新的曙光。

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黄顺伟 沙舟

中山大学附属第一医院重症医学科

摘要

2011年对心力衰竭（HF）的研究是具有里程碑意义的一年，本文主要综述了在心衰方面所发表研究进展的文献。预测方面：空腹血糖（未患糖尿病的老年人），载脂蛋白（Apo）B/apo A-1 对男性心衰有预测作用，而甘油三酯对女性心衰有预测作用(无心血管疾病病史的人群)，^{123}I-MIBG心肌显像在预测HF方面被证实有价值。风险预测方面，两个生物标志物的组合使用优于单一生物标志物。病理生理学方面：miRNA 在心衰发病机制中的研究取得进展。遗传学研究发面：发现肾上腺素受体-1 和一种终止其信号的蛋白激酶（GRK5）可以显著影响HF的结果。治疗方面：流量触发的自调节通气（servo ventilation）治疗和醛固酮的使用对心衰的治疗有较好的效果，而远程病人监护应该得到重视与推广。除了ICD 以外，心脏再同步化治疗(CRT）的应用应得到重视。

责任作者及联系方式：黄顺伟，E-mail：huangshunwei@gmail.com

2011年有关心力衰竭研究的进展

Progress in the 2011 Heart Failure

Shun-wei Huang, Zhou Sha

Department of ICU, the First Hospital Affiliated to Zhongshan University

Corresponding Author: Shun-wei Huang, E-mail: huangshunwei@gmail.com

流行病学及预防

众所周知，糖尿病和肥胖与心衰的发病密切相关。新的流行病学研究侧重于这些风险，包括血糖状态，代谢综合症，BMI和脂蛋白。一项包括6000人的芬兰大型队列研究表明，BMI指数增加与腹型肥胖和心衰发病率增高有关。在来自《HEALTH》关于衰老的研究表明，未患糖尿病的老年人中，空腹血糖增高是心衰的独立危险因素。AMORIS针对未患心血管疾病人群的大型观察性队列研究中显示，各组脂蛋白组与HF显著相关，特别是载脂蛋白（APO）B/apo A-1比例对男性心衰有预测作用而甘油三酯对女性心衰有预测作用，在这项研究中发现珠蛋白和尿酸增加了ApoB/apoA-1的预测价值，但血糖却没有这样的作用。来自Framingham 心脏研究分析证实了血脂异常是HF的独立预测价值。一项包括534名患者的Framingham的心脏研究中，评估了射血分数下降心衰患者与射血分数正常心衰患者危险因素之间的差异，在多变量分析中发现，有左束支传导阻滞与心肌梗死病史的患者，发生射血分数下降心衰的概率减少(odds ratios：0.21 and 0.32, respectively)。而房颤，女性，收缩压升高这些因素，发生射血分数正常心衰的概率增加。不考虑射血分数下降心衰与射血分数正常心衰之间的差异，中位生存期为2.1年，死亡率令人失望，在未来几年心衰危险因素的研究将变得重要，研究方向可能从冠状动脉疾病合并心力衰竭研究转为心力衰竭危险因素的研究。^{123}I-MIBG心肌显像被证实在HF预测中有效，但这些检测设备昂贵，广泛应用的可能性极低，特别是在心血管造影应用增加的情况下。在没有先进的心血管造影设备或者心脏运动试验的地区，采用修正后的Naughton踏步机预测心衰患者的死亡率是相当好的，运动时间1分钟的变异，其死亡风险增加7%。

生物标志物

越来越多的生物标记物被发现，目前正研究努力从单一的危险因素预测标记物发展到联合的预测因子。新的生物标志物，需要显示的不仅是独立的危险因素。心房钠尿肽其价值日益增加。最近一项关于传统的生物标志物肌钙蛋白T，B 型利钠肽（BNP）和C-反应蛋白的分析表明两个生物标志物的结合使用进行风险预测优于单一生物标志物。虽有大量关于如何将多种生物标志物运用于实际的研究，但没有就生物标志物直接运用上达成共识。因此，一个生物标志物被整合到客观的临床预后评分系统中，可能会减少对相对主观的症状及NYHA心功能分级的依赖。正如BATTLESCARRED（NT-pro BNP的辅助治疗，以减轻心脏病再入院和死亡）试验和REDHOT（快速心力衰竭急诊实验）的中性结果所证明的。

病理生理学

Tang and Francis 所述，miRNA在心肌疾病发展介导的基因表达中扮演着复杂而重要的作用。来自van Rooij的实验表明，3个肌球蛋白基因，Myh6，Myh7，和Myh7b，编码相关的内含子miRNA，可反过来控制肌球蛋白含量、肌纤维的识别和肌肉性能。正如Williams所述，进入转录过程的融合miRNA扩大了肌肉细胞中基因调控的精度与复杂性。因为一个miRNA可以调控数百个mRNA,而一个mRNA也可以被数百个miRNA所调控。另一个例子表明，心脏的正确功能取决于肌球蛋白重链（MHC）蛋白质Myh6（MHC）和Myh7（MHC）的表达。心肌损伤中成人肌球蛋白基因Myh6的表达下降，而胚胎肌球蛋白基因Myh7的表达增加。Williams等总结，关于不同形式的人类心脏疾病的miRNA全球分析表明，miRNA的表达针对不同形式，对相关的心脏疾病有诊断意义，如扩张型心肌

病，缺血性心脏病及主动脉瓣狭窄等。在这方面，基于miRNA的诊断可能是作为确定具体形式的心脏疾病和疾病进展手段。

遗传学与基因组学

在一项包括白种人以及非裔美国人2000人的前瞻性队列研究中，Cresci发现肾上腺素受体-1和一种终止其信号的蛋白激酶（GRK5），显著影响HF的预后。调整这些基因变异使β受体阻断剂对HF生存率的治疗效果不存在差异。在一项回顾性研究中，受试者参与有关HF亚组的遗传风险评估的A-HeFT 试验，作者报道了有等位基因I555的非洲裔美国人收缩期心肌运动功能失调的药理学相互作用。这种等位基因几乎只存在于非洲人种，并假定其破坏了BNP的合成。在这项尚未被重复的研究中，该等位基因的杂合体受试者，HF入院治疗的死亡风险比非杂合子更高。在A-HeFT 亚组研究里，已接受神经激素拮抗剂的受试者中，固定剂量的硝酸异山梨酯和肼苯哒嗪药物治疗可以减轻这种风险。Matkovich等展示出的准确而实用的测序，以确定以前未知的罕见基因变异，比较在不同人群中表达的多态性，确定心脏信号子基因组，HSPB7多态性和偶发收缩期心衰之间的新关联。这一见解的重要及潜在的准确性可能为探寻HF综合征的差异铺平了道路。许多目前归类为特发性或继发性心肌病的心肌炎遗传基础的证据正不断增加，正如发现扩张型心肌病与新的基因突变有关。快速发展的基因突变知识使基因筛查与咨询的重要性日益受到重视。Lakdawala等进行了一系列连锁的多代同堂家庭间的研究，报道了一种新型α-肌球蛋白基因的致病性错义突变。值得注意的是，体外功能分析D230Nα-肌球蛋白基因突变的钙处理显示了相反的效果，这导致扩张型心肌病以及D175Nα-肌球蛋白基因突变，从而导致肥厚性心肌病。另有三项今年发表的遗传研究确定了新型扩张型心肌病基因。Brauch 等人确定了在结合基序蛋白20 RNA 的9号外显子上的错义突变。Moulik 等人确定了在编码的心脏锚蛋白重复蛋白的ANKRD1突变。Hassel 等确定了编码nexilin（一种新型的蛋白质Z -盘）的NEXN突变。第四个基因的研究发现HF和调节钾的基因KCNE1的单核苷酸多态性之间的关联，之前被认为与心房纤颤有关。

心力衰竭的药物治疗，今年见证了正处于探索阶段的醛固酮拮抗剂在HF上的作用。对临床上有轻度至中度稳定心衰症状和射血分数正常心力衰竭（HFREF）的患者，可使用依普利酮（Eplerenone）治疗。Bansal 等提出了一个有说服力的观点，即对常规使用的袢利尿剂抵抗的患者，应用高剂量醛固酮拮抗剂。对于容量负荷过重的失代偿期或晚期患者，醛固酮拮抗剂（螺内酯50毫克/天）可能是一种选择。醛固酮拮抗剂的竞争利钠反应与肾素-血管紧张素-醛固酮系统相关，较高的肾素-血管紧张素-醛固酮系统活性，就需要较高剂量的醛固酮拮抗剂。

亚急性心肌梗死心力衰竭的疗效与生存分析的研究表明，依普利酮（Eplerenone）较早应用于治疗心肌收缩功能异常性的心力衰竭7天内是安全的，但在用药7天后未能观察到的更好的疗效。期待EMPHASIS-HF（依普利酮与安慰剂在NYHA分级2级的慢性收缩性心力衰竭入院患者治疗的死亡率的比较）可以界定出可能受益于醛固酮拮抗剂的患者的范围。HEAAL（高剂量与低剂量的氯沙坦对心衰患者临床疗效的对比）的研究表明，氯沙坦150毫克/d相比氯沙坦50mg/d，可减少左室射血分数小于40％的心衰患者的入院率和死亡率，并减少不耐受的血管紧张素转换酶（ACE）抑制剂的发生。这些研究结果证实了上调血管紧张素受体阻滞剂的临床价值。FAIR-HF（Ferinject 评估铁缺乏与慢性心衰的患者）的实验表明，采用静脉注射三氯化铁是有缺铁的慢性心衰患者的疗法。

非药物治疗

研究者一直寻找着治疗睡眠呼吸暂停综合征与心力衰竭的方法。Gottlieb 等一项前瞻性随访研究中，对40岁及更老的患者，用多导睡眠监测没有心脏冠状动脉疾病和HF的1927男子和2495名女子，多种危险因素显示，阻塞性睡眠呼吸暂停是冠状动脉疾病的一个显著预测指标，但仅限于70岁以下男士。Kasal等人指出，相对于持续气道正压治疗来说，伴有潮式呼吸中枢性睡眠呼吸暂停的患者可能从流量触发的自调节伺服通气（servo ventilation）治疗中获得更大的好处。Gottlieb 等指出在稳定的HF患者中，夜间BNP改变与严重夜间低氧血症有关，而与睡眠呼吸紊乱发作或相关的觉醒的频率类型无关。Yumino等提出了一个新观念，认为夜间延髓头端液体转向（nocturnal rostral fluid shift）是造成心衰患者的阻塞性和中枢性呼吸暂停的发病机制。夜间延髓头端液体运动的幅度与睡眠呼吸暂停及其主要类型有关。这种液体的转向与下肢浮肿的程度以及坐位休息时间直接相关，而与体力活动的程度呈负相关，这为日后治疗措施提供了一些可能的线索。

远程病人监护可降低心衰病人反复入院引起的社会成本的增加，美国与欧洲指导委员会鼓励使用远程病人监护仪，通过外部或内部植入式监护设备使用结构化的电话通信和传输生理参数的电子传送装置。Meta分析最新证实，这种方法可以降低死亡率和住院率。对DIAL（慢性心力衰竭患者电话干预的随机试验）后续研究的结论表明即使在电话干预结束后，心衰患者的入院率仍持续按年减少。2个关于用植入式设备评估患者的胸阻抗监测的研究发现，胸阻抗的显著减低与随后的心衰入院率的关联有统计学意义。医生指导患者自我监测的观念可明显改善NYHA心功能分级，左心室射血分数，上调ACE抑制剂和β-阻断剂，减少每天两次袢利尿剂的使用剂量。

心脏移植

心脏移植术后生存期不断改善，如何取代目前心内膜心肌活检这个金标准，并使成本合理和监测方法准确一直是研究的热点问题。两项研究结果显示，外周血标本基因表达分析和心脏磁共振成像是急性移植排斥反应无创诊断或确诊的有力工具。

机械辅助装置

关于病人对合适的机械循环支持和左心室辅助装置植入最佳时间的选择的争论仍在继续。对几个风险评分系统进行了多变量分析显示，西雅图HF模型和APACHEⅡ评分可更好地预测1年死亡率。INTERMACS Coordinators' Council确定了临时机械循环支持的入院患者与有静息症状在家的患者有差异，修正了2个文件并定义了新的修饰词，1个是针对医院的临时辅助循环装置，1个是针对在家的病人再入院频率。而Stewart注意到辅助设备置入患者的左心室阈值与生存率之间的关系，结果是可喜的。对105例有射血分数正常心力衰竭病人的采访中显示，当预期死亡时间在6至12个月，活动力小于一个街区时，多数考虑接受左心室辅助设备。Heart Mate II关于左心室辅助设备作为移植研究的过度的研究报道了连续流动左心辅助装置植入1至6个月内的肝和肾功能变化。针对不符合移植要求的人群的随机对照试验，对比了脉冲流动装置（Heart Mate XVE）与连续流动装置（Heart Mate II），结果表明连续流动设备在生存率增加，生活质量、锻炼能力和设备的耐用性方面更优越。HeartMate左心室辅助装置被美国食品和药物管理局批准为对症治疗方式。然而，随着随访时间的增加，有越来越多的证据表明连续流动的再出血（胃肠及脑血管）风险增加，也许是存在动静脉畸形及血管性血友病的病理基础有待进一步研究。

新型疗法

一些新的治疗方法，如针对性的心肌钙处理，包括AAV1/SERCA 2a的CUPID实验，人重组neuregulin-1输液，日益凸显了一个概念，那就是肌力获益取决于增加收缩力的机制，区别于肌力通过磷酸二酯酶抑制剂所带来的长期恶化影响。由于大量结果一致的实验显示了ACE 抑制剂对HF的疗效。众所周知，血管紧张素转化酶Ⅰ是一个膜结合的锌指蛋白，是血管紧张素Ⅰ向血管紧张素Ⅱ转变，独立的肥大细胞对血管紧张素Ⅱ的ACE识别系统提示长期应用ACE抑制剂可能无法完全抑制血管紧张素Ⅱ的产生，通过激活血管紧张素Ⅱ受体亚型1和2，可能会造成不良的左室重构。糜蛋白酶、血管紧张素Ⅱ形成的丝氨酸蛋白酶主要是在肥大细胞和人类的心脏发现，也见于心脏间隙。wei等使用小鼠和仓鼠模型的实验表明，糜蛋白酶抑制显著减少左心室组织间液空间血管紧张素II水平表明肥大细胞糜蛋白酶在调节心脏血管紧张素Ⅱ水平的重要性。这些结果表明，糜蛋白酶抑制剂可能是一个除了ACE 抑制剂在治疗HF上有益的选择。

心肾综合征

无论是从机制上还是临床上，更完全的阐明心肾间的相互作用仍然是该领域的重大挑战，Bock和Gottlieb 回顾总结了问题的存在范围和复杂的病理生理机制。在临床上，2个回顾性亚组分析的意见发人深思的。第一，使用的数据COACH（心力衰竭咨询和辅导的统筹研究成果的评价），得出的结论是急性心力衰竭从入院任何时间起肾功能恶化，12个月内的随访再住院或死亡的风险增加。第二，回顾性研究分析表明，急性心力衰竭受试者在治疗过程中遇到血液浓缩和接受高剂量袢利尿剂，有更高的肾功能恶化率，而180天的调整死亡率则下降。显然，还没有掌握导致肾功能的变化或肾功能改变时如何预测哪些病人死亡风险增加的心脏和肾脏之间复杂的相互作用。最后，肾功能恶化在这些研究中的混杂因素是不一致。在这方面的大型的前瞻性临床试验是迫切需要的。

心律失常和心力衰竭治疗设备

REVERSE MADIT-CRT 研发正在进行，在这两项研究中观测的超声心动图表明，在NYHA心功能分级I和II患者，逆转结构和功能重构的心脏再同步化治疗（CRT）出现关联结果。期待着RAFT（动态再同步除颤心脏衰竭实验）结果进一步证实心脏再同步化治疗可能给予NYHA心功能II级和III级患者的生存获益。Mishkin等报道在ICD除颤器后的进展性HF的随诊和管理十分必要，因为心源性猝死的风险转变成增加了心力衰竭事件发生的风险。Kanoupakis 指出胶原蛋白血清标志物可以用在ICD接受者心律失常事件的预测。在研究心衰住院的医疗保险受益老年人的心脏除颤器的临床效果，使用ICD心脏除颤器显著降低死亡率的相对风险度超过3年。继发于左心脏疾病的肺动脉高压在需要随机临床试验评估可用的，包括内皮素受体拮抗剂，磷酸二酯酶-5抑制剂和前列腺素治疗的情况下仍是一个问题，证据依然缺乏。

围产期心肌病随机试验研究表明，标准HF治疗联用溴隐亭，与标准治疗相比，显著提高6个月内射血分数，NYHA心功能分级和生存率，且无良副作用。期待这个有前景的新疗法的大型临床试验在未来几个月内出现。

中华医学会第十二届全国儿科危重症大会

中华医学会儿科分会急救学组、中华医学会急诊分会儿科学组暨《中国小儿急救医学》杂志将于2012年11月2～5日在重庆市召开“中华医学会第十二届全国儿科危重症大会”。

征文要求：（1）凡未在国内刊物上公开发表的论文均可投稿，优秀论文将在《中国小儿急救医学》杂志上优先发表；（2）请寄1000字以内结构式摘要，应包括目的、方法、结果、结论四部分。首页请写清论文题目、作者姓名、工作单位、详细地址、邮编、手机号码或联系电话、Email地址。投稿方式：本次会议只接收电子邮箱投稿，征文请发至《中国小儿急救医学》杂志编辑部电子邮箱，邮件主题请注明“儿科危重症大会征文”字样。 截稿日期：2012年8月31日。

联系方式：《中国小儿急救医学》杂志编辑部联系电话：024-23926295，联系人：吴繁。Email：xejjyxzzh@yahoo.com.cn

郭冰 韩金玉

天津医科大学附属肿瘤医院

摘要

随着计算机技术的发展，靶控输注（target controlled infusion,TCI)系统已在临床麻醉中广泛应用。80年代初由Schuttler[1]首先报道，在1990年由Kenny和White改进[2]。TCI系统现已发展成为一种通过靶控输注来输送镇静催眠药、阿片类药及其他类麻醉药的标准输注系统。现今，TCI技术已经变成麻醉从业人员的一项常规麻醉技术。现将靶控输注在临床麻醉中的应用进展概述如下

关键词：靶控输注；静脉麻醉

责任作者及联系方式：郭冰,E-mail:hanjinyu1199@sina.com

靶控输注在临床麻醉中的应用进展

Target-controlled Infusion in the Application Progress of Clinical Anesthesia

Bing Guo, Jin-yu Han

Tianjin Medical University Affiliated Cancer Hospital

Abstract

With the development of computer technology, the target control infusion (target controlled infusion, TCI) system has been widely used in the clinical anesthesia. It was first reported At the beginning of the 80s by Schuttler [1], and improve in 1990 by Kenny and White [2]. TCI system has become a kind of standard infusion system which through the target control infusion for covering sedative-hypnotic medicine, medicine and other kind of opiates drug. Today, TCI technology has become a routine anesthetic techniques for anesthesia workers. Now overview the progress of the target control infusion in clinical anesthesia application as the following.

Key Words: Target control infusion; Intravenous anesthesia

Corresponding Author：Bing Guo，E-mail: hanjinyu1199@sina.com

一、靶控输注的定义

靶控输注(TCI)是以药代动力学和药效动力学理论为基础,以血浆或效应室的药物浓度为指标,由计算机控制给药输注速率的变化,达到按临床需要调节麻醉、镇静和镇痛深度的目的。计算机的参与使复杂的运算变得简单易行，在给药的同时可以显示目标血浆药物浓度、效应室药物浓度、给药时间和累积剂量等。应用TCI麻醉医师可以像开闭吸入麻醉挥发罐一样自如地控制静脉麻醉深度,即方便又可以提高静脉麻醉的控制水平[3-6]。

二、TCI的原理

TCI的核心为控制算法，理论基础是药代动力学。静脉麻醉药多采用经典的3室药代动力学模型，其微分方程较为简单，可用解析方法求出输注方案[8-10]。生理药代动力学模型因其高阶次、非线性等特点，求解算法还处于理论研究阶段[11]。

输入TCI系统的药代动力学数据首先从大量的临床测量中获得，包括诸如年龄、性别、体重等。这些数据来自于广泛的不同病人群体，随后被预先设定到一个药代动力学模型里，作为计算机程序的一部分，该程序可描述药物在体内的分布及清除[12]。TCI系统用这些数据信息来预测血药浓度。用于麻醉诱导及维持的药物靶部位浓度由麻醉医师输入到TCI系统。通过其药代动力学模型，TCI系统决定了需要达到设定靶部位浓度的初始给药量以及给药速率，从而完全自动化地控制静脉输注。

由输注泵控制的所用药物的药代动力学系统允许使用者调节血浆靶浓度。药物经血液流至效应室，在那里药物以活性形式存在[13-15]，并发挥药效。药物在机体内的运转规律相当复杂，数学方程只是近似地表达药代动力学过程。

大多数TCI系统的输注方式都是开环式的，在这种模式里，病人的反馈信息不能经输系统自动分析，需麻醉医师评估病人接下来所需的靶浓度。而闭环模式的药物输注是系统自动评估实时监测的病人信息。复合双频谱指数(Bispectral Inedx，BIS)和平均动脉压（Mean Artery Pressure，MAP）等，经计算机分析判断镇静深度，再对TCI泵发出指令控制药物输注速率。Fernando Squeff Nora[16]认为复合BIS和MAP监测，应用靶控输注静脉麻醉药有利于维持满意的麻醉并减少药物的应用。用BIS自动控制意识在临床上优于人工控制[17]。

三、影响TCI性能的因素

1. 机械因素

现有的输注泵由于机械惯性的原因，瞬时流量误差常随时间出现积累。随着计算机运算速度的不断提高，硬件造成的误差已非常小。

2. 药代动力学模型参数

TCI系统内嵌药代动力学参数是影响TCI系统性能的重要因素。由于系统内嵌的药代动力学参数多来自于群体，与个体之间存在着差异，故可导致预期血药浓度和实际血药浓度出现一定差别。此外，群体药物动力学(PPK)的估算方法也

能影响到TCI系统的性能。药代动力学变异存在于药代动力学分析的全过程及个体间.Mertens等[18]研究了5种瑞芬太尼群体药物动力学参数TCI系统的准确性，结果5种参数所得出的各评价指标均不相同，组间具有统计学差异。

3. 药物相互作用

由于药代动力学和药效学的相互作用，复合应用不同静脉麻醉药TCI系统的性能也会不同。麻醉药物之间的药代动力学相互作用可能是通过血流动力学变化引起的药物分布或清除的改变、药物与蛋白结合的改变、酶诱导或抑制引起的药物代谢改变这3种途径而产生。由于药代动力学和药效学的相互作用，TCI过程中设定的目标浓度受所使用的辅助药物的影响。Hoymork等[19]发现复合异丙酚和瑞芬太尼TCI给药时，TCI的性能变化较大，瑞芬太尼和异丙酚的执行误差(PE)分别是22%和49%。

4. 血药浓度检测

色谱技术是检测血药浓度的常用方法，常用的有气相色谱和高效液相色谱。色谱法的特点为分离度好、灵敏度高、专属性强。放射免疫法也是测定血药浓度的常用方法，其特点是灵敏度高、特异性强、取样量及消耗试剂量小、比较快速、受检者不接受同位素照射、工作效率高、适于批量测定。另外，动脉和静脉血药浓度存在一定的差异，评价TCI系统的性能以动脉血药浓度更加敏感。

5. 其他因素

年龄对TCI系统有重要影响，不同年龄的人群有着不同的药代动力学模型。比较意识消失所需的丙泊酚靶浓度，在50%病人中40岁较20岁病人降低约为40%[20]。从20岁以后，意识消失所需的效应室异丙酚靶浓度每10年下降0.24ug/ml[21]；手术刺激增加机体的应激反应，使血流动力学发生改变从而影响药物的代谢;低温使心输出量降低，肝脏血液灌注量下降，从而降低药物的清除率及房室间的转运速率;大量或快速输液可增加循环血量，使肝脏血流灌注增加，可能会增加药物的清除率，缩短血浆浓度的半衰期。患者以丙泊酚2.4ug/ml效应室靶浓度靶控输注时，急性高容量血液稀释可加深镇静深度，当效应室靶浓度升为6ug/ml时，对其镇静深度无明显影响[22]。女性的药物清除率和分布容积较男性大，有研究提示女性比男性需要更大剂量的异丙酚用于麻醉诱导和维持[23-24]，但也有研究表明异丙酚的药代动力学在性别上没有差异[25]。慢性酗酒者在丙泊酚的药代动力学上只有轻微的改变，但是，在麻醉和手术中或者是苏醒期睁眼后，丙泊酚的药代动力学有明显的不同[26]。

近几年中，对TCI系统影响因素的探讨逐渐深入。TCI的发展方向之一是提供尽可能准确的药代动力学模型。此外，由于TCI技术的优势并不在于实测血药浓度与预期血药浓度绝对相等，而在于实测药物浓度与预期药物浓度保持平行，可以根据实际临床需要成比例地调整目标药物浓度。只要系统偏离性 < 15%，绝对误差 < 30%，即可应用于临床麻醉。

四、靶控输注的应用

1. TCI与镇静催眠

静脉麻醉药用于麻醉维持，需要了解麻醉药产生意识消失的血药浓度、以及理解这些药物的药代动力学，同时还要了解药物代谢产物是否具有催眠作用。现国内已有咪达唑仑的靶控输注(TCI)系统，但所用计算机程序内嵌入的咪达唑仑药代动力学参数均为国外标准，是否适用于国人尚有待进一步研究。徐波等[27]采用反相高效液相法测定咪达唑仑血药浓度，将其算出的药代动力学参数嵌入TCI系统，评价该系统的精确度和稳定性较好。麻醉中可根据手术刺激大小与病人的反应进行调节。脑药效学的反馈可以帮助麻醉医师来调节靶浓度并减少个体间的差异，而BIS则可以充当这一反馈信号[28]。

在有自主呼吸病人的镇静中，比起单独注射丙泊酚，联合应用丙泊酚和瑞芬太尼在结肠镜检查中能提供更好的条件[29]。Irwin等[30]将TCI技术和病人自控镇静技术结合起来进行研究，研究发现平均0.85ug/ml的靶浓度就可以提供满意的镇静效果，但个体间差异很大。这种病人自控镇静系统并不能保证对所有病人提供镇静，因此麻醉医生仍有必要进行仔细的临床观察以确保病人的安全。

2. TCI与镇痛

利用TCI技术给予阿片类药物进行术中镇痛已经有许多研究。研究表明，联合丙泊酚和瑞芬太尼TCI麻醉诱导时，预先给予靶浓度为4ug/ml的瑞芬太尼能减少输注丙泊酚而引起的剧烈疼痛，而且是安全的，这种方法能为病人提供一个舒适的条件[31]。Gregory Slepchenko等[32]研究表明取自正常人的舒芬太尼药代动力学参数能准确地预测病态肥胖病人的血浆舒芬太尼的浓度。术后利用TCI技术输注镇痛药可为病人提供一个合理的方法来延续术中的镇痛效应。TCI技术在某种程度上，能克服持续输注所伴随的缺点，病人能够在术后自己调控止疼方案。

3. TCI与肌松

神经肌肉阻滞程度的控制在临床麻醉中一般有两大问题。一是机体对肌松药的反应个体差异很大，而引起这差异性的原因尚未明了，也没有可靠的方法在用药前评估个体对肌松药的敏感性。二是临床麻醉中传统的应用肌松药的方法常导致神经肌肉阻滞程度大幅度波动于过度抑制和抑制不足之间。过度抑制是对机体生理不必要的干预，抑制不足又满足不了手术需求。靶控输注根据药代动力学给药，又可以根据反馈指标以秒为单位进行调整，并在靶控期间维持该肌松水平恒定。用计算机对维库溴铵进行靶控输注的临床效果要优于传统的间断单次静脉给药方式，实际肌松水平更接近设定水平，肌松波动范围小，用药量和恢复时间与传统间断给药方式相比没有差别，且没有蓄积效应[33]。与静脉输注比较，TCI维库溴铵可减少工作量，术后肌松恢复较快[34]。目前TCI肌松药系统尚存在一定问题，计算机不能识别术中应用电刀对肌松监测产生的干扰值，会造成不必要的给药调整。目前国外已经出现抗电刀干扰的软件，而且在程序中加入了误差识别，使计算机对干扰出现的非实际肌松值不做反应，而且出现了便携式肌松靶控系统，方便了临床应用。

4. TCI在小儿及老人的应用

近年来，TCI在国内、外已成为丙泊酚用药的主要方式，并已扩展到小儿麻醉。然而，国内用于小儿麻醉的TCI系统内嵌的丙泊酚药代动力学参数均套用成人或来自于国外小儿，由于存在种族、年龄等因素影响，是否适用于中国小儿尚待研究。在国内可供小儿丙泊酚靶控输注的思路高TCI—Ⅲ系统已经上市，它是根据国内儿童药动学特点，参考了国外小儿用 “Paedfusor”[35] 模型设置了“Pediatric模型”，用于小儿丙泊酚靶控注射，但其在临床应用中的性能尚无定论。研究表明，儿童所有异丙酚药代动力学参数经过体重标准化后均大于成人[36]，提示儿童的药代动力学参数与成人存在明显差异，且参数的个体差异明显[37]。比起成人，孩子要用更大的靶浓度来达到同样的镇静程度[28]。

高龄病人进行丙泊酚TCI时，如果加深麻醉，增加Ct（靶浓度）后，需较长时间才能达到相应麻醉深度，应避免Ce（效应室浓度）与Ct尚未达到一定程度平衡而进一步增加Ct引起过深的麻醉。老年高血压患者在丙泊酚靶控输注复合瑞芬太尼诱导期间血压较其非高血压组波动更加显著， 但是其波动性仍在可接受范围内， 该方法用于老年高血压患者全麻手术诱导安全、有效[38]。用TCI诱导时，丙泊酚效应室浓度在（1.9±0.3）μg/ml时也许可以使老年病人无意识。瑞芬太尼效应室浓度 4.0ng/ml加上丙泊酚效应室浓度 （2.8±0.3）μg/ml 可以提供合适的诱导水平。比起三步TCI技术（初始靶浓度为2ug/ml，然后每三分钟增加1ug/ml,直到血浆靶浓度为4ug/ml.）和无阶梯式TCI技术（直接接受4ug/ml的丙泊酚靶浓度），两步TCI技术（初始靶浓度为2ug/ml，三分钟后再加到4ug/ml）似乎更适合于老年人的诱导[39]。

五、TCI系统的优势与不足

在临床实践中，最佳的麻醉条件是药物在中枢神经系统内(实际上是效应室）的浓度是稳定的，而这依赖于稳定的血药浓度。由于药代动力学特征的复杂性，麻醉医师不能知道所应用药物的确切血药浓度及效应室浓度。TCI系统的数学运算法则能持续的自动计算静脉麻醉药物的分布及清除，而且能成功地调节输注速率来维持预设的血药浓度。比起手控输注系统，TCI能使血药浓度持续得到控制，更好地控制药物浓度及麻醉深度。TCI-设备也能使麻醉药物的使用依据其各自的药代动力学类型，而不需要由麻醉师进行复杂的计算。

TCI系统的目的是迅速达到一个靶浓度并维持其平衡，具有麻醉诱导平稳、系统易于操作的特点，使患者血流动力学稳定，呼吸抑制轻，麻醉药用量少，消除了因分次静脉给药使血药浓度产生较大波动的不足，患者苏醒快并可预测，增加了静脉麻醉的可控性。比起手控输注瑞芬太尼，TCI瑞芬太尼能减少丙泊酚的用量，仅有很低的窒息和呼吸抑制的发生率[29]。在房颤消融术中应用靶控输注全凭静脉麻醉是一种很好的选择，因为它能速麻速醒，这样有利于神经功能的立即评估[16]。

TCI系统独特的特征是能根据人口统计学，生理，及疾病状态这些变量（即病人的特点）来修改药物的分布。比如，一个已知的药代动力学研究表明年龄、体重、性别影响药物的清除或分布，这些影响因素可以被设入这个药代动力学模型而应用于TCI系统。如果生理学的变量是已知的（如肝肾功能）或是疾病状态（比如充血性心力衰竭）其也能被设入到模型里。由此可见，TCI模式代表了近年国内外静脉麻醉给药系统的发展趋势。

但是当一个变量改变一个药代动力学参数时，用计算机输注泵来完全调节这一变量因子是不可能的，因为变量以一种很复杂的方式影响着剂量方案，这是TCI系统明显的不足之处。

全麻诱导中常用的效应室靶控输注模式是根据预设的靶浓度将诱导药物以1200ml／h的速度零级输注(Flash 模式)，其诱导过程迅速，但不可避免产生血浆药物浓度的超射，可能导致患者血流动力学波动，增加麻醉诱导的风险[40]。李钊等通过与常规效应室TCI诱导的比较，评价异丙酚分步效应室TCI(药物效应室浓度分1→2→3ug／ml三步达到)诱导模式在妇科腹腔镜手术患者全麻诱导中应用的效果,结果显示异丙酚分步效应室TCI诱导模式对血流动力学的影响较轻，可安全有效地应用于全麻诱导[41]。

尽管现在的计算机控制输注泵既精致又精确，但是比起调节吸入麻醉罐仍显不足。因为目前的技术仍然不能做到实时监测静脉麻醉药物的血药浓度及药代动力学的变化，虽然Cyrill Hornuss[42]等报道认为应用离子分子型反应质谱分析仪也许能持续且无创地监测全麻时病人呼末丙泊酚水平，但目前尚未应用于临床。即使经临床采样可测量静脉麻醉药的浓度，其参考值的意义仍然很模糊。静脉麻醉药的药代动力学常用Cp50来描述。Cp50是指防止50%病人对伤害刺激产生反应的血浆药物浓度。但这个概念没有考虑到血浆与效应室之间的延迟，在两者浓度达到平衡以前，Cp50有很大程度的误差。由于界定Cp50的方法还没有像界定肺泡最小有效浓度（minimal alveolar concentration,MAC）那样完全标准化（一些Cp50和意识的消失有关，有的和运动及血液动力学有关，有些则是在有其他一些药物存在时估算的），怎样将静脉麻醉药Cp50应用于TCI目标的选择对于麻醉技术来说还没有被很好的定论。类似于“MAC”的静脉药物参数的彻底性研究现在还没有完全得到发展。现在很多医生还不习惯于考虑静脉麻醉药的合适靶浓度而是更多的考虑合适的输注速率。

通过计算机控制输注泵进行药物的输注要求操作者了解不同的知识库如药理学、生理学等，而不是基于临床经验和文献的建议来设定输注速率。因此成功地应用计算机控制输注泵要求使用者依据合适的治疗浓度进行思考而不是合适的输注速率。

六、TCI的发展前景：

药代模型的生理化：高速运算的计算机可以更精确地模拟人体内的药代动力学变化，对多变量的数学模型也能轻松处理，因而在预测浓度的精确性上有很大提高。此外，能够

通过计算机的升级来改善用非房室的药代模型通过多次迭代运算的准确性。

输液泵的便携化：随着病人自控概念的深入，更加需要实现TCI的便携性。正如Diprifusor将控制软件整合到输液泵中。TCI系统的小型化和便携化是其发展的另一个趋势。

控制系统的自动化：设定靶浓度后，TCI能自动达到并维持稳定的靶浓度，但是临床麻醉深度及手术刺激的改变需要不断调整所设定的浓度，目前的TCI系统却不能完成这项工作。如果效应信息能反馈给靶控系统并自动完成浓度的调节，即可形成所谓的闭合环路麻醉。效应信息的来源有两个：一是药物效应，如用BIS或MAP作为反馈信息形成闭合环路麻醉；二是药物浓度，目前的浓度监测还不能对静脉麻醉药的血药浓度进行实时测量。但是随着生化技术的发展，静脉麻醉药有望像吸入麻醉药那样做到随时监测体内的即时浓度，并通过药物浓度来控制麻醉深度。

除了在麻醉中的临床应用以外，TCI作为一种研究工具将在麻醉时评估药物间相互作用方面及围手术期镇静、镇痛药物应用等新的控制技术的发展中发挥重要作用。

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2012年全国危重病学术交流会

2012年全国危重病学术交流会拟定于2012年8月在广东省广州市召开，会议由中国中西医结合学会急救医学专业委员会主办，广东省中医院承办。现将征文事宜通知如下：

征文要求：1.全文在3000字以内（须附400字中英文摘要，包括目的、方法、结果、结论）。要求标点符号准确，著者顺序排列。请自留底稿。2.投稿采用Word文档格式，以电子邮件发出，并于发出后72小时内确认是否收到。

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联系方式：联系地址：广东省广州市大德路111号（邮编510120）

广东省中医院急救中心联系人：罗翌 电话：15918448626 E-mail：lyzmbb@qq.com

叶烨 电话：13434158860 E-mail：zhxyjh2012@126.com

尹灵子 岳云
首都医科大学附属北京朝阳医院麻醉科 北京100020

摘要

本综述将重点介绍术后慢性疼痛的流行学定义；分别描述不同手术类型术后慢性疼痛的发生率；阐明术后慢性疼痛发生的可能机制并大致介绍目前一些预防性的治疗措施。

关键词：术后；慢性疼痛；发生率；预防措施

术后慢性疼痛发生率及预防性措施

Incidence and Protective Factors of Chronic Postsurgical Pain

Ling-zi Yin, Yun Yue
Department of Anesthesiology, Beijing ChaoYang Hospital, Capital Medical University, Beijing, 100020

Abstract

Most patients who undergo surgery recover uneventfully and resume their normal daily activities within weeks. Nevertheless, chronic post-surgical pain develops in an alarming proportion of patients. In this review, the epidemiology of chronic post-surgical pain is reviewed. Different surgerys involve different incidence which is higher than expected. The surgical, psychosocial, genetics, and patient-related factors confer greater risk of developing chronic post-surgical pain. The pain syndromes associated with many individual types of operation is discussed briefly. Evidence is then reviewed for a preventive multimodal analgesic approach to surgery. While there is some evidence that chronic post-surgical pain can be minimized or prevented by an analgesic approach involving aggressive perioperative multimodal treatment, other studies fail to show this benefit.

1989-1992年期间，英国的研究人员大规模调查了国内10所医院因慢性疼痛就诊的5130名患者，结果发现这些患者中有大约20%的患者其慢性疼痛是由手术发展而来。这项调查结果瞬时引起了社会各界的广泛关注，此后越来越多的人开始研究术后慢性疼痛。术后慢性疼痛的发生率随不同手术类型而变化，其表现也各不相同，除疼痛外常伴有其他感觉异常。它的危险因素包括年龄，性别，肥胖，手术操作，心理因素，术前持续疼痛等。研究者其发生机制有很多研究，包括急性痛向慢性痛的转化，中枢神经痛觉敏化，外周神经系统病理性改变，最新研究发现术后慢性疼痛的发生有遗传倾向，可能与多核苷酸多态性有关。尽管它的机制尚未明确，但已有许多研究证明预防性的治疗措施可以明显降低它的发生率并减轻疼痛的程度。术后多模式镇痛是一种发展趋势，已经有研究证实在胸科手术，乳腺手术后使用多模式镇痛方法可以很大程度的改善术后慢性疼痛的发生率并提高患者术后生活质量。以下将具体介绍术后慢性疼痛的流行学定义；分别描述不同手术类型术后慢性疼痛的发生率和影响因素；阐明术后慢性疼痛发生的可能机制并介绍目前有关术后慢性疼痛预防性措施的研究。

一、术后慢性疼痛的定义

目前将长期无法解决的疼痛或者在一定时间段内如3-6个月内不能治愈的疼痛定义为慢性疼痛[1]。但这不足以定义术后慢性疼痛，它有其特殊的附加条件。在许多病例中，术后疼痛是一种新的症状，如胆囊切除术中损伤神经，术后会出现与术前因胆囊结石引起的疼痛完全不同的疼痛并伴有其他感觉变化。但也有一些病例，尤其是术前存在与手术无关的疼痛的患者，术后疼痛就很难区分是术前疼痛的延续还是新出现的症状。因此为了明确术后慢性疼痛的定义，国际疼痛协会（IASP）有以下几条标准[2]：

1）疼痛是由术后发展而来；

2）疼痛至少持续2个月(研究者尤其质疑2个月的时间窗，一些手术后产生的持续炎症的病程可能超过2个月)；

3）必须排除其他原因导致的疼痛（如恶性肿瘤或慢性感染引起的疼痛）；

4）排除或解决术前疼痛延续为术后疼痛的可能性。

遗憾的是，目前的各种研究中关于术后慢性疼痛的定义是不严格的，它依然没有公认的明确统一的定义。

表1 不同手术类型术后慢性疼痛的发生率

研究者	手术类型	样本例数	随访时间	术后慢性痛发生率（%）	文献
Tasmuth et al. (1997)	MRM或BCT伴腋窝淋巴结清扫	90 MRM=53 BCT=40	1年	胸部区域疼痛MRM：17，BCT：33 上臂区域疼痛MRM：13，BCT：23	3
Aasvang et al. (2006)	疝修补术	694	1年	腹股沟疼痛:56.6 射精痛:18.3:	4
Gotoda et al. (2001)	开胸手术	91	1年	无痛:59 轻微痛:39 中度痛:2 重度痛:0	5
Nikolajsen et al. (2004)	剖宫产	220	~1年	腹部伤口痛:12.3	6
Richardson et al. (2006)	截肢术	52	6个月	幻肢痛:78.8 残肢痛:51.2	7
Borly et al. (1999)	开腹胆囊切除术	80	1年	疼痛:6	8
Meyerson et al. (2001)	心脏开胸手术	318	1年	术后疼痛：28 疼痛严重程度（>30/100）：13	9
Nikolajsen et al. (2006)	髋关节置换	1048	12-18个月	慢性髋部疼痛=28.1 中到重度痛导致活动受限:12.1	10

BCT: 乳腺癌保乳手术；MRM: 乳腺癌改良根治术

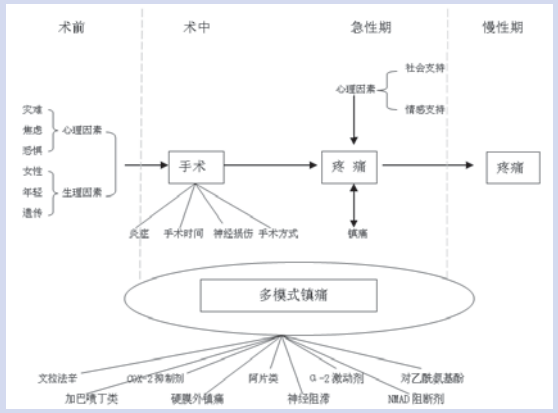
二、术后慢性疼痛的流行学调查

表1显示了不同手术类型术后慢性疼痛的发生率，它的发生率因手术而异，但无论手术大小，其发生率都是令人吃惊的。

三、术后慢性疼痛的危险因素

术后慢性疼痛的危险因素包括手术的类型，手术方式，躯体化程度，对疼痛的反应性，术前持续存在的疼痛，心理因素，年龄，性别，肥胖等。（图1示）

图1 术后慢性疼痛的危险因素



1. 乳腺切除术后慢性疼痛

乳腺手术不同的手术方法其术后疼痛的发生率大不相同，Wallace调查了乳腺切除术，乳腺切除后重建术，隆胸术，乳腺部分切除术后的患者，结果显示乳腺切除后重建术的疼痛发生率（53%）比单纯乳腺切除（30%）高出许多。

手术并不是导致乳腺切除术后慢性疼痛的唯一因素，Vecht等[11]调查了38名乳腺切除术后有上臂痛的患者，只有8名患者可以很明确的诊断其术后疼痛是术中神经损伤引起，其他患者的术后痛原因包括肿瘤细胞浸润臂丛神经，放疗，神经根型颈椎病，腕管综合征，肩关节炎等。这项研究还发现术后疼痛通常出现在术后几周内，而癌细胞浸润或放疗导致的疼痛往往平均延迟5年后出现。

此外，疼痛并不是乳腺切除患者术后唯一的症状，一项研究[12]调查了126名乳腺癌根治术伴腋窝淋巴结清扫的患者，其中有70%患者主诉胸壁麻木感，其余1/3患者分别主诉疼痛，无力感，上臂肿胀，僵硬，39%的患者认为上述症状影响日常生活。

2. 胸科术后慢性疼痛

肋间神经走行于肋骨下缘，外科医生开胸时会拉开肋骨或切除一部分肋骨，所以常常导致肋间神经损伤。过去的研究已证实许多严重的术后疼痛都是由局部受损的神经引起，因此

这种机械性损伤不可避免的会引起开胸术后的疼痛。表3总结了一些关于开胸术后慢性疼痛发生率的调查。

不同患者开胸术后疼痛的程度是大不相同的，80%的患者术后疼痛VAS评分在4-10之间。Matsunaga[13]等回顾性调查了90位开胸术后的患者，结果发现其术后慢性疼痛的发生率与术后急性痛期镇痛有很大关系。在这90位患者中，有32位患者在术后14天内每天要求术后镇痛，其中91%的患者6个月后仍存在疼痛。有45位患者术后没有要求镇痛，其术后6个月疼痛的发生率只有44%。而在另一项前瞻性调查中，Kakz等[14]发现开胸术后早期急性疼痛是术后慢性疼痛发生的唯一明确的危险因素。显然，术后急性疼痛与术后慢性疼痛的关联还没有明朗化，还需要更多的调查研究。

还有一些调查是关于不同开胸手术方式对术后慢性疼痛的影响，可惜大多数调查规模很小，就目前的研究没有有力的结论证明开胸方法与术后长期疼痛有关。胸腔镜术后慢性疼痛的发生率可能比开胸术后慢性疼痛发生率低，但也没有明确的证据。唯一肯定的是胸腔镜手术术后慢性疼痛的发生率依然很高。

3. 截肢术后慢性疼痛

截肢术后慢性疼痛的发生率是所有手术类型中最高的。截肢后的疼痛主要分为两种，即残肢痛和幻肢痛。残肢痛的发生率在不同研究中各不相同，Pohjolainen的研究显示残肢痛的发生率仅有5%，但Sherman等人通过调查美国退伍军人，

表2 乳腺切除术后慢性疼痛

研究类型	样本量	疼痛评估	随访时间	研究结果
调查	314 有效人数： 215	自述，VRS	16m-32y	幻觉痛36% 麻木39-78% 疼痛22-32% 感觉异常19-35% 感觉敏化23-34%
前瞻性研究	120 有效人数： 110（1y）	自述	1y	幻觉痛：3w 13% 1y 13% 伤口痛：3w 35% 1y 23%
前瞻性研究	120 有效人数： 110（1y） 69（6y）	自述	6y	6y后幻觉痛17% 6y后伤口痛31%
回顾性探究	467	VAS, VRS, MPQ	~9-58m	疼痛：49% 感觉异常：54%
调查	95	MPQ, 癌痛问卷表	未记录	20%
调查	126	未描述	6m-4年	1y：45% 1-2y：37% 2-4y：28% 4y：20%

VRS: 语言描述评分　VAS: 视觉模拟评分　MPQ: 麦吉尔疼痛问卷调查表

表3 胸科术后慢性疼痛发生率

研究类型	样本量	疼痛评估	随访时间	研究结果
回顾性调查	391 有效人数： 343	VAS，VRS	≧3m	开胸术后 1y 44% >1y 29% 胸腔镜术后1y 30% >1y 22%
前瞻性研究	56	VAS	≧2m	疼痛：54%
前瞻性研究	50	VAS, MPQ 镇痛药物	6y	后外侧开胸：12% 开胸前侧：8%
回顾性研究	1000 有效人数： 883	未描述	≧2m	2m 22% 12m 14%, 重度疼痛15%
调查	238	疼痛评估	≧3m	术后疼痛：11%
调查	90 有效人数： 77	未描述	6m-18m	术后疼痛：67% 要求疼痛治疗：20%

VRS: 语言描述评分　VAS: 视觉模拟评分　MPQ: 麦吉尔疼痛问卷调查表

发现其发生率高达62%。过去，截肢的患者常常主诉残肢特定的某处疼痛，于是外科医生试图通过手术寻求病因，但进一步的手术不仅没有减轻截肢术后长期的疼痛，反而加重了患者的疼痛或者使他们安装假肢变得更困难。

幻肢痛的发生率大约为50%-85%。Carlen[15]等人对某战后截肢术后的患者做了一项调查，发现其幻肢痛发生率为67%。他们同样对幻肢痛出现的时间做了调查，结果显示有12%的患者术后即刻就出现幻肢痛，10%出现在术后第一天，12%出现于术后一周，5%于术后两周发生，16%术后三周出现幻觉痛，2%出现于三周后，其余患者无幻肢痛或者不确定具体时间。

许多研究者都尝试寻找幻肢痛的危险因素，但结果往往存在争议。它的出现与年龄，性别，截肢的部位，截肢的原因，种族，文化水平都不相关。有两项研究表明使用假体与术后幻肢痛并无关系，但有一项研究结果显示从患者截肢到使用假体的时间长短与幻肢痛明显相关[16]。可这仍不足以证明使用假体可以预防幻肢痛的发生。目前，只有残肢痛，截肢术前疼痛和非痛性幻觉已被证实与术后幻肢痛有关。

4. 其他手术术后慢性疼痛

有调查显示[17]疝修补术后12个月疼痛发生率为63%，其中12%的患者有中到重度疼痛；2年后，54%的患者仍有疼痛，中到重度疼痛者为11%。一项回顾性研究[18]调查了约500位全髋置换术后的患者，10年内有16%的患者坐时疼痛，35%的患者行走时疼痛。可见，术后慢性疼痛无论手术大小，即使是最低的发生率也是无法令人接受的。

四、术后慢性疼痛发生的可能机制

1. 急性痛向慢性痛的转化

有证据提示在急性痛转化成慢性痛的过程中脊髓扮演了重要角色。例如外科手术可以导致大鼠脊髓小胶质细胞COX酶的激活以及前列腺素的释放等。经椎管内给予大鼠COX抑制剂尤其是COX-1抑制剂，可以减少痛觉敏感形成，更重要的是可以持续预防慢性痛觉过敏的形成。最近的临床试验中，将COX-1抑制剂痛力克经椎管注射，初步的结果提示有术后镇痛作用，现在正在检验它是否能降低围术期的痛觉过敏并减少术后慢性疼痛形成的风险。

其他的研究显示术后伤口周围的机械痛敏与术后慢性疼痛形成有一定的相关性。De Kock等对静脉应用NMDA受体拮抗剂氯胺酮或硬膜外应用阿片类、局麻药、或可乐定是否可以改变结肠切除手术患者围手术期的急性痛敏和术后的慢性疼痛的发生进行了研究。根据这些探究结果得出两个主要结论：首先，术后48h内降低伤口痛觉敏感性的治疗效果与术后一年后疼痛降低的效果显著相关。一些治疗措施，如静脉小剂量的氯胺酮对急性围术期疼痛及吗啡的使用影响很小，但对伤口周围的痛觉过敏及慢性疼痛的发生率影响较多，这点提示除了关注围手术期的疼痛以外，还必须高度关注敏化现象从而预防手术后慢性疼痛的发生。其次，许多降低脊髓活性的措施如硬膜外应用阿片类、局麻药、或可乐定能明显的降低术后慢性疼痛的发生。

2. 慢性疼痛发生时伴随的神经系统的改变

一些研究者认为处于慢性疼痛的患者，其神经损伤不管是由于机械损伤，肿瘤浸润或病毒感染，均可使神经系统的某些部位发生改变。外周神经损伤后至少在4个位点能观察到感觉传导的变化，业已证明这些改变是慢性神经病理性疼痛形成的基础。外周神经损伤后会发生两个基本改变。首先，外周神经损伤后会导致外周神经的兴奋性增加。这表现为神经及神经末梢的兴奋性离子通道（如对辣椒素，热和低PH敏感的瞬时型感受器TRPV-1通道）及受体的表达增加。静息膜电位去极化，动作电位阈值降低，继而引起单脉冲或短刺激的自发性放电增加，对正常刺激的敏感性增加，出现痛觉过敏和异常。第二个变化是兴奋性增高，表现为电压门控离子通道表达增加，引起自发性和重复放电。

另一个导致慢性疼痛形成的神经可塑性变化的位点是脊髓。外周慢性炎症和神经损伤后，信号传入脊髓层面的多个方面发生了改变。胶质及神经元均有变化，总体上是兴奋性机制提高而抑制性机制下降。Aβ纤维在脊髓的解剖位置（传入位点）可发生改变，正常情况下仅存在于伤害性感受器的兴奋性神经递质如CGRP等合成上调。异常的小直径（可能有部分大直径的）神经纤维经正常传递系统传入，不仅仅可以导致自发性疼痛，而且会导致与中枢敏化相一致的一系列的脊髓变化。经典理论认为：这些过程与P物质及谷氨酸释放后激活NMDA受体和NK1受体有关，相应的会导致脊髓神经元活化转录因子（包括CREB，cFos等）的异常表达，继而引起离子通道和受体表达的改变。可能还有脊髓抑制张力的降低，主要通过GABA能神经元及阿片受体的永久性丢失或活性的降低。

根据闸门控制理论，脊髓接受更高中枢的下行兴奋和抑制的影响，继而调节脊髓的疼痛的状态。外周神经损伤会改变高位中枢对脊髓的下行影响，导致中枢敏化。大脑中枢透射到脊髓，释放包括抑制性（去甲肾上腺素）和兴奋性（5-羟色胺）儿茶酚胺及其他神经递质。炎症和神经损伤后下行抑制及易化的相互关系较为复杂，具体与损伤的时间和疼痛的特点有关。总体看，如果神经损伤持续存在，下行抑制方面变化很小，而下行易化则大大加强。由此推论如果摧毁位于脑干的下行抑制中枢就可能消除神经损伤后动物的超敏反应。综上所述，慢性疼痛的传导基础包括异常的大、小直径纤维的传入，脊髓神经元基因表达的改变，抑制作用的降低，大、小胶质细胞的激活以及下行易化的激活等。

五、预防性措施

许多学者对预防术后慢性疼痛的发生作了研究，包括术前预防性给予阿片类药物或硬膜外预防性镇痛，术后给予不同剂量药物镇痛，多模式镇痛等。

1. 胸科手术

有三项研究对术前硬膜外预防性镇痛是否能降低胸科术后慢性疼痛的发生率或者减轻慢性疼痛的程度做了分析。[19,20,21]Obata et al.[20]将140位开胸手术的患者随机分为两组，一组术前72h连续硬膜外注射甲哌卡因，另一组不作任

何处理，6个月后，术前接受硬膜外镇痛的患者术后慢性疼痛的发生率明显减少。但这项结果遭到Ochroch et al.[21]的质疑，他将175位将要开胸的患者随机分为两组，一组术前硬膜外注射布比卡因和芬太尼，另一组不作任何处理，结果显示两组开胸术后慢性疼痛的发生率并无明显区别。Senturk et al.[19]将69位将要开胸的患者随机分为三组，分别为术前硬膜外注射布比卡因，术后吗啡硬膜外PCA和术后吗啡、布比卡因硬膜外PCA或吗啡静脉PCA。结果6个月后两组硬膜外镇痛术后慢性疼痛的发生率无明显差别，但较静脉吗啡PCA有明显降低且疼痛程度有所下降。

加巴喷丁和普加巴林是抗癫痫药物，在人体疼痛模型中具有抗痛觉过敏特性。加巴喷丁以被认为对开胸术后慢性疼痛有较好的疗效。镇痛效应的作用机制尚不明确，已明确的是加巴喷丁类药物可以结合电压门控钙离子通道，阻断神经递质释放。更新的观点认为加巴喷丁可能是通过替换一种内源性配体缓慢发挥作用。最近一项研究[22]招募了开胸术后4周内有中到重度疼痛（VAS>5且LANSS>12)的患者。一组接受加巴喷丁治疗，另一组接受NSAID药物治疗，60天后，加巴喷丁组患者重度疼痛明显减少。尽管这项研究并不完善，但它提供了一条线索：如果术前预防性服用加巴喷丁并且术后连续服用加巴喷丁是否可以预防开胸术后慢性疼痛的发生。

2. 乳腺手术

Fassoulaki et al.[23]将接受乳癌根治手术的患者随机分成两组，一组为治疗组，接受多种治疗包括术前一天每6小时服用加巴喷丁400mg,手术当天局部皮肤使用EMLA，术中罗哌卡因浸润臂丛神经。另一组为空白组，分别接受三种安慰剂治疗。术后，治疗组连续服用加巴喷丁8天（400mg，q6h），局部涂抹EMLA3天，空白组连续服用安慰剂8天（400mg，q6h），局部涂抹安慰剂3天。3个月后，治疗组的腋下痛（14% vs 45%），上臂痛（23% vs 59%），镇痛药物用量（0vs23%）明显较空白组降低许多。（如图1）

Iohomet al.[24]研究了多模式镇痛对乳腺癌根治并腋窝淋巴结清扫术后慢性疼痛的发生率的影响。他将29位患者随机非双盲分为两组，标准组（S组）术前两天每6h肌注吗啡0.1 mg/kg，口服双氯芬酸钠（12h），右丙氧芬盐酸盐32.5mg和对乙酰氨基酚片650mg（6h）。N组术前12小时静脉注射帕瑞昔布钠（COX-2抑制药）40mg，术后继续注射帕瑞昔布钠40mg（12h）并口服塞来考昔（COX-2抑制药）200mg直至术后5天。此外，N组患者术前行椎旁神经阻滞并置管，术后两天持续给予0.25%的布比卡因10ml（12h），每天口服对乙酰氨基酚片1g（6h）。所有患者均为全身麻醉。结果显示术后48小时S组疼痛程度明显低于N组。但3个月后N组术后慢性疼痛发生率为0，而S组为85%。虽然还没有证据证明COX-2抑制剂对长期疼痛发生有预防作用，但这项研究确实显示帕瑞昔布钠和塞来考昔可以降低术后慢性疼痛的发生率。当然，使用COX-2抑制剂也存在一定风险，有心血管疾病，血栓形成，NSAID药物禁忌的患者应该慎用。

3. 妇科手术

Katz et al.[25]的研究中，将45位开腹子宫全切患者分为3组，所有患者均为常规全身麻醉。第一组不使用阿芬太尼，第二组切皮前静脉给予低剂量阿芬太尼，并术中追加剂量,第三组切皮前给予大剂量阿芬太尼，并术中持续泵入。结果发现术后6小时大剂量组的疼痛评分和吗啡用量明显低于小剂量组和不使用组，这些结果并没有任何临床意义。6个月后随访发现各组间术后慢性疼痛发生率和程度没有任何区别。研究者解释这是因为所有手术操作都是在全麻后进行，而围术期中使用标准阿片类药物的剂量已经足以对手术带来的损伤提供保护，所以不需要额外镇痛药物的使用。在Katz et al.的另一项研究中[26]，妇科腹腔镜手术切皮前，硬膜外注射利多卡因和芬太尼组较常规组术后48h疼痛和吗啡使用量减少，术后3个月疼痛发生率也有所下降，但6个月后两组的疼痛发生率和一般状况并无差别。

近年来NMDA受体拮抗剂氯胺酮被广泛用于术后镇痛，有证据显示氯胺酮联合阿片类，局部麻醉和其他镇痛药对于术后镇痛很有效。在一项研究中[28]，研究者将60位将要进行开腹子宫全切术的患者分为3组。分别为对照组，氯胺酮组和加巴喷丁组。结果显示术后疼痛评分加巴喷丁与氯胺酮组明显低于对照组，术后吗啡的使用量分别较对照组降低了35%和42%。6个月后，加巴喷丁组术后慢性疼痛有所改善，而氯胺酮组比对照组无明显差别。

4. 截肢术

Schley et al.[27]将手指至前臂截肢的患者随机分为两组，所有患者术后7天均接受臂丛连续阻滞（0.375%罗哌卡因，5ml/h），并可以根据患者需要给予追加量。不同的是，术后4周内一组患者每天注射NMDA受体阻滞剂美金刚，另一组术后4周内每天注射安慰剂。结果表明术后第1周内，美金刚治疗组的患者对局部神经阻滞的要求明显低于安慰剂组。术后4周，术后6个月，治疗组慢性疼痛的发生率明显低于安慰剂组，且较安慰组的患者，治疗组中发生慢性疼痛的患者其疼痛程度也有所减轻。

六、未来展望

术后慢性疼痛是一种常见的但未得到充分诊断和重视的术后并发症， 它对病人个体以及整个社会造成严重的影响。遗憾的是，目前仍缺乏足够的证据提出理想的治疗方案， 因此还需要研究者们更多更完善的临床研究。近期的研究以证实COX-2抑制剂、加巴喷丁等复合其他镇痛方法的多模式镇痛可以减轻术后急性疼痛，减少阿片类药物的应用，但其减少术后慢性疼痛发生率的机制和具体方案还需进一步研究。此外，心理因素在术后慢性疼痛的发生发展中有很重要的地位，应进一步研究术后慢性疼痛的心理因素，在预防性治疗慢性疼痛的同时辅助心理治疗。最新的研究已发现单核苷酸多态性(SNPs)可能与疼痛有关， 其中研究得最充分的物质之一是儿茶酚胺-O-甲基反式转移酶的功能性基因的多态性;这种酶的特定单体不仅参与增加对实验性疼痛的敏感性,也与颞颌关节疼痛的发展相关，因此，疼痛基因的发现和研究可能会为术后慢性疼痛的预防和治疗带来质的飞跃。

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2012北京国际疼痛论坛暨第六届全国临床疼痛学术会议通知

2012年8月17日-20日 北京国际会议中心

世界疼痛医师协会一贯积极倡导多学科疼痛医师交流与合作。多年来国内外多个学科的专家在疼痛诊疗的领域内携手共进，极大地推动了推动世界及中国临床疼痛事业的发展，并于2010年10月在北京国家会议中心成功地举办了第十四届世界临床疼痛大会，80多名海外讲者和60多名国内讲者的讲题涵盖了各学科的疼痛诊疗领域，530余名外国医师与1100余名中国医师现场相聚，切磋疼痛诊疗技艺，极大地推动了国内外疼痛医师之间的的学术传播与交流，在国内外疼痛领域取得了强烈反响和广泛赞誉。2011年8月19－22日的2011北京国际疼痛论坛暨第五届中国临床疼痛学术会议，有1176名医师参与交流，令人难忘。

2012年，为进一步发扬世界疼痛医师协会及其中国分会在推动世界疼痛医学交流和融合中所发挥的纽带作用、加强各国和各学科疼痛医师的交流与合作、展现国际和中国临床疼痛医学事业的快速发展及中国疼痛医师的专业风貌，卫生部国际交流与合作中心、世界疼痛医师协会、首都医科大学宣武医院、中华中医药学会疼痛学分会、中华医学会麻醉学分会、世界神经调控协会中国分会、世界疼痛医师协会中国分会联合发起举办“2012北京国际疼痛论坛暨第六届中国临床疼痛学术会议”。国内外的多个疼痛相关学科的专家、医师和医药器械厂商将再次聚会，共同展示疼痛诊疗的新技术、新设备、新药品和新进展，交流新知，畅叙友谊。

本次会议将于2012年8月17日-20日在北京国际会议中心隆重召开。届时，来自国内外疼痛领域的专家、学者将欢聚一堂，共同推动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。

诊疗仪器、镇痛药品和消耗材料的技术进步促进了疼痛诊疗专业的快速发展，新的影像可视技术为微创介入治疗插上了翅膀，新机制药品使疼痛治疗的疗效和安全性显著提高，为了促进疼痛相关的诊疗仪器、镇痛药品和消耗材料研发机构和生产销售厂商与临床专家的合作，加速疼痛诊疗用品的研发、生产、销售和学术推广，本次会议专门设立若干疼痛诊疗仪器、镇痛药品和消耗材料的产学研论坛。

组织机构

主办单位：卫生部国际交流与合作中心/首都医科大学宣武医院/中华中医药学会疼痛学分会/中华医学会麻醉学分会/世界神经调控协会中国分会/世界疼痛医师协会中国分会

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石海霞 于建设
内蒙古医学院附属医院，麻醉科，内蒙古 呼和浩特 010050

摘要

目的：观察地佐辛用于腹腔镜下胆囊切除手术术后的镇痛效果。方法：ASAⅠ或Ⅱ级择期拟行腹腔镜胆囊切除手术的患者40例，随机均分为地佐辛组（D）和对照组（C）。观察病人清醒时间，拔管时间以及拔管时、拔管后30分钟、1小时、2小时和6小时各时间点的疼痛视觉模拟评分（VAS），术后恶心呕吐情况，病人满意度。结果：D组拔管后1小时、2小时VAS评分均较C组低(P<0.05)，病人满意度D组高于C组(P<0.05)。结论：地佐辛用于腹腔镜胆囊切除手术，可缓解术后疼痛，提高病人满意度。

关键词：地佐辛；胆囊；腹腔镜；疼痛

地佐辛用于腹腔镜下胆囊切除手术术后镇痛的临床观察

The Analgesic Efficacy of Dezocine Post Operation of Laparoscopic Cholecystectomy

Hai-xia Shi，Jian-she Yu
Department of Anesthesiology，the Hospital Affiliated to Inner Mongolia Medical College，Hohhot，Inner Mongolia，010050

Abstract

Objective: Observe the analgesic efficacy of Dezocine post operation of Laparoscopic cholecystectomy.

Method: 40 ASA Ⅰor Ⅱ,scheduled for gallbladder excision, under Laparoscopic cholecystectomy, were randomly allocated in 2 groups: Group Dezocine(Group D) and Group Control(Group C). Observed the awake time, extubation time, recorded VAS at different time points: 30 minutes , 1 hour, 2 hours，6 hours after extubation respectively, the numbers of Postoperative nausea and vomiting, the patients'satisfaction.

Results: Visual analog scale (VAS) at Group D 1 hour, 2 hours, 6 hours after extubation, Group D was less than Group C, In Group D, the patients satisfaction was higher.

Conclusion: Dezocine used post operation of Laparoscopic cholecystectomy, can relieve pain, and improve the patients' satisfaction.

Key Words: Dezocine; Gallbladder; Laparoscopic cholecystectomy; Pain

腹腔镜下胆囊切除术（LC）目前作为治疗胆囊良性疾病的“金标准”，具有疗效确切，手术时间短、创伤小、恢复快，伤口愈合后疤痕微小，疗效肯定的优点，但仍存在术后切口疼痛和不良反应。地佐辛作为一种强效阿片类镇痛药，能缓解术后疼痛，减轻病人痛苦，本研究旨在观察地佐辛超前镇痛对LC术后疼痛的影响。

一、资料与方法

1. 一般资料

本研究经医院伦理委员会批准，患者或其家属签署知情同意书。2011年10至12月，本院择期行腹腔镜下胆囊切除手术（LC术）患者40例，其中男22例，女18例，年龄32～58岁,体重指数（BMI）18～24kg/m2，ASAⅠ或Ⅱ级，预计手术时间30～60分钟，排除麻醉药身体依赖史，心肺肝肾功能不良患者。

2. 方法

患者入手术室后，常规监测心电图（ECG）、血压（BP）、血氧饱和度(SpO^2)，开放上肢静脉，于麻醉诱导前快速静脉输入乳酸林格氏液10ml/kg。麻醉诱导依次予以咪达唑仑（0.03mg/kg），芬太尼（4μg/kg），罗库库溴铵（0.6mg/kg），依托咪酯（0.3mg/kg），气管插管成功后接麻醉机，设定呼吸参数：潮气量VT 8～10ml/kg，呼吸频率f12～14次/分，术中维持呼气末二氧化碳分压($ETCO_2$)35～45mmHg。术中两组均持续静脉泵入异丙酚（4～6mg/kg/h）、瑞芬太尼（0.2ug/kg/h）维持麻醉。手术结束前15分钟地佐辛组静脉注射地佐辛5mg，对照组静脉注射等剂量的生理盐水，所有患者均于胆囊取出体外准备缝合伤口时停止泵入异丙酚和瑞芬太尼。

3. 观察指标

观察病人清醒时间，拔管时间以及拔管时、拔管后30分钟、1小时、2小时和6小时各时间点的疼痛视觉模拟评分（Visual analog scale,VAS），术后恶心呕吐情况，病人满意度。

4. 统计分析

采用SPSS 17.0统计软件,计量资料以(±s)表示，组间比较采用t检验。计数资料比较采用x^2检验，P<0.05认为差异具

有统计学意义。

二、结果

1. 一般资料

两组患者的性别比、年龄、体重指数、手术时间，病人清醒时间，拔管时间差异均无统计学意义。

2. VAS评分

拔管时、拔管后30分钟VAS差异均无统计学意义（P＞0.05）、拔管后1小时、2小时和6小时D组VAS评分低于C组（P＜0.05）（表1）。

3. 术后恶心呕吐情况两组比较无统计学意义（P＞0.05），D组病人满意度高于C组（P＜0.05）（表2）。

表1 两组患者术后各时点VAS评分情况比较(x±s, 分)

组别	例数	拔管时	拔管后30分	拔管后1小时	拔管后2小时	拔管后6小时
D组	20	1.8±0.7	1.7±0.8	2.0±0.6[a]	2.2±0.5[a]	2.8±0.7[a]
C组	20	1.9±0.7	1.7±0.9	2.4±0.8	3.0±0.3	3.9±0.3

注：与C组比较，[a]P＜0.05

表2 两组患者术后病人满意度比较［例(%)］

组别	例数	满意	基本满意	不满意
D组	20	15（75）[a]	5（25）[a]	0（0）
C组	20	9（45）	11（55）	0（0）

注：与C组比较，[a]P＜0.05

三、讨论

LC与传统开腹切除胆囊手术相比，手术创伤小，患者术后疼痛程度相对减轻，但仍有切口痛、腹腔痛、内脏痛等不同程度的不适，需要使用镇痛剂的比例达73%[1]，LC多因素均可导致疼痛，腹腔内残余的气体可增加疼痛程度[2,3]，由于全麻术后镇痛不充分，术后3小时内需予以镇痛的比例约为70%[4]。

阿片类传统药物，镇痛效果确切，但其呼吸抑制、恶心、呕吐、嗜睡、皮肤瘙痒等不良反应的发生率较高，并且发生率与剂量呈一定的相关性[5]。为避免大量应用阿片类药物，目前多模式镇痛与超前镇痛是研究热点。超前镇痛即在伤害性刺激作用于机体之前阻断痛觉传导通路，防止中枢敏化，以减少或消除伤害引起的疼痛。地佐辛是阿片受体混合激动-拮抗剂，完全激动κ受体，缠身脊髓镇痛、震惊和轻度呼吸抑制作用，其镇痛效果与吗啡相当，对μ受体有部分激动作用，但不产生典型的μ受体依赖，其呼吸抑制作用明显低于吗啡[6,7]，其具有超前镇痛作用，单次静脉注射5mg地佐辛后，15分钟起效，作用持续5小时，与本研究结果一致。故本研究在手术结束前15分钟予以药物干预，以便术毕及时发挥药物镇痛作用，但两组拔管即刻、拔管后30分VAS评分无差异，考虑腹腔镜下胆囊切除手术时间短，麻醉诱导芬太尼的镇痛作用仍有残余。地佐辛组术毕亦无呼吸抑制发生，其患者满意度高，可能与其松弛胃肠平滑肌，降低了内脏不适有关。

本研究表明，地佐辛用于腹腔镜下胆囊切除术后镇痛，效果确切，不增加患者术后恶心呕吐、呼吸抑制等风险，可提高患者满意度。

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2012年欧洲麻醉年会

2012年欧洲麻醉年会将于2012年6月9-12日在法国巴黎召开，欧洲麻醉年会是涵盖了麻醉所有方面的的年度大会及展览会，来自世界各地的数千名的学者、专业人士、从业者和业代表出席为期3天的大会。年会的进修课程、交互讨论会、报告会将会刷新与会者的知识构架，探索麻醉领域的前沿信息，与会者也可以与来自世界各地的麻醉专家交流看法。

会议时间：2012年6月9-12日
会议地点： 法国 巴黎
会议网址： http://www.euroanesthesia.org/
联系人：贾莉丽
电话：13520754780
邮箱：ctdmc@hotmail.com

宋韩明 综述 李刚 审校

卫生部中日友好医院重症医学科，北京，100029

摘要

连续性肾脏替代治疗能够清除炎症介质、改善机体内环境、调节免疫功能，在脓毒症的治疗中发挥着重要的作用。对于治疗时机、治疗方式、剂量选择和终止时机，都需要结合临床情况仔细判断。

关键词：连续性肾脏替代治疗；脓毒症；急性肾损伤

责任作者及联系方式：李刚，E-mail：xdysw@163.com

连续性肾脏替代治疗在脓毒症治疗中的作用

The Effect of Continuous Renal Replacement Therapy in the Treatment of Sepsis

Han-ming Song, Gang Li

Department of Intensive Care Unit, China-Japan Friendship Hospital, Beijing, 100029

Abstract

Continuous renal replacement therapy, which can eliminate mediators of inflammation, improve internal environment and regulate immune function, is now playing an important role in the treatment of sepsis. The timing, modality, dose and termination deserve precise decision according to the clinical setting.

Key Words: Continuous renal replacement therapy; Sepsis; Acute kidney injury

Corresponding Author: Gang Li,E-mail:xdysw@163.com

脓毒症被定义为感染所引发的全身炎症反应，是当前临床上最具威胁性的感染并发症，已成为重症患者中后期死亡的主要原因，若伴有器官功能损害，则称为严重脓毒症[1]。美国为期22年的流行病学研究显示，脓毒症患者占住院患者总数的1.3%，并以每年8.7%的速度增长，死亡率也从1979年的21.9/10万人增至2 000年的43.9/10万人[2]。我国一项涉及3665例ICU患者的研究显示，严重脓毒症的发生率为8.68%，其中44.7%的严重脓毒症患者在入住ICU 28天内死亡[3]。由于其逐年增高的发病率及死亡人数，脓毒症受到越来越广泛的关注。著名的“拯救脓毒症”运动提出了一系列治疗措施，包括早期应用抗生素、早期液体复苏等[4]。而其中连续性肾脏替代治疗(continuous renal replacement therapy; CRRT)在脓毒症，特别是严重脓毒症治疗中的应用日益受到人们的关注。

一、基本原理

所谓连续性肾脏替代治疗，是指每天连续24小时或接近24小时的一种连续性血液净化技术。其主要特点包括：延长了血液净化时间，增大体外循环中的血流量，使用通透性高、生物相容性好的滤器，配备大量的置换液，设置精准的液体平衡系统，稳定患者的内环境[5]。CRRT对脓毒症治疗的机制主要体现在以下3个方面。

1. 清除炎症介质

这是最常被提到的作用机理。脓毒症的本质是感染诱发的促炎与抗炎介质平衡紊乱，过度的炎症反应导致广泛的内皮损伤，继而引起多脏器功能损害。CRRT使用高通量血滤器，能够通过对流清除各种中大分子毒素，包括导致炎症反应的细胞因子，这已被诸多试验证实[6,7]。但临床实践中发现了一些现象。一方面，一些研究者未能检测到患者血中炎症因子的下降。例如Cole等[8]在确诊12小时内，使用2L/h的置换液量对24名严重脓毒症患者进行了CRRT，连续观察72小时，结果显示，患者血清中的肿瘤坏死因子(tumor necrosis factor;TNF)-α、白细胞介素(interleukin;IL)-6、8、10及补体C3a和C5a等炎症介质的水平均未见明显变化。另一方面，一些研究者观察到了患者血中炎症因子的变化，但在超滤液中未检测到相应的炎症介质。例如南京军区总医院[9]观察了5例接受CRRT的严重脓毒症患者，结果显示，在治疗过程中，患者血清的TNF、IL-8及一氧化氮(nitrogen monoxide; NO)浓度有明显下降，但超滤液中未检测出相应成分。由此作者认为，炎症介质的清除以吸附为主。这里应当注意两个问题[10]：第一，高通量滤器在清除促炎因子的同时也清除了抗炎因子，故对疗效应做综合评价；第二，不同膜的通透性和吸附功能有不同，使用一种膜进行临床研究得出的结论不能直接用于另一种膜。

2. 改善机体内环境

严重脓毒症和急性肾损伤(acute kidney injury; AKI)有着密切的关系，一方面，有50%的严重脓毒症患者继发急性肾损伤；另一方面，ICU患者的急性肾损伤有50%是由严重脓毒症造成的[11]。脓毒症和急性肾损伤均可导致严重的内环境紊乱，包括体温过高或过低、水电解质平衡紊乱、酸碱平

衡失调等，当药物治疗无效时，CRRT可以通过改变置换液的温度、配方及酸碱度等方式改善内环境，保证组织器官的灌注需求。同时，脓毒症患者对液体平衡要求较高，CRRT可通过对液体出入平衡的精确调节，保证组织灌注，保护重要脏器功能，防止器官功能衰竭，保证液体复苏、抗生素应用及营养支持等治疗手段有效地进行。

3. 调节免疫功能

为了从根本上遏制脓毒症的恶性循环，不仅需要清除已产生的有害炎症介质，还需要从源头上调控促炎和抗炎因子的生成。CRRT能够改善机体的免疫功能，纠正内皮细胞的功能障碍，重建机体的免疫稳态。Lonnemann等[12]使用聚砜膜进行的研究显示，在严重脓毒症时，外周血单个核细胞TNF-α的产生会受到内毒素的抑制，而CRRT能够解除这种抑制，提示CRRT具有免疫调节作用。Morgera等[13]使用聚酰胺膜进行的研究显示，严重脓毒症患者接受CRRT后，CD3＋T细胞计数增加，提示细胞免疫功能改善。

由上可知，对于严重脓毒症患者来说，连续性血液净化的作用已不单纯是替代肾脏功能，而是作用全身，改善机体内环境，改善免疫功能，从而改善患者预后，已成为救治严重脓毒症患者的重要手段。

二、临床应用

目前关于CRRT治疗的研究，目前主要集中在开始治疗的时机、治疗的方式和剂量，以及何时终止治疗，下面分别予以阐述。

1. 开始治疗的时机

大多数研究认为，一旦合并了急性肾损伤，则CRRT开始得越早越好。Karvellas等[14]的荟萃分析纳入了15个临床试验，共涉及1494名患者，其中有2个随机研究、4个前瞻性队列研究、9个回顾性队列研究，结果显示，与晚期开始的患者相比，早期开始的患者死亡相对危险度为0.45，95%置信区间0.28-0.72。但作者指出，这15个试验大多数是回顾性分析，对早晚的定义各不相同，所以结论的临床意义需要进一步讨论。Liu等[15]对243名患者进行了回顾性研究，调查CRRT开始前患者血清尿素氮的水平，中位数为76mg/dl(27mmol/L)，将尿素氮小于76mg/dl者定义为早期治疗，大于76mg/dl者定义为晚期治疗。结果显示，与早期治疗的患者相比，晚期治疗的患者死亡相对危险度为1.85，95%置信区间1.16-2.96。Chou等[16]的回顾性研究利用RIFLE标准对370名合并急性肾损伤并接受CRRT的脓毒症患者进行了归类，将处于RIFLE 0级或处于危险阶段即接受CRRT定义为早期治疗，处于损伤或衰竭阶段接受CRRT定义为晚期治疗，两组患者住院期间死亡率分别为70.8%和69.7%，无显著性差异。可见，关于治疗开始的时机，目前还没有强有力的循证医学研究提供证据。比较公认的观点是，当脓毒症合并血流动力学不稳定、组织灌注低下等表现，特别是当液体复苏及血管活性药物无效时，即可考虑开始CRRT[5]。

2. 治疗的方式

最经典的方式仍是连续性静脉静脉血液滤过(continuous venovenous hemofiltration; CVVH)，其他方式，如连续性静脉静脉血液透析(continuous venovenous hemodialysis; CVVHD)[17]、连续性静脉静脉血液透析滤过(continuous venovenous hemodiafiltration; CVVHDF)[18,19]等也有应用。其中滤器的选择至关重要。前面已经说过，CRRT清除炎症因子主要依靠对流和吸附，相关研究也主要集中在滤器膜的通透性和吸附性上。通透性越高的滤器对于炎症因子的清除效果越好。Morgera等[20]将30名合并了急性肾损伤、血流动力学不稳定，需要持续泵入去甲肾上腺素维持血压的脓毒症患者随机分为2组，分别使用大孔径(10nm)高通量血滤器和普通血滤器进行CRRT。结果显示，前者去甲肾上腺素的用量有明显的下降，血清炎症因子IL-6和IL-1ra的水平也有明显的降低，而后者未观察到类似现象，提示增加滤过膜孔径有助于提高炎症介质的清除效率。对于吸附的作用，Vriese等[10]进行了细致的研究，他们采用AN69高通量血滤器为15名合并急性肾损伤的脓毒症患者进行了CRRT，治疗过程中每隔12小时更换滤器1次，连续监测滤器动脉端、静脉端及超滤液中TNF-α、IL-1β、IL-6、IL-1ra及IL-10等炎症因子的浓度，通过血流量及超滤率计算清除总量和对流清除量，二者的差为吸附清除量。结果显示，清除总量中吸附所占的比重更大，且在新滤器使用之初更明显，随着时间的推移，吸附速度变慢，提示滤器膜逐渐饱和。当然，不同炎症介质与不同滤器膜之间的相互关系有所不同，应根据炎症介质的性质恰当选用。

3. 剂量的选择

就对流机制而言，置换液量越大，毒素清除效果越好。而治疗剂量与患者预后的关系，亦有较多研究。Ronco等[21]将425名合并急性肾损伤的患者随机分为3组，分别采用20ml/kg/h、35ml/kg/h和45ml/kg/h的置换液流速实施CVVH，结果显示，第1组患者的生存率明显低于第2组和第3组。作者指出，此类患者进行CVVH时，置换液量至少应为35 ml/kg/h。后来，Ratanarat等[22]进一步提出了间歇性高容量血液滤过的概念，即在24小时的连续治疗过程中，日间采用85 ml/kg/h的置换液量，维持6-8小时，其余16-18小时采用35 ml/kg/h的置换液量，这样既提高了置换液总量，又避免夜间频繁操作影响患者休息。但也有研究得到了不同的结果。Bouman等[23]将106名患者随机分为高容量组(置换液量3-4L/h)和低容量组(置换液量1-1.5L/h)，采用三醋酸赛璐珞膜进行CVVH，结果显示，两组患者的 28天死亡率无显著性差异。近年来发表于新英格兰医学杂志的两项大型研究同样得到了阴性结果。2008年发表的前瞻性研究[24]纳入了1124名合并急性肾损伤并接受CRRT的患者，随机分为两组，置换液量分别为20 ml/kg/h和35 ml/kg/h，结果显示，两组患者的60天生存率、肾功能恢复的比例及其他器官受损的情况均无显著性差异。2009年发表的前瞻性研究[25]共纳入了1508名患者，随机分为两组，置换液量分别为25ml/kg/h和40ml/kg/h，以90天生存率为观察指标，也同样得到了阴性结果。得到阴性结果的原因是多方面的，很重要的一点就是，置换液量影响的是对流清除的效果，CRRT治疗脓毒症，靠的不仅仅是清除炎症介

质，而清除炎症介质也不仅仅是对流在起作用，如果一种滤器对炎症介质的清除是以吸附为主，那么清除效果受置换液流量的影响就比较小了，如果滤器的吸附已经达到饱和，再增加置换液量就没有意义了。

4. 治疗的终止

关于何时终止CRRT，相关的研究较少。Uchino等的回顾性研究[25]纳入了1006名患者，分析了成功脱离CRRT者的特点。结果显示，在不使用利尿剂的情况下尿量＞400ml/d或在使用利尿剂的情况下尿量＞2300ml/d，则患者有80%的可能性脱离CRRT。但这个结论还缺乏前瞻性研究的支持。

以上介绍了CRRT在脓毒症治疗中的作用及相关研究进展。可以看出，CRRT在脓毒症的治疗，特别是对于炎症因子的清除、机体内环境的改善以及免疫功能的调节方面发挥了重要的作用。在临床应用方面，目前主张早期介入、使用通透性高、生物相容性好的滤器，适当采用较高的置换液流量进行操作，但在很多方面还存在争议，需要进一步的临床试验研究。

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2012年广东省医学会麻醉学学术会议

为了进一步加强我省麻醉学界的交流，提高我省麻醉学术和技能水平，促进学科的发展，我会拟于2012年8月在梅州市召开2012年广东省医学会麻醉学学术会议，现将会议征文有关事项通知如下：

一、征文要求：

1、论文要求：凡未在国内外公开刊物发表的麻醉相关论文均可投稿，论文要求科学性强，论点明确，文字精练，有较好的临床指导意义；论文要求全文或摘要各一份，全文4000字以内，摘要500～800字，内容按目的、方法、结果、结论格式书写。

2、知识更新专题讲座的文章要求全文一份，5000字以内。

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菅敏钰 韩如泉
首都医科大学附属北京天坛医院麻醉科 北京 100050

颅脑术后血肿的危险因素

Risk Factors of Post Craniotomy Hematoma

Min-yu Jian,Ru-quan Han
Department of Anesthesiology,Beijing Tiantan Hospital, Capital Medical University.
Corresponding Author: Ru-quan Han, E-mail:hanrq666@yahoo.com.cn

神经外科颅脑术后血肿（Post craniotomy hematoma）是神经外科最严重的术后并发症之一，其发生率在0.8%～6.9%之间[1]。颅内血肿会使颅内压增高，使脑组织发生缺血、缺氧、水肿，颅内压力逐步增高，迫使部分脑组织发生移位而被挤进颅内生理孔道，形成危及生命的脑疝。颅内血肿发生后的临床症状有剧烈头痛、呕吐、进行性意识障碍、瞳孔改变、锥体束征等，甚至引起呼吸循环障碍，发生在颅后窝的血肿可以引起呼吸心跳骤停。术后血肿患者死亡率高，感染率高，平均住院日长，预后差[2]。近年来神经外科、麻醉科对颅脑术后血肿的危险因素进行了大量研究，本文就此做一综述。

一、人口因素

1. 性别

目前为止大部分研究的主要调查对象都是男性，也有少部分研究的主要对象为女性，但是这些研究并没有发现性别与PCH之间有明确的相关性[3,4]。

2. 年龄

老年患者术前合并症多，存在全身血管硬化、血管弹性降低等病理生理学特点，而且老年患者多有脑萎缩，术中占位病变切除以及使用脱水利尿药后颅内压显著降低，脑体积缩小、塌陷，也容易造成术后血肿[5]。Palmer等研究表明，与对照组相比，发生术后血肿组的年龄更大[6]（55 vs. 48岁），因此，高龄可能是术后血肿的一个危险因素。

二、既往疾病因素

1. 糖尿病

糖尿病可以引起血管炎、影响伤口愈合，这些都可能会引起术后出血。Bierska等指出糖尿病可以增加血浆渗透压，从而引起术后血肿[7]。Yamamoto 等则认为高血糖可以引起血液粘度增加，促进动脉粥样硬化，激活血小板聚集和促进凝血功能，这可以减少出血的风险[8]。因此，糖尿病是否是PCH的危险因素尚不明确。

2. 脑淀粉样血管病

脑淀粉样血管病是由于淀粉样物质沉积在脑内导致的症状性脑血管功能障碍，其病理特点为大脑皮质及软脑膜的小血管壁内中层和弹力层有淀粉样物质沉着，尤其在老年患者中，这一变化导致了血管内皮功能不足，阻碍了血小板的粘附与聚集。这类血管自愈能力差，进一步增加了术后出血的风险[9]。因此这类患者进行颅脑手术时应加以注意，仔细止血。

3. 动脉粥样硬化

正常情况下，当脑灌注压发生变化时脑血管的自动调节功能保证脑血流的稳定。动脉粥样硬化可以引起心脏疾病、脑血管疾病和周围血管疾病，当脑血管发生动脉粥样硬化如颈动脉狭窄时，脑血管自动调节功能受损，影响了术中脑灌注，可造成术中持续的脑血流降低。Reinhard等认为由于动脉粥样硬化时血管壁的顺应性下降，血管壁压力的增加导致血管壁变得脆弱，从而引起颅内血肿[10]。

4. 高血压

高血压引起全身血管的疾病，包括脑出血、动脉瘤的形成及破裂[11]。脑血管自动调节功能受损时，动脉血压的变化可以直接导致脑血管灌注压的变化。神经外科手术血脑屏障遭到破坏时，高血压还会引起血管源性水肿。随着颅内容物体积的增大，颅内压随之上升，也会造成术后血肿的发生。在围术期，血压的上升可能会影响血小板的功能。Basali等在2000年的一项研究中发现，围术期血压高于160/90mmHg是术后血肿的主要危险因素[12]。

此外，高血压对手术止血也有负面的影响，临床实践中经常维持术中低血压以减少出血，促进止血。有学者认为，术毕通过升高血压以便于术者发现潜在出血点的方法会增加术后血肿的风险，手术结束后应该缓慢的减浅麻醉避免血压波动，这样有助于术后恢复[13]。

三、血液学因素

1. 血小板

止血过程最重要的步骤就是血小板粘附聚集形成血小板栓子，进而激活生理性的止血过程。任何使血小板减少的因素都可以增加出血的风险。Chan等指出，血小板计数快速减少到100,000/μL以下可以导致术后血肿风险显著增加[14]。

与慢性血小板减少相比，急性的血小板下降的患者血肿倾向更明显。而且，对血小板输注的反应也很重要，如果血小板输注后血小板计数仍然没有增加也预示着血肿的发生。

2. 弥漫性血管内凝血

弥漫性血管内凝血时由于纤溶系统的激活导致血小板不可逆转的损失，如严重创伤和蛛网膜下腔出血时，由于脑组织含有大量的凝血酶，DIC会对大脑造成严重损伤。其它因素如酸中毒、缺血、缺氧等与凝血功能障碍共同作用，会导致微血栓形成和去纤维化，血小板的枯竭和纤溶亢进会加重组织损伤和血肿的发生[15]。

3. 其他因素

术中大量输液、输血可以引起稀释性血小板、凝血因子减少。酗酒可以影响血小板的功能，减少其寿命，急性和慢性的酒精摄入都可以导致血小板减少和骨髓抑制，这样患者就会因为血小板的减少和凝血因子的缺乏而增加术后血肿的风险。

四、药物因素

1. 抗血小板聚集药物

非甾类抗炎药，如阿司匹林可以抑制环氧化酶，减少血栓素A2的合成，从而抑制血小板聚集，因此广泛的在冠脉支架或房颤患者中用于预防血栓形成。阿司匹林影响血小板的聚集，破坏血小板的功能，因此显著增加出血时间。Palmer等指出抗血小板聚集药物的使用是PCH最常见的危险因素，血小板循环周期大约是一周，因此建议在所有神经外科手术之前至少7天停止抗血小板聚集药物的使用[6]。对于急诊患者，建议使用去氨加压素DDAVP进行止血,它可以增加W因子来增加血液的凝血能力，增加血小板膜糖蛋白受体的浓度，以及增加第VIII因子[16]。然而，DDAVP只在特定的人群有效，因此只能作为使用血小板时的辅助用药[17]。

氟比洛芬酯等非甾类抗炎药常被用于神经外科术中或术后镇痛，然而，这类药物也有一定的副作用[18]。与阿司匹林类似，氟比洛芬酯也可以影响血小板聚集，增加术后血肿的危险。已有很多文献报道非甾类抗炎药用于非神经外科手术对术后凝血功能的影响，但是目前并没有文献报道该类药物用于神经外科手术是否增加术后血肿的危险。在非神经外科手术中，Maund等人研究表明，术后出血可能并没有致命的风险[19]，但是，如果应用于神经外科特别是颅后窝的手术，仍有可能增加术后的死亡率[6]。

2. 抗凝药

肝素是常用的抗凝剂，可以抑制因子IXa和因子Xa与凝血酶III 的反应，常用于停止华法林后的替代治疗或围术期防止血栓的形成。神经外科的某些肿瘤如胶质瘤、脑膜瘤等可能释放一些促凝的物质，降低纤溶活性，因此神经外科患者处于高凝状态，常需要肝素预防深静脉血栓[20]。然而，Perry等指出，颅脑术后长期使用低分子肝素抗凝会明显增加血肿的发生率[21]。

低分子肝素可以通过抑制因子Xa来抑制凝血反应，因此也被广泛用于静脉血栓疾病的预防和治疗。Dickinson等指出，至少应该在神经外科术前18h停止低分子肝素的使用[22]。如果使用过量，可以用鱼精蛋白来对抗低分子肝素的抗凝作用。

华法林是维生素K拮抗剂，可以抑制凝血因子II、VII、IX、X的合成，常被用于冠心病患者和心脏瓣膜病患者，可以预防卒中和治疗静脉血栓栓塞。对于神经外科手术，华法林必须于术前5天停止使用，如果必须使用抗凝药物，可以使用肝素替代。如果是急诊手术，可以在术前注射大量维生素K，但这需要至少24h才能有效[23]。因此，患者必须同时使用凝血酶原复合物(PCC)和包含有凝血因子的新鲜冰冻血浆（FFP），PCC不需要解冻，因此紧急情况下使用更为合适。

五、疾病因素

1. 颅内肿瘤

颅内肿瘤的切除方式与术后血肿密切相关，肿瘤未全切的患者术后并发症的发生率高，尤其是术后血肿。对于一些血供丰富的肿瘤，防止术后出血最有效的方法是将肿瘤全切[24]。然而对于一些无法全切的肿瘤来说，要尽量的切除被肿瘤浸润的脑组织。肿瘤周围异常的血管使受损的血管愈合变得非常困难。此外，肿瘤内酶的活性也会破坏肿瘤与脑之间的屏障，在脑组织减压后可能会导致出血。因此我们应当在术前进行血管造影明确肿瘤的血供，栓塞供血血管，尽可能全切肿瘤，术中仔细止血[25]。

2. 动静脉畸形

动静脉畸形手术是PCH的危险因素之一。正常灌注压突破综合征(Normal perfusion pressure breakthrough)是指由于脑动静脉畸形盗血，造成畸形周围的正常脑供血不足，使脑组织慢性缺血。因而这部分血管处于扩张状态，丧失了自动调节能力。一旦动静脉畸形被切除，或其主要输入动脉被闭塞，原来被动静脉畸形盗取的血液重新流入慢性扩张的血管，以高流量注入微循环，使病理性扩张的血管不能耐受这种改变，导致血管源性水肿，毛细血管破裂，脑实质出血。这一理论可解释某些术后数h或数天内发生的颅内血肿和脑水肿。然而，Young等认为动静脉畸形患者的脑血管自动调节功能是正常的[26]，在这类患者手术过程中，应该保证患者的血压维持在正常值的低限，以保证脑组织和血管的正常灌注。

3. 颅脑创伤

颅脑创伤后很容易因为再次出血而形成血肿。如前所述，受损的脑组织会释放促凝物质，启动凝血机制，这可能会导致DIC，这种情况在颅脑创伤的患者中占有很大比例。受损的血管可能会缓慢的渗血，也有可能在血块溶解和血运重建后快速的形成血肿，迟发型血肿可能发生在远离术野的地方，减压术后也有可能会出现血肿，导致更严重的脑损伤。

六、围术期因素

1. 手术止血

不同于其它手术止血主要采取结扎止血方法，神经外科主要采用局部电凝止血，或需要纤维蛋白凝胶、泡沫胶或抑肽酶，双极电凝可以暂时控制出血，但是也可以导致底层的

脑组织出血，因此术者术中应该仔细止血，保持术野“干燥”[27]。

2. 患者体位

患者的体位对术后血肿的危险尚不明确，垂直体位可能会导致术后血肿，这是因为垂直体位时动脉血流减少，恢复仰卧位后术野血供丰富，可能导致术后血肿。还有一种观点认为垂直体位时颅内压的改变导致了血管壁受损，在恢复仰卧位后受损的血管容易出血[28]。

3. 术中失血

Zetterling等认为术中失血大于500ml是发生术后血肿的危险因素之一。术中大量失血可以导致血小板和凝血因子的丢失耗竭。因此对于大量失血的患者，在床旁监测全血凝血功能的基础上，应及时补充新鲜血浆和血小板[29]。

4. 手术经验

手术医生的技术水平与术后血肿的发生有密切的关系，然而有些文章却发现在一些高年资医生手术后血肿的发生率反而更高，这可能是由于高年资医生往往进行一些更为复杂和风险更大的手术[30]。

七、颅脑术后血肿的监测

1. 术中监测

术中CT及术中MRI已被广泛应用于神经外科手术，包括肿瘤活检及切除。术中MRI可以用于监测血肿的发生，然而其高额的费用限制了它的使用。与此相比，术中CT更加经济。Schwartz等在受检的200例患者中发现了两例术后血肿的患者[31]。对于一些术中不可见的视野，CT或MRI的使用非常有必要[32]。即使对于正常的CT或MRI也不能放松警惕，因为有些患者可能出现迟发的血肿。

2. 术后监测

术后应该密切观察患者的临床表现和监测神经功能。麻醉后未能及时苏醒或一些观察指标的持续恶化可能意味着术后血肿的发生，需要临床医生及时进行影像学检查。术后进行影像学检查的时机目前尚有争议，有些观点建议在术后24h、48h和7天常规给予影像学检查[33]。

3. 颅内压监测

有些学者认为颅内压监测在术后血肿和术后脑肿胀方面非常重要，尤其是在临床表现和体征尚不明显时。根据Monro-Kellie学说，闭合的颅腔为一常量，颅内血容量与脑脊液容量的变化相互影响，颅内压的增加会导致脑血流的减少，许多研究都表明术后高颅压的患者预后不良。肿瘤血供丰富、术中大失血或术后需要保持镇静状态的患者术后应常规检测颅内压[34]。

综上所述，颅脑术后血肿是多因素作用的结果，其危险因素目前尚不明确，需要进一步大规模的临床实验证实。目前可以避免术后血肿的方法主要有：按时停止一切抗血小板聚集和抗凝血药物的使用，术前检查确保血小板数量、功能正常，积极治疗既往疾病尤其是高血压；术中避免高血压和大量失血，及时补充新鲜冰冻血浆，仔细止血，缓慢减浅麻醉使患者苏醒；术后避免高血压，患者尽量保持仰卧位，术后6h严密观察患者生命体征，监测颅内压或术后尽早行影像学检查。

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李胜华[1] 赵继蓉[1] 罗威[1] 陆铭[1]
王晓莉[2]
上海市嘉定区妇幼保健院 1麻醉科 2新生儿科
上海 201800

摘要

目的：观察麻醉前扩容对产妇和新生儿脐血血气的影响。方法：ASAⅠ~Ⅱ级，孕38~40周、第1胎，择期剖宫产手术的产妇160例，随机分为4组(n=40)。A组麻醉前输注5ml/kg平衡液，B、C、D组在麻醉前分别输注5ml/kg、10ml/kg、15ml/kg万汶。输注结束后，行L3－4腰硬联合麻醉，调整麻醉平面于T6以下。术中血压下降大于基础值的30%或收缩压低于90mmHg的病例，静脉注射麻黄素10mg/次，并记录相应的给药次数。观察产妇入室(T1)、输液完成(T2)、鞘内注药5min（T3）、10min（T4）、20min（T5）时的MAP、HR、SpO2值和新生儿1min、5min的Apgar评分。采集产妇入室后、输液完成时的动脉血，胎儿取出时的脐动脉血，行血气分析。结果： A、B组患者在T3、T4、T5各时间点的MAP值均较T1下降(P<0.05)，尤以A组的T4下降明显(P<0.01)，C、D组各时间点间无明显变化(P>0.05)；A组麻黄碱的使用率为30%(12/40)，B组为10%(4/40)，两组之间有显著的统计学差异(P<0.05)，C、D组没有患者使用麻黄碱。四组产妇液体输注后的动脉血pH值、 PaO2、PaCO2与输注前相比没有统计学差异(P>0.05)；四组新生儿的脐动血气分析值和新生儿1min、5min的Apgar评分值之间均无统计学差异(P>0.05)。结论：麻醉前扩容能够一定程度缓解产妇孕晚期的碱血症，预防母体低血压对新生儿脐血血气和Apgar评分带来的不良影响。

关键词：预扩容；产妇；脐血；血气分析

责任作者及联系方式：李胜华，Email：shlsh009@yahoo.com.cn

麻醉前扩容对产妇和新生儿脐血血气分析的影响

The Influence of Preanesthesia Volume Expansion to Puerpera and Neonatal Umbilical Cord Blood Gas Analysis Results

Sheng-hua Li[1], Ji-rong Zhao[1], Wei Luo[1], Ming Lu[1], Xiao-li Wang[2]
Maternal and Child Health Hospital, Jiading District, Shanghai, 201800,China
1.Department of Anesthesiology
2.Department of Neonatology

Abstract

Objective: To observe the influence of preanesthesia volume expansion to puerpera and neonatal umbilical cord blood gas analysis.

Methods: One hundred and sixty ASA I~II primipara scheduled for elective Cesarean delivery were enrolled in this prospective and randomized study. Patients were randomized to Group A (preload of 5mL/kg lactated Ringer's solution), Group B (preload of 5ml/kg Voluven), Group C(preload of 10 ml/kg Voluven) or Group D(preload of 15 ml/kg Voluven). After infusion, performed L3~4 Spinal-epidural anesthesia and level below T6. Intravenous Ephedrine 10mg/times when Systolic pressure less than 90mmHg or 70% of baseline, record the times of drug given. Mean arterial blood pressure, Heart rate, Saturation of pulse blood oxygen were recorded upon entering the operating room (T1), after infusion(T2), 5min (T3)、10min (T4)、20min (T5) after injection of the anesthetic, as well as 1min, 5min Apgar Scores. Blood gas analysis were performed before and after infusion, as well as the umbilical artery blood.

Result:: MAP in group A and group B at T3、T4、T5 were lower than that of T1 (p<0.05), especially in group A at T4(p<0.01). There is no significant difference between group C and group D(p>0.05). The application proportion of Ephedrine was 30%(12/40) in group A and 10%(4/40) in group B, which has statistical differences between groups(p<0.05). No patients received Ephedrine in group C and D. There were no statistical differences of Apgar scores among four groups either 1-min or 5-min (p>0.05). Still there were no difference of Blood gas analysis (include pH,PaO2,PaCO2,BE).

Conclusion: Preanesthesia volume expansion can ease alkalemia in late trimester pregnancy to some degrees, and can prevent the adverse effect on the umbilical artery Blood gas analysis and Apgar scores contribute to the maternal hypotension.

Keywords: Preloading; Puerperal; Umbilical cord blood; Blood gas analysis

Corresponding Author: Sheng-hua Li，E-mail:shlsh009@yahoo.com.cn

随着腰硬联合麻醉在剖宫产手术中的广泛应用，腰麻后产妇的低血压已成为术中最常见的一种并发症，其发生率远高于非妊娠妇女。严重的低血压不仅会造成产妇恶心呕吐甚至意识丧失、循环骤停，还会造成子宫胎盘血流减少，可能引起胎儿缺氧、血液pH值下降、酸中毒甚至是中枢神经系统的损伤[1-2]。麻醉前预扩容能够有效减低低血压的发生率[2-4]，但其对产妇和新生儿内环境的影响报道很少，本研究将观察预扩容前后产妇血气分析的变化情况，探讨术中低血压与新生儿脐血血气之间的关系。

一、资料与方法

1. 一般资料

本研究经本院伦理委员会批准和患者的知情同意。ASA I或II级，孕38～40周、第1胎，羊水清亮，无胎窘、妊高

征、糖尿病，凝血功能正常，拟行择期剖宫产手术的产妇160例，年龄22～35岁，随机等分为4组(n=40)。A组麻醉前输注5ml/kg平衡液，B、C、D组分别输注5ml/kg、10ml/kg、15ml/kg万汶，输注速度均为20～30ml/min，术中输注平衡液10~15ml/Kg/h。

2. 麻醉与管理

术前禁水2h、禁流质4h、禁食6h，入室监测心电图(ECG)、脉氧饱和度(SpO2)、无创血压(NBP)，开放上肢静脉，四组病例按分组要求输完液后，均采用针内针法行腰硬联合麻醉：L3～4椎间隙穿刺，鞘内注射5μg舒芬太尼+0.75%罗哌卡因1.6ml(12mg)（用脑脊液稀释至2.4ml)，注射时间为20秒钟，鞘内注药后，向头侧置入硬膜外导管3cm，调整麻醉平面于T6以下。术中血压下降大于基础值的30%或收缩压低于90mmHg的病例，给予麻黄素10mg/次静脉注射。硬膜外腔出血、麻醉效果阻滞不全、术中出血量大于500ml的病例排除在本研究外。

3. 监测项目

观察产妇入室(T1)、输液完成(T2)、鞘内注药5min（T3）、10min（T4）、20min（T5）时的NBP、HR、SpO2和新生儿1min、5min的Apgar评分。采集产妇入室、输液完成时的动脉血以及新生儿脐动脉血，行血气分析。记录各组病例静脉注射麻黄素的次数。

4. 脐血采集

在新生儿娩出且尚未建立自主呼吸时，用两把止血钳钳夹一段脐带，以肝素化注射器抽取该段脐带的动、静脉血，标本密封立即送检。

5. 统计学处理

采用SPSS 11.0统计软件进行统计分析，计量资料以 表示，组内比较采用单因素方差分析，组间各时间点的数据间比较采用t检验，率的比较采用χ2检验。以P<0.05为差异有统计学意义。

二、结果

1. 患者的一般情况

表1 产妇的基本情况、术中出血、手术时间 (n=40, x±s)

组别	年龄(y)	身高(cm)	体重(Kg)	术中出血(ml)	手术时间(min)
A组	26.50 ± 3.03	160.25 ± 4.60	71.18 ± 6.44	246.52 ± 13.17	28.87 ± 2.02
B组	26.00 ± 3.32	159.63 ± 3.81	72.86 ± 7.08	241.18 ± 12.35	30.42 ± 3.15
C组	26.43 ± 3.38	161.42 ± 3.94	70.93 ± 8.16	250.39 ± 17.10	29.10 ± 2.27
D组	26.38 ± 2.75	161.28 ± 3.71	71.08 ± 8.22	243.08 ± 14.40	29.43 ± 2.52

四组患者的年龄、身高、体重、术中出血、手术时间比较，差异均无统计学意义(P >0.05)，见表1。

2. 患者不同时间点的生命体征变化

A组、B组患者在T3、T4、T5各时间点的MAP值均较T1下降(P<0.05)，其中A组患者在T4时的降低尤其显著(P<0.01)。C组、D组各时间点间的MAP值比较，无明显变化(P>0.05)，见表2。A组患者麻黄碱的使用率为30%(12/40)，B组为10%(4/40)，两组间有统计学差异(P<0.05)，C组、D组均没有患者使用麻黄碱。SpO2 在四组患者中，无论组内各时间点，

表2 产妇不同时间点的平均动脉压变化 (mmHg，n=40, x±s)

时 间	A组	B组	C组	D组
T1	95.70 ± 8.40	94.04 ±12.61	94.47 ± 9.36	93.03 ± 9.58
T2	95.50 ± 8.94	94.79 ±10.29	95.08 ± 7.92	98.03 ± 9.25
T3	86.55 ±14.41①	88.43 ± 12.03①	93.60 ± 11.56	98.75 ± 10.58③
T4	80.10 ±13.89②	85.75 ± 14.67①③	92.81 ± 10.49③	96.48 ± 12.65④
T5	84.85 ±12.00①	87.64 ± 13.63①	93.38 ± 9.96③	96.28 ± 12.67④
T5	84.85 ±12.00①	87.64 ± 13.63①	93.38 ± 9.96③	96.28 ± 12.67④

还是组间相应时间点之间均无差异(P>0.05)。

3. 患者的血气分析情况

表3 产妇输液前后的血气分析比较 (n=40, x±s)

组 别	项 目	pH	PaO2(mmHg)	PaCO2(mmHg)
A组	输注前	7.44 ± 0.02	104.50 ± 8.48	31.60 ± 2.70
	输注后	7.43 ± 0.01	103.45 ± 7.19	31.60 ± 2.52
B组	输注前	7.45 ± 0.02	109.08 ± 8.32	31.58 ± 3.15
	输注后	7.44 ± 0.02	111.25 ± 10.45	31.73 ± 3.19
C组	输注前	7.45 ± 0.02	106.62 ± 9.70	30.67 ± 2.78
	输注后	7.43 ± 0.02	105.88 ± 10.55	30.50 ± 2.51
D组	输注前	7.45 ± 0.02	103.98 ± 7.32	30.73 ± 2.52
	输注后	7.42 ± 0.02	103.08 ± 12.45	31.30 ± 2.57

四组产妇在液体输注后，其pH值、PaO2、PaCO2与输注前相比，均无统计学差异(P>0.05)。见表3。

4. 新生儿脐血血气和Apgar评分情况

各组新生儿脐动血的pH值、PaO2、PaCO2、BE和新生儿1min、5min Apgar评分之间比较均无统计学差异(P>0.05)。见表4。

表4 新生儿脐血血气和Apgar评分 (n=40, x±s)

组 别	A组	B组	C组	D组
pH	7.29 ± 0.05	7.28 ± 0.03	7.28 ± 0.04	7.27 ± 0.03
PaO_2(mmHg)	11.10 ± 3.67	12.18 ± 4.14	11.37 ± 4.42	11.55 ± 3.86
$PaCO_2$(mmHg)	56.15 ± 8.36	56.23 ± 5.55	56.15 ± 5.77	56.58 ± 5.78
BE(mmol/L)	-5.92 ± 3.28	-6.01 ± 2.96	-6.32 ± 3.82	-6.29 ± 4.03
1分钟Apgar	9.00 ± 0.00	8.95 ± 0.22	8.95 ± 0.22	9.00 ± 0.00
5分钟Apgar	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00

三、讨论

Apgar评分是根据新生儿娩出后呼吸、循环、生理反射及肌肉张力等临床状况，评价新生儿有无窒息及其程度的一种简便有效的方法[5]。由于其受产妇应用镇痛镇静药和医务人员经验等因素的影响，对诊断窒息的敏感性、特异性均不强，容易造成误诊或漏诊。脐血血气值反映切断脐带前整个分娩过程中，胎儿机体内的血气及酸碱代谢状态，这一客观指标虽比Apgar更具特征性[6]，但也受胎龄、母亲酸碱平衡情况、生产方式、胎儿血红蛋白等因素的影响[7]。引起脐血血气异常的常见原因有：产妇酸中毒经过胎盘传递给胎儿、严重胎盘功能不全、胎儿宫内窘迫、产妇低血压、子宫切开—胎儿娩出(U-D)时间延长[8]。陈自励等报道显示，低Apgar评分的出现率随pH值的降低而升高，高Apgar评分的出现率随pH值的降低而减少，两者呈正相关；从个别pH值和Apgar评分来看，脐血pH值与Apgar评分又不完全平行一致[9]。

本研究的四组资料中，A组、B组患者术中出现了低血压，MAP 在T3、T4、T5均较T1下降(P<0.05)，两组患者麻黄

碱的使用率分别为30%(12/40)和10%(4/40) (P<0.05)。 C组、D组患者术中的血压值无明显变化(P>0.05)，也没有使用麻黄碱。四组新生儿脐动血pH值、PaO2、PaCO2、BE和新生儿1min、5min Apgar评分均无统计学差异(P>0.05)，这可能和麻醉前预扩容后，术中低血压的程度低、维持时间短有关。Kangas-Saarela T等报道：对于健康产妇，短暂（<2min）的母体低血压和绒毛间血流量减低不会对新生儿造成不良影响；但对于绒毛间血流量已处于边缘状态的产妇，母体低血压可导致新生儿神经功能恢复延迟[10]。另有文献报道：采用敏感的神经功能检查方法发现，轻度母体低血压（MBP<70mmHg持续2～5min）虽然对新生儿Apgar评分和酸碱平衡无明显影响，却可导致吸吮反射和寻找反射的明显抑制，提示新生儿处于抑制状态[11]。

孕妇妊娠早期潮气量持续增加直至妊娠晚期，静息通气量上升，分钟通气量增加，导致过度通气甚至呼吸性碱中毒，对妊娠子宫的循环和胎儿均不利。本研究的四组资料中，液体输注后产妇的pH值与输注前比较，虽然未能达到统计学意义的显著差异，但相对数值均降低，提示麻醉前预扩容能够一定程度缓解产妇孕晚期的碱血症，具体机理尚有待进一步探讨。

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中国心脏大会国际心血管麻醉会议暨第八届国际华人心血管麻醉论坛

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3.请自留底稿，未经采用者，不退稿。所采用的稿件均刊登在“中国循环杂志”（核心期刊，国家优秀期刊）上。

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请注明：中国心脏大会-国际心血管麻醉会议暨第八届国际华人心血管麻醉论坛

付江泉 王迪芬 刘 辉
贵阳医学院附属医院 ICU 550004

摘要

目的：比较不同浓度神经生长因子（NGF）预处理离体幼鼠脑皮质培养细胞对脑缺血/再灌注(cerebral ischemia-reperfusion injury,I/R)损伤的保护作用。方法：取出生24h内的SD乳鼠脑皮质细胞,体外培养至第7日随机分为正常对照组、药物损伤组、及10、50、100ug/l神经生长因子预处理组。各预处理组分别以对应浓度的药物进行预处理，24h后除正常对照组外，各组予200μmol/L谷氨酸损伤0.5h，换正常培养液继续培养24h后进行观察。检测神经细胞存活率（MTT法）、乳酸脱氢酶（LDH）漏出率、细胞凋亡率；苏木素-伊红（HE）染色后倒置相差显微镜下观察细胞形态变化。结果：各浓度神经生长因子预处理组的细胞存活率高于药物损伤组，LDH 漏出量和细胞凋亡率不同程度的低于药物损伤组；各药物预处理组细胞形态的受损程度均较药物损伤组轻。三个预处理组中以50ug/l组效果最佳。结论：不同浓度的神经生长因子提前24h预处理离体幼鼠脑皮质培养细胞对脑I/R损伤均有保护作用,其中50ug/l神经生长因子预处理效果最佳。

关键词：神经生长因子；谷氨酸；预处理；脑缺血/再灌注损伤

责任作者及联系方式：王迪芬，E-mail:dfwang6@yahoo.com.cn

神经生长因子预处理对鼠脑皮质培养细胞缺血/再灌注损伤的保护作用

Preconditioning Effects of Nerve Growth Factor on Cerebral Ischemia-reperfusion Injury of Primary Cultured Cortical Neurons

Jiang-quan Fu, Di-fen Wang, Hui Liu
Department of ICU, The Affiliated Hospital of Guiyang Medical College, Guiyang 550004, China

Abstract

Objective: To compare the preconditioning effects of Nerve Growth Factor(NGF) on cerebral ischemia-reperfusion（I/R） injury in rat primary cultured cortical neurons and to discuss their possible mechanism.

Methods: ortical neurons harvested from SD mouse aged no more than 24 hours had been cultured for 7 days , then randomly divided into control group、I/R group and NGF of 10、50、100ug/l preconditioning groups. Preconditioning groups were treated by drugs correspondindingly . After another 24 hours, 200μmol/l glutamate were given into all groups except for control group for half an hour. Then all groups were changed back to normal culture medium.24 hourslater, determinated the survival rate,the efflux rate of LDH and the rate of apoptosis .Observed the cellular shape and ultrastructure by hematoxylin- eosin（ HE）dye and electronic microscopy correspondindingly.

Results: The survival rate of NGF groups were significantly higher than those in ischemia group ; The efflux rate of LDH and the rate of apoptosis in NGF groups were significantly lower than those in ischemia group. The cellular shape of NGF groups were destructed more slightly than ischemia group's. 50ug/l NGF preconditioning group had the best results among those groups.

Conclusions: NGF preconditioning 24 hours before cerebral I/R have protective effects. 50ug/l NGF preconditioning group had the best results in this study.

Key Words：Nerve Growth Factor；Glutamate；Preconditioning；Ischemia-reperfusion injury

Corresponding Author: Di-fen Wang, E-mail:dfwang6@yahoo.com.cn

缺血性脑血管病是严重危害人类健康的常见病,近年来的研究发现缺氧缺血性脑病(HIE)脑细胞的损伤可分为由急性能量衰竭造成细胞坏死及迟发性神经元损伤两个阶段,后者即为神经凋亡。预处理调动机体内源性抗损伤能力,保护缺血缺氧的组织细胞,是近年来脑血管领域的研究热点。预处理方法多种多样,许多刺激都可以行预处理,诱发机体发生一系列变化,对继之而来的脑缺血产生保护作用。由于药物预处理具有相对安全、方便、易于控制等优点,成为研究脑保护的一种新途径和发展趋势。神经生长因子(NGF)在脑内有广泛的分布,对神经细胞的发育、成熟、存活起着重要的作用。目前大量实验已证实神经生长因子预处理可促进胚胎和成体神经元的存活。但对体外培养的神经细胞的促存活作用报道较少。本试验通过建立体外谷氨酸诱导的原代培养的大鼠乳鼠大脑皮质神经细胞损伤模型，研究不同浓度神经生长因子对脑缺血再灌注损伤的保护作用，并初步探讨神经生长因子的最佳给药浓度。

一、材料和方法

1. 材料

新生SD乳鼠（出生24小时内，由贵阳医学院实验动物中

心提供）；

DMEM/F12培养基（HyClone 公司,美国）；标准胎牛血清（天津市海洋生物制品科技有限公司）；注射用鼠神经生长因子（武汉海特生物制药股份有限公司）；即用型SABC免疫组化染色试剂盒（武汉博士德生物工程有限公司）；LDH测试盒（南京建成生物工程研究所第一分所）；MTT细胞增殖及细胞毒性检测试剂盒（凯基生物科技发展有限公司）。

2. 乳鼠大脑皮层神经细胞原代培养

取生后1d之内的新生SD乳鼠,碘酒和75%的酒精消毒皮肤后取双侧大脑皮质,剔除软脑膜和血管，D-hank′s液冲洗两遍，用眼科剪剪成1mm3左右的小块，终浓度0.125%胰蛋白酶常温下消化3-5min,边消化边用巴士管吹打，至肉眼看不到细胞团块，立刻用培养基中止消化，200目筛网过滤成单细胞悬液，细胞计数板计数，加培养基适量，调细胞浓度为105-106/L的细胞悬液，接种于96孔培养板、24孔培养板、盖玻片、50ml培养瓶中，置37℃、5%CO2培养箱中孵育，第三天用含2.5μg/ml阿糖胞苷[1]培养基换液一次,抑制神经胶质细胞及纤维细胞生长，第六天用培养基换液，准备大脑皮质神经细胞鉴定和实验分组。

3. 实验分组

随机分为五组：A组（正常对照组）；B组（药物损伤组）；C1组（10ug/l神经生长因子预处理组）；C2组（50ug/l神经生长因子预处理组）；C3组(100ug/l 神经生长因子预处理组)。

4. 大脑皮质神经细胞鉴定

脑皮质细胞体外培养至第七天,取出24孔培养板内的盖玻片，参照即用型SABC 免疫组化染色试剂盒说明书操作，然后观察。

5. 药物预处理

脑皮质细胞体外培养至第七天，细胞C1组、C2组、C3组、D组去掉原培养基,分别加入10ug/l神经生长因子培养基、50ug/l神经生长因子培养基、100ug/l神经生长因子培养基、100umol/l依达拉奉培养基，继续培养24h。

6. 谷氨酸毒性神经细胞损伤模型建立[2]

培养8天的皮层神经细胞去掉原培养基,B组、C1组、C2组、C3组、D组,加入含Glu的无血清培养基(Glu终浓度200μmol/L),作用半小时，D-Hank′s冲洗两遍后,所有组均换含10%胎牛血清的 DMEM/F-12培养基,继续培养24小时。

7. 指标检测（所有细胞生长至第九天）

（1）MTT法测定神经细胞存活率:将接种细胞的96孔板，每孔加50μl1×MTT,在37。C孵育4小时，使MTT还原成甲月赞，吸出上清液，每孔加150μl二甲基亚砜，使甲月赞溶解，轻轻震荡，使其充分溶解，酶标仪在550nm波长处检测每孔的光吸收值（OD），减去本底OD值，然后按下式计算细胞存活率：细胞存活率%=（加药组细胞OD值/对照组细胞OD）×100%。

（2）LDH漏出率的测定：24孔培养板吸取每孔培养液，参照试剂盒说明书测定各孔中OD值，留下的24孔培养板，加培养液，量与吸取的相同，用力吹打，显微镜下见细胞基本无存活，参照试剂盒说明书测定各孔中OD值。根据公式计算LDH漏出率[3]细胞培养液LDH漏出率=培养液LDH的OD值/（培养液LDH的OD值+细胞匀浆液LDH的OD值）×100%。

（3）流式细胞仪检测细胞凋亡率:将各组细胞消化离心，收集于离心管,制成单细胞悬液,按凋亡试剂盒要求加入试剂,6h内流式细胞仪上检测凋亡。

（4）HE染色，倒置相差显微镜下观察神经细胞的形态学变化。

（5）透视电镜检查：将各组细胞分别收集，细胞固定液固定，送往贵阳医学院电镜室检查，观察细胞器的变化。

8. 统计学处理

量化指标以均数标准差（x±s）表示，分析组间差异显著性用SPSS13.0统计软件进行方差分析和q检验，以P＜0.05为差异有统计学意义。

二、结果

1. 大脑皮质神经细胞鉴定

细胞生长至第七天，随机抽取，进行NSE（神经元特异烯醇化酶）免疫组化染色，阳性着色为棕黄色，本实验反映成阳性，说明所培养细胞是脑皮质细胞。如图1

2. 神经细胞存活率（MTT法）测定（表1）

神经细胞存活率（MTT法）：各组MTT检测值中正常对照组与损伤组比较P＜0.01；NGF预处理各组与损伤组比较P＜0.05，但50ug/lNGF组P值最小P＜0.01。

3. LDH漏出率（表1）

各组LDH漏出率检测值中正常对照组与损伤组比较P＜0.01；NGF预处理各组与损伤组比较P＜0.05，但50ug/lNGF组P值最小P＜0.01。

4. 神经细胞凋亡率（表1）

各组细胞凋亡率值中正常对照组与损伤组比较P＜0.01；NGF预处理各组与损伤组比较P＜0.05，但50ug/lNGF组P值最小P＜0.01。

表1 各组神经细胞存活率、LDH漏出率、细胞凋亡率比较

组别	细胞存活率（n=28,%）	LDH漏出率（n=8,%）	细胞凋亡率（n=5,%）
正常对照组	0.25±0.05	0.41±0.09	7.88±0.70
药物损伤组	0.19±0.04**	0.56±0.03**	14.52±0.77**
神经生长因子1组	0.21±0.04△	0.50±0.06△	10.77±1.07△△
神经生长因子2组	0.23±0.04△△	0.46±0.07△△	10.38±0.70△△
神经生长因子3组	0.21±0.04△	0.50±0.02△	13.34±0.57△

**P<0.01vs正常组，△P<0.05vs谷氨酸损伤组，△△P<0.01vs谷氨酸损伤组

5. HE染色后倒置相差显微镜下细胞形态变化

正常对照组细胞形态基本正常，谷氨酸损伤组胞体皱缩成球形，胞核大部分破碎，轴突皱缩明显，有的突起断裂,网络消失,细胞数量明显减少，不少细胞破裂死亡。50ug/l神经生长因子组，依达拉奉组细胞数量减少不明显。细胞基本联成网状。较多细胞保留突起,仅少数细胞肿胀,坏死。（见图2-6）

图1 免疫组化染色，光学显微镜×1000

图2 HE染色正常组（200×）

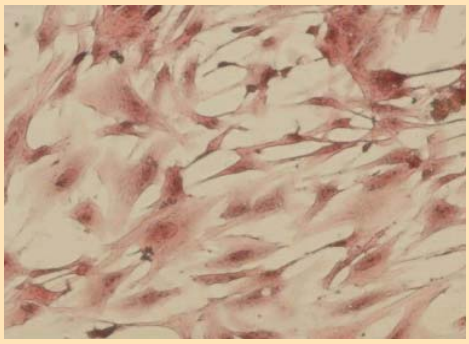


图3 HE染色谷氨酸损伤组（200×）

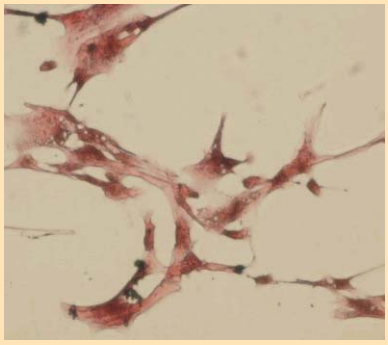


图4 HE染色神经生长因子10ug/L组（200×）

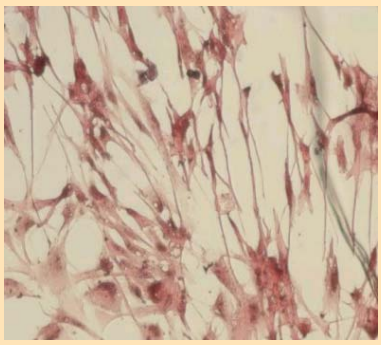


图5 HE染色神经生长因子50ug/L组（200×）

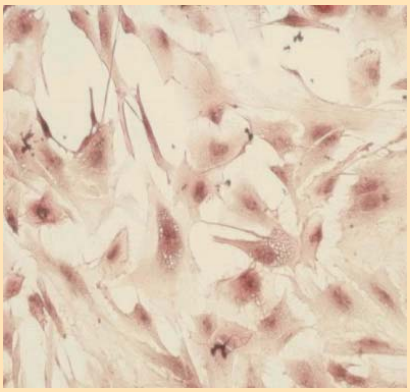
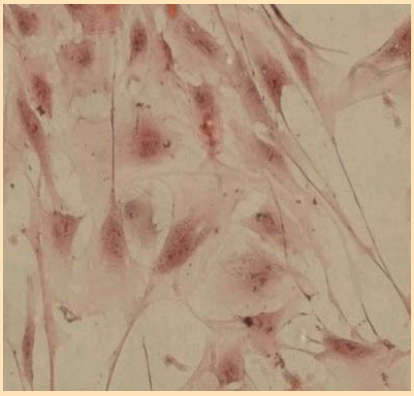


图6 HE染色神经生长因子100ug/L组（200×）



讨论

近年来，关于药物预处理对脑缺血再灌注损伤保护作用机制的研究很多。但大多是通过活体动物实验来进行。随着科学研究的发展与深入，神经细胞原代培养已成为研究神经细胞形态、功能以及损伤、缺血等病理变化的重要方法之一。本试验选择新生24h内的SD乳鼠取材，采用酶学方法分离神经细胞，建立了相对稳定、可靠的获得神经元的方法。由于神经元在培养过程中的各种改变与体内相似，所以可通过直接施加试验因素来了解其对神经元的存活、生长、发育、形态功能及衰老死亡等变化的影响，可将生物体内复杂的生物过程通过单因素分析来阐明可能的细胞机制。因此相比较活体动物实验而言，细胞培养具有影响因素单一、受机体复杂因素干扰少和结果容易分析等优点[4]。

脑血管疾病是目前严重威胁人类健康的疾病之一，因此，探讨脑缺血再灌注损伤的发病机制及其药物保护问题就显得十分必要。目前关于缺血再灌注损伤的发病机制有若干学说如：(1)氧自由基大量生成学说；(2)钙超载学说；(3)兴奋性氨基酸大量释放学说；(4)能量代谢障碍及酸中毒学说；(5)内皮素的作用、NO的合成等。这些学说并不是孤立存在的，而是密不可分，互相联系的。脑缺血引起的神经元损伤包含凋亡与坏死两种方式[5]，凋亡又称程序性细胞死亡[6]，是指细胞

在一定的生理或病理条件下,遵循自身的程序,结束生命的过程,是一个主动的、高度有序的、基因控制的、一系列酶参与的过程。凋亡是延迟性神经元死亡的重要通路。

研究表明采用轻度的脑缺血预处理可以改善致死性缺血性损伤所引起的神经元损害。而药物预处理是在缺血预处理的理论基础上,通过药物模拟缺血预处理样作用,对脑缺血再灌注损伤产生保护作用,具有很好临床应用价值,目前发现不少药物性预处理均有保护作用。药物预处理对脑缺血再灌注损伤保护作用机制有如下几个主要方面：减轻炎症反应，增强酶的活性，清除自由基，减轻钙超载等[7]。

缺血再灌注损伤的发病机制中有一重要的机制为兴奋性氨基酸大量释放学说，据研究表明,Glu兴奋毒性作用的可能机制是Glu通过与其受体结合对神经细胞产生兴作用的。在病理状态下突触间隙内Glu大量增加,可过度激活Glu受体:(1)非N-甲基-D-门冬氨酸（NMDA）受体过度激活,Na+内流,Cl-、H_2O亦被动进入,造成细胞肿胀。(2)NMDA受体过度激活,Ca2+内流。细胞内钙浓度上升触发一系列生化过程包括激活蛋白酶、磷脂酶,产生花生四烯的代谢产物,自由基形成,线粒体功能障碍,能量耗竭,最终导致细胞死亡。其中,通过NMDA受体的钙内流在Glu神经毒性机制中起关键作用。(3)在正常情况下,Glu与胱氨酸通过Glu/胱氨酸转运体进行转运,维持细胞内谷胱甘肽的合成。当细胞外Glu过多时,可抑制Glu/胱氨酸转运体的功能,使胱氨酸进入细胞减少,Glu可使细胞内氧化型和还原型谷胱甘肽均减少,对还原型谷胱甘肽的耗竭作用尤为明显[8]。谷胱甘肽是脑细胞内清除活性氧成分的主要物质[9],因此细胞外Glu过多时细胞内活性氧成分堆积,从而对细胞产生毒性作用。本实验用高浓度谷氨酸模拟脑缺血时兴奋性神经递质的大量释放，以此来建立一种类似于缺血再灌注损伤的损伤模型，大量研究资料表明,在谷氨酸(Glu)介导的神经细胞损伤中,既有急性的细胞坏死存在,又有迟发性的细胞死亡,即凋亡的存在。而在本实验中无论是从流式细胞仪检测的凋亡细胞率，还是从MTT和LDH检测及形态学上看，正常组和谷氨酸损伤组有着显著差异，说明本实验造模成功，谷氨酸对于神经细胞确有毒性。

本实验中MTT比色原理是利用活细胞线粒体脱氢酶能将MTT盐还原成蓝紫色甲瓒颗粒,以颗粒溶解后呈现的颜色深浅反映细胞活性。增殖生长旺盛的细胞将还原更多的MTT,并具有较高的光吸收值;反之,则光吸收度越低[10]。LDH广泛存在于各种组织细胞中,在病理情况下细胞膜通透性增高时LDH漏出增加。在细胞学实验中常以LDH漏出率反映细胞的损伤的程度。流式细胞分析法可对单个细胞或其它生物微粒进行快速定量分析与分选,是定量检测细胞凋亡的重要方法之一。在本实验中神经生长因子组与谷氨酸损伤组相比较在MTT，LDH漏出率，细胞凋亡率三方面均有显著差异。在形态学上，在相差显微镜下，谷氨酸损伤组胞体皱缩成球形,突起断裂,网络消失,细胞数量明显减少，不少细胞破裂死亡。神经生长因子组，细胞数量减少不明显。细胞基本联成网状。较多细胞保留突起,仅少数细胞肿胀,坏死。

NGF是神经营养因子家族的重要成员，是一种靶源性细胞因子，在中枢神经系统的发育成熟及维持其神经元生存与结构和功能正常方面均具有重要作用。外源性NGF具有抑制受损神经细胞凋亡的作用，NGF减少神经细胞损伤的机制目前还不十分明确,大量实验表明NGF对中枢神经元保护作用可能主要有以下几方面机制：(1)抗自由基作用，NGF可增加大鼠皮层神经元中超氧化物歧化酶和谷胱甘肽还原酶的活性，因此，NGF通过增加过氧化氢酶，超氧化物歧化酶等自由基清除剂的活性．对减轻神经元损伤有重要作用[11]。(2)拮抗兴奋性氨基酸的神经毒性，王艳辉等[12]的实验证明了这一点。(3)稳定细胞内Ca水平，脑缺血损伤后，细胞内钙超载可通过多种机制引起神经元的凋亡和坏死，NGF能稳定细胞内自由Ca的水平来抵御缺血的损伤。(4)抑制神经细胞凋亡，谭永星[13]采用夹闭沙土鼠双侧颈总动脉造成全脑I／R损伤模型。采用NGF侧脑室注射法进行预处理。得出结论：NGF预处理通过调节凋亡相关调控基因Bcl－2及Bax的不同表达能明显减轻沙土鼠全脑I／R损伤引起的神经细胞凋亡。结合本实验，NGF可能是通过拮抗谷氨酸引起的细胞内钙超载和活性氧成分堆积而发挥保护作用的。而本实验结果也支持这一点。

在本实验中，神经生长因子以50ug/L组的保护效果最好，而并没有呈现出剂量效应依存关系。考虑可能原因是：如前所述，NGF的生物学活性是通过与效应细胞上的特异受体结合而实现的。TrkA是一种酪氨酸蛋白激酶受体,被认为是NGF的功能受体。TrkA主要在神经系统细胞上表达,NGF与TrkA结合后,通过多种途径促进神经元存活。TrkA不仅能启动促进细胞存活的信号,同时能抑制P75NTR启动的死亡信号[14]。当NGF的浓度达到一定值时，NGF与TrkA结合就达到了饱和。即产生了受体饱和现象。所以NGF的保护作用并没有随剂量的增加而加强。

综上所述，通过离体细胞培养实验，神经生长因子对于谷氨酸介导的神经细胞类缺血再灌注损伤确有一定的保护作用。但其保护作用的具体机制还有待进一步的探索和研究。

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王春耀 秦君平 胡小芸
彭劲民 杜 斌
北京协和医院内科ICU，北京，100032

摘要

目的：报道一例静脉联合肝素治疗高甘油三酯血症相关急性重症胰腺炎的病例，并复习相关文献。

内容：一例急性重症胰腺炎（急性生理和慢性健康评分II 20分，Ranson评分6分）的孕妇患者来我院就诊。留取静脉血标本时发现明显脂血，总甘油三酯85.07 mmol/L，诊断考虑高甘油三酯血症相关急性重症胰腺炎。在治疗过程中除常规的水化、抗感染和抑制胰酶分泌治疗外，通过静脉肝素联合胰岛素泵入，于24小时后将甘油三酯降至15.80 mmol/L，并于72小时后将甘油三酯降低至3.68 mmol/L，从而控制了病情的进展。本文对有关文献进行了综述。

结论：肝素联合胰岛素静脉泵入治疗可以在短时间内有效降低高甘油三酯血症相关急性重症胰腺炎患者的血清甘油三酯水平，有可能成为一种在该类患者中替代血浆置换的治疗手段。

关键词：高甘油三酯血症；急性重症胰腺炎；肝素

肝素联合胰岛素治疗高甘油三酯血症相关急性重症胰腺炎1例

Hypertriglyceridemia-induced Acute Pancreatitis Treated with Intravenous Heparin and Insulin: A Case Report and Review of Literature

Chun-yao Wang, Jun-ping Qin, Xiao-yun Hu, Jin-min Peng, Bin Du
Department of ICU, Pecking Union Medical College Hospital,100032

Abstract

Purpose: A case of hypertriglyceridemia-induced acute pancreatitis who was managed with insulin and heparin is reported. And relevant literatures are reviewed.

Summary: A 32-year-old pregnant female with severe acute pancreatitis presented at the emergency department, with Acute Physiology and Chronic Health Evaluation II score of 20, and Ranson score of 6. The blood sample exhibited a milky appearance, and blood chemistry confirmed severe hypertriglyceridemia (85.04 mmol/L). Hypertriglyceridemia-induced severe acute pancreatitis was diagnosed. Apart from fluid therapy, prophylactic antibiotics, and somatostatin to inhibit pancreatic exocrine secretion, combined with intravenous unfractionated heparin (500 IU/L) and insulin, resulting in a rapid decrease of serum triglycerides to 15.80 mmol/L at 24 hours, and 3.68 mmol/L at 72 hours after hospital admission. The patient was transferred to the general ward 21 days later. We reviewed relevant literature thereafter.

Conclusion: Intravenous heparin combined with insulin caused a rapid decrease of serum triglycerides, and might be a promising alternative to plasmapheresis in the treatment of hypertriglyciderenia induced pancreatitis.

Key Words: Hypertriglyceridemia; Acute Necrotizing Pancreatitis; Heparin

病例摘要

患者女性，32岁，孕28周+5，因腹痛伴呼吸困难1日入院。

患者入院前1日午餐后出现上腹阵发性绞痛，后加重呈持续性，伴烦渴、呼吸急促、少尿。于当地医院就医，查腹部B超提示“胰腺增粗”，考虑急性胰腺炎，遂转至我院急诊。来我院时患者出现发热，体温38.5C，端坐呼吸，呼吸频率50次/分，心率200次/分左右，血压130/90mmHg。查体示：双肺满布湿罗音，腹部膨隆，弥漫压痛。心电图示室上性心动过速，静脉采血为乳糜样脂血。血常规：白细胞13.75x109/L，血红蛋白129 g/L，血小板343x109/L；尿常规：酮体+++。胰功：血淀粉酶1329IU/L，脂肪酶6000IU/L。血糖17.1mmol/L。血脂：总甘油三酯85.04 mmol/L。动脉血气(储氧面罩吸氧)：pH 7.16，pCO_2 12 mmHg，pO_2 122 mmHg，SaO_2 98%，HCO3-4.3mmol/L，BE -21.4mmol/L，乳酸5.7 mmol/L。腹部超声显示胰腺体部、尾部稍增粗，边界回声欠清晰，胆总管显示不清，胆囊未见结石及占位。经补液、降糖消酮、止痛、控制心室率等处置后，患者症状无改善。胎心监测连续1分钟未见搏动，考虑胎死宫内。遂以急性胰腺炎、糖尿病酮症酸中毒收入内科重症监护病房(ICU)。患者妊娠期间曾发现血糖升高，未进一步明确，血脂情况不详。无高脂血症家族史。入院诊断：高甘油三脂相关急性重症胰腺炎，急性呼吸窘迫综合征，妊娠相关糖尿病，糖尿病酮症酸中毒。

入院当日即于快速顺序诱导下行经口气管插管、呼吸机辅助呼吸、去甲肾上腺素泵入，维持平均动脉压70mmHg。入院时急性生理和慢性健康评分(APACHE) II 20分，Ranson评分6分。继续静脉输液治疗，同时应用亚胺培南西司他丁钠预防感染，生长抑素抑制胰酶分泌。因考虑患者系高甘油三酯血症相关急性胰腺炎，联合应用普通肝素500U/h静脉泵入及胰岛素持续静脉泵入。血糖水平维持在10mmol/L左右。入院后24、48和72小时复查血甘油三酯，结果分别为15.80、7.18和3.68mmol/L。尿常规显示酮体转阴。血淀粉酶从572 U/L下降至88U/L。遂停用肝素及胰岛素。入院48小时人工破膜后引产一死婴。同日行CT检查显示腹腔内积液，胰腺周围广泛渗出，未见胆管结石，考虑CT分期E。遂于CT引导下行腹腔脓肿及胰腺周围脓肿穿刺引流，患者症状逐渐缓解。入院后第10日尝试脱机失败。再次复查腹部CT并重新留置腹腔脓肿引流，引流液培养结果为万古霉素耐药肠球菌。根据药敏结果

应用利奈唑烷，此后患者症状逐渐缓解。入院后第19日成功脱机并拔除气管插管，入院21日后转出ICU。

讨论

在急性胰腺炎的常见病因中，高甘油三酯血症位居第三位，仅次于饮酒和胆石症[1,2]。高甘油三酯血症相关急性胰腺炎占急性胰腺炎的1-4%，占妊娠期胰腺炎病因的56%[3]。除原发性家族性高甘油三酯血症外，导致甘油三酯升高的其他常见原因还包括1型和2型糖尿病、糖尿病酮症酸中毒、酗酒、甲状腺功能低减等继发因素。患者的妊娠期糖尿病未经积极治疗，急诊就诊时血糖升高且尿酮体阳性，考虑其高甘油三酯血症可能继发于妊娠糖尿病、糖尿病酮症酸中毒。

血甘油三酯超过10mmol/L(1000mg/dl)时可诱发急性胰腺炎。究其原因，可能为甘油三酯通过胰腺脂肪酶代谢分解后，导致胰腺血液循环内的细胞毒性游离脂肪酸浓度升高，进而损伤血管内皮细胞，引发胰腺缺血损伤和炎症反应。持续性高甘油三酯血症可导致上述情况反复发生，胰腺组织不断破坏，导致急性胰腺炎进行性加重，形成恶性循环[4]。本例患者无饮酒、胆石症情况，考虑其急性重症胰腺炎（APACHE II评分>8，Ranson评分>3）的病因为高甘油三酯血症。

文献报道[2]，血甘油三酯如能迅速降低至5mmol/L以下，高甘油三酯血症相关急性胰腺炎的临床情况可明显改善。因此，针对高甘油三酯血症相关急性胰腺炎，除急性胰腺炎的传统治疗措施如水化、止痛和减少胰酶分泌外，降脂治疗（如血浆置换、胰岛素和肝素等）非常重要[5-13]。本例即通过静脉肝素联合胰岛素治疗，迅速降低血甘油三酯水平，控制了病情的进展。

口服降脂药物是最常用的降脂方法，但起效时间较慢。另外，急性胰腺炎患者多采用早期禁食，从而限制了口服药物的使用。因此，口服降脂药物仅作为辅助方法用于已经建立空肠营养通路的患者。

快速降低血脂的最直接方法是血浆置换。当患者不合并高血糖，且无其他禁忌症（如生命体征不稳定、不能耐受中心静脉置管）时，应考虑进行血浆置换清除血清中的甘油三酯。文献报道，一次血浆置换可使甘油三酯平均下降41%[5]。当血浆置换后血清甘油三酯低于5mmol/L时，即可终止血浆置换。

然而，昂贵的价格和医疗条件的制约，限制了血浆置换的普遍应用。当没有条件进行血浆置换或患者不能耐受，且血糖超过27.8mmol/L(500mg/dl)时，可选择静脉胰岛素治疗。静脉胰岛素可通过加强脂蛋白酯酶活性，从而促进血清内乳糜颗粒分解为甘油和游离脂肪酸，进而降低胰腺血液循环中的甘油三酯水平。在高甘油三酯血症相关急性重症胰腺炎患者中，静脉胰岛素较皮下胰岛素更有效[6,7]。常用胰岛素剂量为0.1-0.3U/kg/h泵入，每4小时监测血糖，维持于8.3-11.1mmol/L。该方案可于7日内使血甘油三酯降低至5mmol/L以下。文献报道，对没有糖尿病病史的患者，胰岛素同样可以有效降低甘油三酯[8]。

近年发现，静脉肝素也能够迅速降低血甘油三酯水平。大量脂蛋白酯酶通过硫酸乙酰肝素蛋白多糖的寡糖链被锚定于内皮细胞上[14]。当注射肝素时，较硫酸乙酰肝素亲和性更强的肝素诱导内皮细胞内的脂蛋白酯酶入血，在提高血清脂蛋白酯酶的同时，降低了内皮细胞内的游离脂肪酸水平。肝素应用早期可提高循环内脂蛋白酯酶水平，随肝素代谢分解后，脂蛋白酯酶储存减少，反而增加乳糜颗粒水平[15]。故目前多数病例报告主张联合应用胰岛素和肝素降脂[9-14]。

有关肝素的剂量和用药途径尚未达成共识。报道的用药途径包括皮下和静脉用药，但样本量尚不足以比较两种用药途径的差别[9-14]。现有资料显示，无论何种给药方式，24小时肝素用量多为10000-20000U，分2-3次给药。肝素治疗期间部分凝血活酶时间的目标水平尚不清楚。研究表明，静脉肝素治疗多可于24小时内使血甘油三酯水平降低50%以上。本例24小时应用静脉肝素12000U，血甘油三酯水平下降63%，疗效与文献报道一致。

国内有报道联合应用低分子肝素及持续床旁血滤治疗HTGP[16]。治疗期间皮下应用低分子肝素100U/kg q12h。结果显示，3日后甘油三酯水平下降约50%(17.5±6.3mmol/L vs.8.4±3.7mmol/L)，提示低分子肝素对于高甘油三酯血症的疗效可能与普通肝素相同。但是，上述研究结果受到血液滤过治疗的影响。因此，单独应用低分子肝素的疗效尚需进一步临床实验证实。

总之，快速降脂治疗是高甘油三酯血症相关急性胰腺炎的一种重要辅助治疗措施。目前针对高甘油三酯血症相关急性胰腺炎尚无标准的降脂治疗措施，肝素联合胰岛素治疗不失为一种迅速降低血甘油三酯水平的有效方法。

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陈广福[1] 王迪芬[1] 刘怀清[2] 卢建明[2]

1.贵阳医学院附属医院重症医学科 550004

2.重庆航投集团南桐总医院麻醉科 400802

CRRT治疗重症急性胰腺炎成功1例报道

One Case Report on CRRT Successful Treatment for Severe Acute Pancreatitis

Guang-fu Chen[1], Di-fen Wang[1], Huai-qing Liu[2], Jian-ming Lu[2]

1.The Intensive Care Unit, Guiyang Medical College 550004

2.Department of Anesthesiolody,Nantong General Hospital, Chongqing Nengtou Group 400802

重症急性胰腺炎（SAP）属于急性胰腺炎的特殊类型，是一种病情险恶、病因复杂、并发症多、预后不良、病死率较高的急腹症，占整个急性胰腺炎的10%～20%[1]。20世纪80年代，多数病例死于疾病早期，直至近10年来，随着医疗技术水平的提高和发展，治愈率有明显提高，但总体病死率仍高达20%左右[1]。对临床医师的诊断治疗也是一种考验。现将连续性肾脏替代治疗（CRRT）成功救治重症急性胰腺炎1例报告如下：

一、病例摘要

患者男性，38岁，因“上腹部持续疼痛3天”于2011年10月29日16时急诊入院。3天前患者饮酒后出现上腹部隐胀痛，可忍受，未处理，约6小时后感疼痛较前明显加重，呈持续性疼痛，难忍受，感全身发热，出汗，不伴腰背部放射痛，无恶心、呕吐，无皮肤巩膜黄染，无畏寒、心慌、胸闷、腹泻、呕血、黑便等，小便稍黄。患者既往有高血压病史7年，自行口服“降压药”治疗，血压控制可，有明确的酗酒和暴饮暴食史。住院期间患者突感胸闷、腹胀、呼吸急促，血氧饱和度下降至80-88%左右，并行气管切开术，后于2011年11月1日转入我科重症监测治疗。转入时查体：患者病情危重，神志清楚，平车推入，气管切开处呼吸机辅助呼吸，T：36.9℃；P：151次/分；R：41次/分；BP：113/70mmHg；全身皮肤、巩膜无黄染。腹膨隆明显，腹式呼吸受限，腹肌紧，全腹压痛，尤以剑突下左上腹压痛为重，轻度反跳痛及肌紧张，肝区叩击痛（＋），移动性浊音（＋），辅助检查血常规：白细胞计数30.34G/L，中性粒细胞比例84.3%，红细胞数2.85T/L，血红蛋白87.00g/L，血小板数214.00G/L；肾功能：尿素氮17.25mmol/L，血肌酐187.55umol/L；电解质：钾(K)3.98mmol/L，钠(Na)135.37mmol/L，氯(Cl)104.40mmol/L，钙(Ca)1.18mmol/L，磷(P)0.52mmol/L，镁(Mg)0.65mmol/L；肝功能：谷丙转氨酶(ALT)35.27u/L谷草转氨酶(AST)92.34u/L总胆红素(TBIL)15.64umol/L直接胆红素(DBIL)5.63umol/L间接胆红素(IBIL)10.01umol/L总蛋白(TP)49.62g/L；动脉血气分析（上呼吸机后）：PH7.41，PCO2 29.70mmHg，PO2 61.00mmHg，HCT38%，HCO3 17.7mmol/L，BE -6.9mmol/L，SaO2 90%，Lac1.4 mmol/L,血淀粉酶：170.25U/L；尿淀粉酶：2242U/L。DIC全套：AT-Ⅲ81%，D-二聚体＞4ug/ml，Fib 11.7g/L，PT 14.7sec，APTT 34.5sec，TT 16.9sec。胸腹部CT检查报告：1；重症急性胰腺炎CT改变，腹腔大量积液，建议治疗后复查。2；双侧胸腔积液并左下肺膨胀不全。3；重度脂肪肝，肝右叶钙化灶。4；盆腔实质脏器CT平扫未见明显异常。胸,腹部B超检查报告：1；急性胰腺炎声像。2；肝内光点细密集，请结合临床。3；胆囊腔内等回声光点，考虑胆汁淤积可能。4；脾肿大。5；腹腔积液。床旁胸片报告：1；左侧胸腔积液并左下肺膨胀不全。测定膀胱内压为30cmH20。腹水常规检查：淀粉酶112.54u/L，氯(Cl-)109.00mol/L乳酸脱氢酶(LDH)6751.90U/L，APACHE-Ⅱ评分17分。诊断：1.重型急性胰腺炎；2.Ⅰ型呼吸衰竭并ARDS；3.腹腔间隔室综合征；4.原发性高血压；5.重度脂肪肝。

二、诊治经过

呼吸机辅助呼吸；维持循环功能稳定，维持水电解质及酸碱平衡，内环境稳定；抗感染，抑制消化液分泌，预防消化道溃疡、急性胃粘膜病变；行经口空肠置管术营养支持，维护各脏器功能及相关对症支持治疗；左侧腹腔置入引流管，左侧胸腔置管闭式引流；生大黄低压灌肠排便，持续芒硝腹部敷治疗，针灸科、双侧足三里胃复安注射改善腹胀；留置导尿等处理。患者转入次日即予经皮左股静脉导管置入建立临时血管通路，应用Aquarius连续性血液净化机及M100血滤器行床旁CVVHDF每天连续治疗10个小时共8次，总共80个小时，血流量：100～200ml／min，透析液量：1000ml／h，前置换液量：500～1000ml／h；超滤量：50～250ml／h；

抗凝：采用低分子肝素抗凝法。总透出液6450ml，总灌洗出液2000ml，总超量滤19300ml,在CVVHDF治疗前后、次日均采血，按常规每天进行肝肾功能、血淀粉酶等相关生化检查。疗效：CRRT治疗后腹胀明显减轻，腹水明显减少，腹引管和胸引管引流量逐渐减少，左侧腹腔引流管引流出暗红色坏死液3895ml，左侧胸腔闭式引流管引出胸水365ml，体温逐渐恢复正常，心率血压逐渐平稳，呼吸频率由原来转入时41次/分治疗后恢复至19次/分，血氧饱和度维持在96-100%，气促，呼吸困难，胸闷等症状逐渐消失。患者经过治疗25天，11月25日，复查血淀粉酶：26.12U/L；尿淀粉酶：112U/L。膀胱内压13cmH20。患者停呼吸机，自主呼吸19次/分，血氧饱和度96-100%，心率86次/分，血压136/85mmHg（胃注降压药）。11月26日查血常规(全血):白细胞计数(WBC)6.67G/L、血红蛋白(HGB)110.00g/L,红细胞压积(HCT)32.90%,血小板计数(PLT)339.00G/L，中性粒细胞百分率(N)63.5%.11月26日查血气分析：PH7.46，PCO239mmHg，PO2111mmHg，HCT29%，HCO3-27.7mmol/L，Lac0.5mmol/L，BE3.9mmol/L，患者病情稳定，于11月26日转回普通病房继续治疗。

二、讨论

重症急性胰腺炎中70%～80%的患者是由于胆道疾病、酗酒和暴饮暴食所引起的。其发病机制是一个十分复杂，多因素综合参与的病理生理过程，相关学说有“胰腺胰酶自身消化”、“胰腺血循环障碍”、“白细胞过度激活”和“肠道细菌移居胰腺组织”等。而“白细胞过度激活”被认为是SAP致死亡的重要原因[2]，目前最支持的观点是胰液对胰腺及其周围组织自身消化的结果。SAP早期由于炎症介质的大量释放、毛细血管通透性升高，大量液体渗出，致有效血容量严重不足、心率增快、血压下降、尿量减少等休克表现。同时多种炎性细胞因子“瀑布样级联反应”而导致的全身性过度炎症反应，最终并发SIRS和MODS而导致死亡。其主要临床表现为腹痛，腹水，黄疸，休克，高热，呼吸异常，神志改变，消化道出血，皮肤黏膜出血，脐周及腰部皮肤表现。本例患者既往有明确的酗酒和暴饮暴食史，发病前日喝烈酒2斤多，并且饮食无规律，发病后病情发展迅猛，很快出现休克、意识障碍、ARDS、腹腔间隔室综合征、大量腹水和胸水，提示：符合SAP诊断标准[3]。

近年来大量的临床和实验研究结果表明，血液滤过可早期缓解过度炎性反应而有效的保护器官功能[4,5]，使重症胰腺炎的治愈率明显提高。CRRT最大的特点是治疗时血流动力学稳定，可保持稳定的平均动脉压和有效肾灌注，保持颅内压的稳定，保证良好的脑血流灌注，可持续而平稳地控制氮质水平,可有效而平稳地保持重症病人水、电解质、酸碱的平衡。有助于纠正代谢紊乱和血容量不足，从而使血流动力学易于维持稳定[6]。CRRT可以通过对流和吸附清除炎性介质，还能清除细胞因子、代谢产物、淀粉酶、脂肪酶、胰蛋白酶、磷脂酶等，能清除体内过多水分、减轻组织细胞水肿、消除肺间质水肿、改善氧合、纠正代谢性酸中毒以及钾、钠、钙等电解质紊乱，提高患者的存活率。本例患者在接受CRRT治疗的第三天后腹胀减轻，第10天后腹胀明显减轻，腹水减少，同时体温下降，提示：CRRT可迅速逆转SAP病理生理过程向恶性方向发展，提高治愈率[7]。国外一些研究表明，在没有器官功能衰竭时开始CRRT治疗，患者住ICU时间和生存率均显著优于至少一个脏器出现衰竭后再接受CRRT治疗的患者[8]。研究还表明，使用CRRT后，腹痛、腹胀缓解时间、APACHEⅡ积分、住院时间及住院费用均较对照组显著降低[9]。本例患者在进入ICU后即采用了CRRT治疗和全面的脏器功能支持治疗，减轻或阻止了病情的进展，改善心、肺、肾、肝脏等器官的功能，最终改善了患者预后。

CRRT是以对流的方式滤过清除血液中的水分、溶质的一种治疗方法，接近正常肾小球滤过生理的肾替代治疗。同时血液灌流(HP)在重症胰腺炎患者的临床应用，这是一种新的血液净化系统。该系统采用动脉血液体外分流的技术，动脉血流入灌流器时受到吸附剂或其他生物材料的作用而得到净化或生化处理，灌流后的血液再经管道返回静脉系统。血液灌流依赖于吸附剂、酶、活细胞等对血液某些成分进行吸附粘除或加工处理[10,11]。还能更好地清除中、大分子如激素、炎性介质、肾素等物质，它已成为药物治疗外的一种有效的辅助治疗。

大量临床研究表明SAP患者早期实行CRRT治疗可以清除炎症因子和减轻肺间质水肿，提高PaO_2水平，有效的改善内环境以及肺氧合功能来有效阻止SAP向MODS进展改善患者预后。

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Effects of Dexmedetomidine on the Cerebral Function of Patients Undergoing Cardiac Valve Replacement Surgery

Fang Kang, Juan Li, Xiao-qing Chai, Jun Ma
Department of Anesthesiology,Anhui Provincial Hospital.230001

Objective: To investigate the effects of dexmedetomidine on the cerebral metabolism and changes of biochemical markers of cerebral injury of patients undergoing cardiac valve replacement surgery.

Methods: 45 patients undergoing selected cardiac valve replacement surgery were enrolled and divided into three groups: control group(C) and low doses dexmedetomidine group(D1) and middle doses group(D2) . Blood gas analysis of arterial blood and jugular bulb blood were tested on time of pre- CPB, clipping of ascending aortic released, CPB stopped, 6 hours and 24 hours after thesurgery. Serum leve ls of S-100 β and NSE were measured at the same time.

Results: The oxygen saturation of internal jugular venous bulb (SjvO2),difference of arterial- venous oxygen saturation (Da-jvO2) and oxygen uptake rate(CERO2) ,serum levels of S100B and NSE in the three groups did not vary significantly before CPB(P> 0. 05). But when clipping of ascending aortic released, SjvO2 decreased, correspondence with the Da-jvO2 and the CERO2 increased in the C and D1 groups. But it was not found in the D2 group. Serum leve ls of S-100 β and NSE inclined after CPB, and to the peak 6h after the sugery in all the patients. And they declined close to the basic level 24h after the sugery. The D2 group changed moderately than the other two groups.

Conclusions: Middle doses of dexmedetomidine can reduce the the cerebral metabolism rate of patients undergoing cardiac valve replacement surgery and has the cerebral protection effect.

Key Words: Dexmedetomidine; Surgery, Cardiac; Crebral function;

Glutamine Improves Vascular Reactivity Via O-GlcNAc Modification and Subsequent Induced HSP70, Reduced i-NOS Expression

Kang Zheng, Liang Jing
Department of Anesthesiology, Zhongda Hospital and College of Medicine, Southeast University, Nanjing, China. 210009

Object: To investigate the mechanisms of Glutamine induced O -linked N -acetyl-glucosamine improving vascular reactivity in septic shock rats.

Methods: Forty male SD rats weighting 250-300g were randomly divided into 5 groups (n=8 each): group S (sham operation group); group C (septic shock group , undergoing cecal ligation and puncture); group G (Glutamine, 0.75g/kg, was injected 1h before CLP); group Q(Quercetin, 0.4 g/kg was intraperitoneal injected 1h before CLP); group A(Alloxan, 90mg/kg was intraperitoneal injected 1h before CLP). Phenylephrine (PE)of the concentrations of 0.5, 1, 2, and 2.5 μg/kg was injected intravenously 6 h after CLP and the MAP increase percentage was calculated. The concentration-response curve of aorta rings from all groups rats were obtained by cumulative addition of PE, and PE Emax, EC50 were calculated. The serum concentration of nitrate/nitrite, the expression of the O-GlcNAc modification, HSP70 and i-NOS in aorta were detected from all groups.

Results: The MAP level induced by PE significantly decreased 47.73% in group C compared with group S(P<0.05).In group G, PE induced MAP level increased 34.43% compared with group C(P<0.05).The Emax and EC50 were significant impaired in group C (P<0.05) compared with group S, but partially restored in group G (P<0.05). The Emax and EC50 in group Q and A were calculated, but there was no statistical different between them and group C. The expression of O-GlcNAc modification, HSP70 were higher (P<0.05) while i-NOS, nitrate/nitrite were lower (P<0.05) in group S than group C. Compared with group G, i-NOS, nitrate/nitrite were higher

while the expression of O-GlcNAc modification, HSP70 were lower in group A, the HSP70 was reduced in group Q.

Conclusions: Glutamine improves vascular reactivity by inducing HSP70, reducing i-NOS, nitrate/nitrite via O-GlcNAc modification in septic shock rats.

Key Words: Glutamine, O-GlcNAc modification, Septic shock, Vascular reactivity, i-NOS, Heat shock protein 70;

Effects of Remifentanil Preconditioning on Adriamycin-induced Heart Failure Following Ischemia-reperfusion in Isolated Rat Hearts

Bin Wang,Ye Zhang

Department of Anesthesioloy,the Second Affiliated Hospital,An'hui Medical University ,Hefei,An'hui,230601.

Abstract: Aim To investigate the effects of remifentanil precondioning on Adriamycin Heart Failure following ischemia-reperfusion in isolated rat hearts.

Methods: All 60 adult male SD rats received 2 mg/kg adriamycin as an intravenous tail vein infusion once a week for 6 weeks at a total dose of 12 mg/kg to establish an adriamycin-induced chronic heart failure model. 60 heart failure rats randomly divided into 6 groups (10 each): control group (Sham), ischemia-reperfusion group(I/R), ischemia preconditioning group (IPC), 10 μg/L remifentanil precondioning group (RPC1), 30 μg/L remifentanil precondioning group (RPC2), 60 μg/L remifentanil precondioning group (RPC3). All heart were linked to the Langendorff apparatus. Left ventricular developed pressure (LVDP), ±dp/dtmax , heart rate (HR), coronary effluent (CF) were recorded and LDH were measured at the end of equilibration and 5 min , 30 min, 90 min of reperfusion. Myocardial infarct size were measured with TTC staining at the end of reperfusion. After reperfusion, phosphor-Akt and total Akt were determined by Western blot analysis.

Results: No differences in baseline hemodynamics and LDH were observed among the groups (P>0.05). Compared with group I/R, group RPC2 and group RPC3 resulted in a significantly improved functional recovery, had a significant increase in LVDP, ±dp/dtmax, CF and a significant decrease in IS(P<0.05). Meanwhile, group RPC2 and group RPC3 also markedly increased the expression of p-Akt compared with group I/R.

Conclusions: 30 and 60 μg/L remifentanil precondioning may effectively protect the hearts against ischemia-reperfusion injure in adriamycin-induced chronic failure isolated rat hearts by activating PI3K/Akt signal pathway.

Key Words: remifentanil; preconditioning; ischemia-reperfusion; adriamycin; heart failure; cardioprotection; PI3K-Akt signal pathway;

The Research on the Acid Lidocaine for the Endotracheal Tube's Penetration Ability

Can Liu,Wei Zhou,Xiao-ju Jin

Department of Anesthesiology,Yijishan Hospital Affiliated to Wan'nan Medical College,Wu'hu City,An'hui Province,241001

Objective: To determine the infiltration ability to endotracheal tube(ETT) cuff of lidocaine carbonate with different concentrations. Discuss the proper dosage and juncture of drug administration in theory.

Methods: Eighteen 7.5mm ID ETT were divided into three groups, each group contained six. Group L was filled with 2% lidocaine chloride 10ml, Group CL1 was filled with 0.865% Lidocaine carbonate 10ml and Group CL2 was filled with 1.73% Lidocaine carbonate 10ml. All ETT were placed in 20ml water for hot bath at 38℃ for 24h. Samples were drawn from bath water at 15min, 30min, 45min, 60min, 90min, 120min, 150min, 180min, 210min, 240min, 300min, 360 min. Lidocaine concentration was detected by HPLC.

Results: (1) Each group demonstrated an increase in both concentration and dose of lidocaine in the sample with time. The highest lidocaine concentration was reached in Group CL2 with 820±84μg/ml while 417±28μg/ml in Group CL1 and 3.7±0.6μg/ml in Group L. (2) Lidocaine infiltration rate in Group LC1 and Group LC2 reached peak

at 240min (1954±951μg/h) and 120 min (4434±286μg/h) respectively, then decreased. (3) By 360min the dose of infiltration lidocaine was 16403±1678μg in Group CL2, 8334±567μg in Group CL1 and 74±12μg in Group L. (4) There was no solution precipitation during the whole testing time and all cuffs remained intact.

Conclusion: Filling ETT cuff with 1.73% lidocaine carbonate 90min prior to the end of surgery or filling ETT cuff with 0.865% lidocaine carbonate 150min prior to the end of surgery can reduce ETT-induced emergence phenomena after general anesthesia and extubation complications with efficacy and safety.

Keywords: lidocaine carbonate, alkalinization, extubation, complication, cough reflex

Effects of Acute Exposure to Sevoflurane and Isoflurane on the Memory and Cognitive Function in Juvenile SD Rats

Zi-pu Yu[2], Ya-ying Huan[2], Shan You[2], Han Lin[1,3], Mei-qin Di[1], Qing-quan Lian[1,2]

Wenzhou Medical College, Zhejiang Wenzhou 325000, China

1.Department of Anesthesiology, Affiliated Sencond Hospital

2. Institute of Environmental Toxicology

3. Department of Environmental Medicine

Objective: To investigate effects and mechanism of acute neonatal exposure to sevoflurane and isoflurane on the memory and cognitive function in juvenile SD rats.

Methods: The model of acute exposure to the inhaled anesthetics was set up. 210 SD male rats on postnatal day (PND) 7 were randomly equally divided into seven groups: control group (CON), sevoflurane group (SEV), sevoflurane + muscimol group (SEV+MUS), sevoflurane + bicuculline group (SEV+BIC), isoflurane group (ISO), isoflurane + muscimol group (ISO+MUS), isoflurane + bicuculline group (ISO+BIC). Muscimol was given 1 mg/kg intraperitoneally 0.5 h before exposure in group SEV+MUS and ISO+MUS, and bicuculline was given 8 mg/kg in group SEV+BIC and ISO+BIC. The rats in group CON were exposed to 60% oxygen in air for 6 h, and the rats were exposed to 3.6% sevoflurane or 2.3% isoflurane in other groups individually. Morris water maze test were carried out for the survived rats on PND 21, then the hippocampus of animals were collected for immunohistochemistry assay and RT-PCR of GABA-A receptor α 1 and BDNF.

Results: The latency periods of rats in groups SEV and ISO were longer than group CON remarkably, and muscimol or bicuculline could not induce significant variation. Immunohistochemistry assays: There were no significant differences in the protein and mRNA expression of GABA-A receptor α 1 between group CON and other groups. Compared with group CON, the protein and mRNA expression of BDNF in group SEV and ISO were reduced statistically. Compared with group SEV or ISO, Muscimol or bicuculline administrated did not change the protein and mRNA expression of BDNF significantly.

Conclusion: Exposure of sevoflurane and isoflurane could inhibit memory and cognitive function in juvenile SD rats significantly. The phenomenon was not induced through GABA-A receptor α 1.

Key words: Inhaled anesthetics; Acute exposure; Memory; GABA-A receptor α 1.

Foundation item: The project supported by the grants of National Natural Science Foundation of Zhejiang Province (Y206467), National Natural Science Foundation of China(308003235), Program of Science and Technology Bureau of Wenzhou (Y20080117)

Corresponding author: Lin Han,

E-mail: nanlinhannansh@qq.com (0577) 88879169

The Effect of Various Lung Recruitment on Respiratory Function and Extravascular Lung Water Index in Patients with ARDS

Cheng-zhi Ding[1], Jian-guo Zhang[2], Zhen-guo Zeng[1], Fen Liu[1], rong Jiang[1], Cheng Nie[1], Ke-jian Qian[1]

1. Department of Critical Care Medicine, the First Affiliated Hospital of Nanchang University, Nanchang

330006, China;

2. Intensive Care Unit, People's Hospital of Linyi, Linyi, 276000, China)

ABSTRACT: Objective To investigate the effects of recruitment maneuvers with sustained inflation（SI）and pressure control ventilation on respiratory mechanics and hemodynamics in patients with ARDS.

Methods: Thirty patients with ARDS were randomized in 2 similar groups. One received RM with continuous positive airway pressure (CPAP) of 40 cmH2O for 40 seconds (CPAP recruitment), whereas the other received pressure control ventilation with positive-end expiratory pressure of 20 cmH2O and pressure control above positive end-expiratory pressure of 20 cmH2O for 2 minutes (pressure control recruitment maneuver [PCRM]). The RMs were performed and repeated once every 12 hours lasting 3 days. Parameters of Oxygenation index(PaO2/FiO2), Peak inspiratory pressure(PIP), Plateau pressure(Pplat), Static pulmonary compliance(Cst) and EVLWI of patients before the trial and at 12h, 24h, 48h, 72h of the test were measured and compared between groups. To monitor hemodynamics changes before and after RM. One-Way ANOVA, t-test and Fisher probabilities in 2×2 table were used to process the data.

Results: The PaO2/FiO2 and Cst of two groups both showed upward trend after treatment and the PIP and Pplat of two groups both showed downward trend after treatment, but the changes were not significantly different between two groups (P>0.05). ②The EVLWI of two groups showed downward trend after treatment(P<0.01), but the differences were not significiant at all time points between two groups (P>0.05). ③The MAP and CI of two groups both showed downward trend and the HR and CVP of showed upward trend during RM(P <0.01). The wave amplitude and duration of the Parameters in PCRM were lower than those of the other group, and the changes were significantly different at the point of 2min after RM and 5min after RM(P <0.01). Conclusion RMs with CPAP and SI could reduce EVLWI, increase oxygenation and lung compliance. The effect of PCRM on hemodynamic was lower than SI.

Key Words: Lung recruitment maneuver; Acute respiratory distress syndrome; Respiratory function; Extravascular lung water index

Sevoflurane Reduces Hepatic Ischemic Reperfusion Injury in Rat Via Activation of PI3K/Akt Signaling

Fu-zhou Hua, Jun Ying, Xiao-hong Du, Guo-hai Xu

Department of Anesthesiology; The Second Affiliated Hospital of Nanchang University, 330006

Objective: To evaluate the role of PI3K/Akt signal pathway of sevoflurane against hepatic ischemic reperfusion injury (HIRI).

Methods: Forty-eight adult male SD rats were randomly divided into 4 groups: sham group (SH group); hepatic ischemic reperfusion injury (HIRI, IR group); sevoflurane+HIRI (SI group); sevoflurane preconditioning + HIRI+ wortmannin (SW group), while all rats except SH group were suffered from segmental hepatic ischemic (70%) for 60min and were followed by reperfusion of 3 hours. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferane (AST) and interleukin-1 β (IL-1 β)were measured. The expression of phosphorylated PI3K, Akt and total Akt were examined by Western-Blotting analysis in hepatic ischemic reperfusion tissue.

Results: The levels of ALT, AST and the concentration of IL-1 β in IR group, SI group and SW group were significantly higher than that in SH group after 3h of ischemic reperfusion; compared to IR group and SW group, the levels of ALT, AST and the concentration of IL-1 β of SI group were obviously decreased; the expression of phosphorylated PI3K and phosphorylated Akt of SI group were significantly increased.

Conclusion: Sevoflurane can pretect hepatic ischemic reperfusion injury. The possibly protective mechanisms maybe related to activating the PI3K/Akt signal pathway.

Key Words: Sevoflurane; Hepar; Ischemic reperfusion injury; PI3K/Akt

A New Video Portable Intubationscope: A Clinical Evaluation of Its Efficacy and Safety of Intubation in Patients with General Anesthesia

Yu Zhou[1], Wei Wang[2], Rui-dong Qiao[1], Ning Zhang[1], Hong-hui Huang[1]

The Affiliated Zhuhai Hospital of Jinan Medical University, 519000, China

1.Department of Anesthesiology

2.Department of Critical Care Medicine

Abstract

Fiberscope is widely applied for operating room and intensive care unit when difficult airway patients need to intubate, but this instrument is so expensive and fragile that it could not be accepted by primary hospitals. This study evaluated a new video portable intubationscope (VPIS) by analyzing its efficacy and safety during intubation. This is a prospective observe study, four anesthetists used this scope for endotracheal intubation in patients undergoing general anesthesia during three months. Intubation time and complications were recorded during the procedure. Tracheal intubation was successful in all 120 patients; 104 patients were intubated on the first attempt, 14 on the second, and 2 on the third. The median time from touching the intubationscope to optimal view of the glottis was 12 s (range, 6–27 s) and to successful intubation was 18s (range, 8–58 s). No complication happened during this study. The intubation time was significantly affected by the operator's experience on the instrument .With this data, the portable video intubationscope is a safe and efficient device for endotracheal intubation.

Key Words: Intubation; Endoscopes; Optic Technology

Corresponding Author: Hong-hui Huang, E-mail: zoe412@126.com

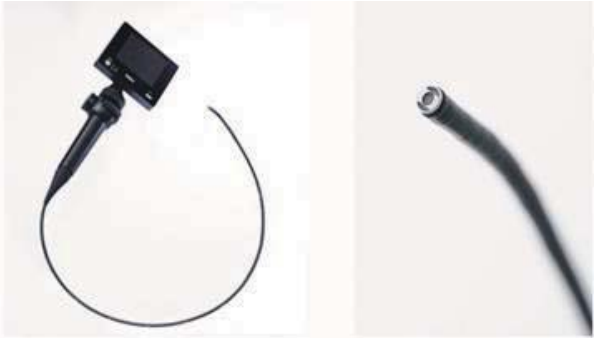
Background

Management of airway is a considerable challenge for anesthetists, difficult airway is one of the major causes of morbidity and mortality. Most of difficult airways can be predicted, such as difficulty in opening of the mouth, lack of mobility of the atlanto-occipital joint, inability to assume the sniffing position, but unexpected difficult intubation often present which range from 1.5-8.5% according to the literature[1-3]. In recent years, more and more technique of optical has begun to play an important role in the management of patients with an unanticipated difficult or failed intubation. More recently, a new video portable intubationscope(Mindhao, Zhuhai, China), has been introduced into clinical practice. The present clinical study was the first time to evaluate the safety and efficacy of this device during routine intubation of general anaesthesia.

Methods

The video portable intubationscope(VPIS, Fig.1) is a soft optic stylet with a 90°distal bend, which consists of three parts: portable liquid crystal display monitor (resolution 320×240; 3.5inch), manipulated part and tube. The device stem is 88-cm long (with 60cm available for use) with a 6-mm external diameter. The tube part enables the loaded endotracheal tube for intubation. In contrast to fiberscope with an external light source and eyepiece, a high-power light-emitting diode(180-200LUX) and digital camera locates in the distal point, facilitating direct visualization on the video screen. The power is supported by lithium-ion battery or AA alkaline battery.

Figure 1 The portable video intubationscope



Four anesthetists with experiences of fiberscope above 2 years were recruited from the hospital. They were asked to undergo the same training of performing a tracheal intubation with the VPIS on a manikin for one day before they using the device on human being (Fig.2). After approval of the Institutional Review Board (IRB) and obtaining written informed consent, 120 patients (ASA physical status Ⅰ-Ⅱ) were recruited of either gender (68 men,52 women) (age: 18–70 yr; weight: 45–90 kg) undergoing elective surgery in the supine position with general anesthesia. Preoperatively, we scored the reclination of the head, the thyromental distance and the view of the oropharynx on mouth opening described. The following exclusion criteria were used: a history of difficult intubation, risk of gastric aspiration, a Mallampati score of 4, complete cervical arthrodesis, interincisor distance at maximal mouth opening ＜3cm and a mental disease.

Figure 2 Anesthetists are trained on the model before they use the portable video intubationscope for intubation during general anesthesia.

General anesthesia was administered according to a standard protocol. Standard monitoring devices were taken before induction of anesthesia, including electrocardiograms, noninvasive blood pressure, and peripheral O_2 saturation (SpO_2). The sniffing position could be achieved using a small pillow behind the patient's head with an appropriate height. After 3 min of administration of oxygen with a face mask, anesthesia was induced with fentanil 4μg/kg and propofol 1.5–2.5 mg/kg and cisatracurium 0.2 mg/kg . Before airway manipulation, appropriate neuromuscular blockade was achieved using a peripheral nerve stimulator (train-of-four count =0). Direct laryngoscopy with Macintosh blade was used for only to assign the Cormack-Lehane score before attempting intubation with the VPIS . The position of the device was adjusted to have the glottis in the center of the screen, and tracheal intubation was performed. An assistant would provide jaw thrust and maintain head stability when necessary. A decrease in SpO_2 below 90% was a criterion for abandoning the intubation attempt. We recorded the Cormack-Lehane classification, the time to optimal view of glottis and intubation, the intubation attempts, and the incidence of adverse events during anesthesia such as aspiration/regurgitation, damage to teeth, and bleeding from the oropharynx. Upon completion of the study protocol, the anesthetists provided a subjective assessment, which was rated as very good, good, and poor.

Statistical Analysis

Data are expressed as median (range), mean±standard deviation(SD) or, when appropriate, as the median and the confidence interval of 95%.

Results:

The research enrolled 120 patients(68 men, 52

women), ranging in age from 18 to 70 years .In all patients, endotracheal intubation was attempted with the video portable intubationscope. All patients were hemodynamically stable before, during, and after intubation. Airway characteristics are shown in Table 1. Tracheal intubation was successful in 104 patients(86.7%) on the first attempt, 14 on the second(11.7%), and 2 on the third(1.6%). The median time from touching the VPIS to optimal view of the glottis was 12 s (range, 6-27 s) and to successful intubation was 18s (range, 8-58 s)(Table 2).The assistant providing jaw thrust and maintained head stability was necessary in most patients. There was no damage to teeth and bleeding from the oropharynx. The resulting picture on the video screen showed excellent optical characteristics in most patients. Subjective assessment of handling was very good in 53 patients, good in 61, and poor in 6. In the 6 patients with poor assessment, common concerns were raised over the comfort (6 of 6) and the colour of pictures (3 of 6), or glottic exposure (5 of 6).

Discussion:

Fiberscope is recommended for difficult intubation as a standard tool. But many intubating fiberscopes do not have an attached camera and monitor. Therefore, only the operator is able to view the progress of the intubation and it needs the operator view the eyepiece directly which makes the manipulation strenuous. This new video portable intubationscope (VPIS) can provide both the operator and the assist or trainees the procedure of intubation. It can be easily mastered with experience of the fiberscope.

Table 1 Patients` characteristics

Mallampati class (I/ II / III / IV)	33/69/18/0
Cormack-Lehane (I/ II / III / IV)	78/34/8/0
Mouth opening (cm)	5±1
Thyromental distance(cm)	6±2
Reclination of the head(＞/＜15°)	113/7

Data are given as mean±SD or numbers

Table 2 Intubation time and assessment

View of glottis time (s)	12 (6-27)
Intubation time (s)	18(8-58)
assessment	Very good(53); good(61); bad(6)

Data are given as media(95%CI) or numbers.

As outlined in the American Society of Anesthesiologists difficult airway management practice guidelines[4] and as good medical practice would dictate, optimum conditions for success should be present before any intubation attempt. So we choose the experienced anesthetists and during the course of each intubation attempt, the assistant provided jaw thrust and maintained head stability to improve intubation conditions when necessary. In 120 patients, all of them were intubated by the VPIS and one attempt intubation success rate is 86.7% . Although most of the patients were not difficult to ventilate or intubate, there were two people who had 3 attempts. Both of them were C/L score III and due to the secretions and the drop of SpO_2 . Most of the second attempt happened during the first month observation. We also observed the reduction in execution time related to the number of executed attempts. It was showed that a sensible decrease in intubation times was revealed after approximately 20 executed cases when using the Bonfils fiberscope [5] which is similar with us. We didn't analyse the difference of the experience of the operators because we need to design a more delicate research about this.

Some limitations of this study should be noted. First, there is a lack of comparison with fiberoptic bronchoscope or other videolaryngoscopes. And we excluded the patients who were expected to be difficult to intubate or ventilate. However, based on this preliminary technical communication, further studies are warranted to compare the VPIS with other fiberscope and the use in the predicted difficult airways. Second, our intraoperative data collection was performed by a nonblinded observer, which is a possible source of bias.

In conclusion, the video portable intubationscope may be suitable for both routine and difficult airway management, and for educational purposes, but these results should be confirmed by further comparative studies.

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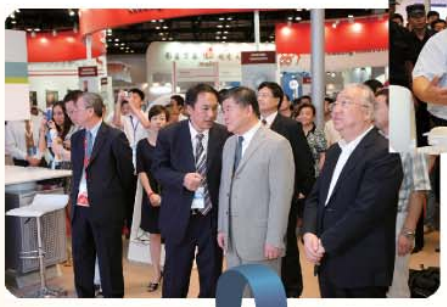

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2012中国卫生论坛 —深化医改，加强慢病防控，可持续健康发展	医改是“十二五”期间，乃至今后一段时间我国医疗卫生工作的中心任务；慢性非传染性疾病是严重危害人民群众健康的重大疾病，已构成对卫生工作的重大挑战，也是影响“十二五”卫生规划目标能否实现的重要问题。 论坛以医改和慢病防控为主题，围绕公立医院改革、慢病防控、多元化办医和国际经验介绍等内容，以主论坛、专题论坛、圆桌会议等形式: ★权威发布——您了解行业发展的最佳窗口 ★交流互动——您参与医改的高层对话平台	中华人民共和国卫生部 国家中医药管理局 国家食品药品监督管理局	相关部委领导 国际组织高级官员 相关国家卫生部长 相关省市领导 国际知名研究机构专家学者等	相关部委代表、国际组织、相关国家卫生官员、医改试点城市有关领导、医院院长、企业高层、国外驻华机构、媒体代表等	1500人	尹海燕 女士 010-88393922 18610105953
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第四届 北京医学影像发展论坛 【授予8学分】	整合产学研资源，打造精品论坛，注重青年培养，推动影像发展。 ★放射学分论坛——华北5省放射学会年会 ★超声医学分论坛: 邀请中日韩3国知名超声医学专家，带来超声医学领域临床科研最新进展 ★分子医学影像——核医学分论坛: 邀请多位国际知名学者介绍分子医学影像新进展及临床应用	中华医学会放射学分会 中华医学会超声医学分会 中华医学会核医学分会 卫生部国际交流与合作中心 中国科学院自动化研究所	国际、国内 知名影像学专家	各级医院医学影像相关科室临床医生、技术人员，设备科长，医学院校科研院所研究人员，相关企业代表等。	1000人	康乐 女士 010-88393917 15801682113
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“2012年第二届全球华人麻醉医师(GCCA)大会及全国中青年麻醉学科医师学术论坛”将于2012年5月31日—6月3日在陕西省西安市联合召开，本次会议由中华医学会麻醉学分会(CSA)主办，中华医学会麻醉学分会青年委员会组织和第四军医大学西京医院组织承办。

综观现代麻醉学的发展，华人、华裔同道做出了不可磨灭的贡献，华人麻醉学家的学术成就也为世人所瞩目。2011年在中国上海召开的首届GCCA大会得到来自欧美、台湾、香港、澳门及新加坡等全球主要华人麻醉团体的大力支持，会议取得空前成功。全国中青年麻醉学科医师学术论坛自创办以来，秉承“带动全国青年麻醉学者更好地开展麻醉学研究，提高中青年麻醉学科医师的学术水平”的宗旨，特别为广大中青年麻醉学者搭建了一个学习交流的平台，先后百余位中青年优秀人才获奖，参与人数逐年增多，学术影响逐年扩大。本次两会的联合召开，将进一步促进海内外麻醉界华人科学家交流与合作，同时也为广大中青年麻醉医师提供了开阔眼界、向世界展示风采的良好机遇，CSA诚挚期待麻醉同仁们热情参与，踊跃投稿，展示自己的研究成果和学术水平，共同推动麻醉、疼痛和危重病学科的健康发展！

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一、投稿类别

本次征文包括“2012第二届全球华人麻醉医师(GCCA)大会”、“2012年全国中青年麻醉学科医师学术论坛优秀论文竞赛”两部分。参赛论文可选择投送其中之一或二者均选。

二、征文内容

1. 麻醉临床与基础研究；

2. 疼痛临床与基础研究；

3. 危重医学临床与基础研究；

三、征文要求

1. 参赛论文必须提交包括中英文摘要各一份（800～1000字）及中文全文，并请在稿件上注明参赛类别和征文内容（见一、二）。

2. 要求一律以电子版投稿，不接受书面投稿，请在邮件标题分别注明“2012第二届全球华人麻醉医师(GCCA)大会”或“麻醉中青年委员会2012年年会投稿——xxx（姓名）”字样；恕不退稿，请自留底稿。

3. 论文格式要求：小四号宋体，单倍行距，A4纸。文稿顺序为参赛类别、征文内容、题目、单位、邮编、作者姓名、中文摘要、英文摘要、全文内容以及第一作者和通讯作者电话和e-mail地址。

4. “2012年全国中青年麻醉学科医师学术论坛优秀论文竞赛”参评者要求年龄在45岁以下（1967年7月1日以后出生），投稿时请提供身份证电子扫描件。本次会议对在读研究生参会者实行费用减免，欢迎投稿。

5. 凡已在国际或全国性学术会议上或公开发行的刊物上发表过的论文，均不予受理。

四、个人邀请外宾来参加会议并拟进行学术交流者，也请通知会议组委会并在上述截稿日期前交来论文摘要，以便统一安排；过期恕不受理。

中华医学会麻醉学分会
第二届全球华人麻醉医师（GCCA）大会
及全国中青年麻醉学科医师学术论坛组委会

2012年中华医学会全国麻醉学术年会

医学术便函（2011）第126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拟定于2012年8月30—9月2日在重庆召开“2012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，麻醉分会各专业学组年会将同时并会召开，因此是2012年度的重要学术盛会。年会将设大会专题报告、各专业学组分会场学术交流等内容，并以专题板块和学术论文报告相结合的形式进行学术交流。现将会议学术论文征文的有关事项通知如下：

一、征文内容及分类：

1、麻醉学科建设
2、麻醉学基础研究
3、临床麻醉与研究
4、疼痛治疗与研究
5、重症监测治疗与研究
6、儿科麻醉
7、神经外科麻醉
8、心胸外科麻醉、体外循环
9、气道管理
10、器官移植麻醉
11、产科麻醉
12、输血及血液保护
13、麻醉相关新技术、新业务进展
14、特殊病例报告
15、麻醉质量管理及麻醉并发症
16、区域麻醉与镇痛
17、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、本次年会仍将举办中青年优秀论文评选，参评条件为1967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。

5、各专业学组征文也按年会要求一并投稿，学科管理学组、疼痛学组、ICU学组、儿科麻醉学组、神经外科麻醉学组、心胸外科麻醉学组、气道管理学组、器官移植麻醉学组、产科麻醉学组、区域麻醉与镇痛学组（筹）等，都将在年会期间组织学术活动。

（注：年会还将继续进行2011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）。

三、投稿方式：

1、网上征文与报名：年会网址：http://www.csaol.cn/；或http://www.cmacsa.org

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收（邮编：100710；投寄的论文请在信封上注明“2012年麻醉年会征文”字样）。联系电话010-85158614，传真：010—85158753；邮箱：csa2012@live.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：2012年3月31日。

五、凡个人邀请外宾来参加全国年会并拟进行学术交流者，请与麻醉学分会办公室白雪联系（联系方式同上）。相关费用原则上由邀请人负责解决。

中华医学会学术会务部
中华医学会麻醉学分会

2012年第11届华东六省一市麻醉学术会议暨江西省麻醉学质量控制研讨会通知

各有关医疗单位及各位代表：

为促进华东六省一市麻醉学科的交流和发展，经六省一市医学会麻醉学分会协商，定于近期召开“2012年第11届华东六省一市麻醉学术会议暨江西省麻醉学质量控制研讨会”，本次会议主题“协作交流，学科发展”，会议内容以麻醉学的新进展与麻醉质量控制为核心，进行学术交流，届时将邀请国内外知名专家作专题讲座。现将有关事宜通知如下：

一、参会人员

(一)特邀中华医学会麻醉学分会主任委员、国内外麻醉专业资深专家；

(二)华东六省一市医学会麻醉学分会委员；

(三)临床麻醉、疼痛、ICU和相关专业工作者；

(四)参会学术论文作者。

二、会议时间

2012年5月26日全天～27日上午，27日下午撤会，25日全天报到。

三、报到地点

(一)省外代表报到：南昌市索菲特泰耐克大酒店(红谷滩新区新府路28号，电话：0791- 88828262)。

(二)省内代表报到：南昌市鑫峰假日酒店(红谷滩会展路29号，电话：0791—88822222)。

四、会议注册

(一)提前注册：2012年5月15日前，省外代表600元／人；省内代表500元／人；研究生凭本人学生证200元／人。

(二)现场注册：省外代表700元／人；省内代表600元／人；研究生凭本人学生证300元／人。

五、其他：

(一)住宿标准：索菲特泰耐克酒店(五星)400元／间／天；鑫峰假日酒店(四星)278元／间／天。

(二)参会与代表授予I类继续医学教育孝分6分。

(三)乘车路线：

1、25日7：00～23：00在南昌火车站及南昌昌北机场设有接站。

2、火车站：乘坐221路公交车到鼎峰中央大夏站下，往回走至十字路口，往左(东)直走200米，抬头看到“TECO东元’’字样即为鑫峰假日酒店。汽车站(青山路口)：乘坐245路公交车在红谷大厦下车(6站)，步行至鑫峰假日酒店(约530米)。鑫峰假曰酒店对面即索菲特泰耐克酒店。

(四)付款方式：银行汇款

户　名：江西省医学会

开户行：中国银行南昌市东湖支行省北支行

帐　号：1947005 5 5584

款　项：请注明“华东六省一市麻醉学术会议”字样。

(五)请于201 2年5月15目前将回执反馈会务组。

联系人：南昌大学第二附属医院麻醉科 胡衍辉

邮编：330006

电话：13970911006

信箱：jxmz@hotmail.com

(由于5月是会议高峰期，房源较为紧张，会议将根据回执预定床位，未寄回执不能确保住宿要求，感谢您的支持与配合)。

(六)会议网址：相关信息请登录http：//www.anesthesia-sh.cn/hdmz查询。

江西医学会

会议讯息

2012

Information of Notification、 Exhibition and Scientific Meeting

展

国内会议信息

2012年全国中青年麻醉学医师学术论坛
时　　间：2012年6月1-3日
地　　点：陕西省西安市
主办单位：中华医学会麻醉学分会
　　青年委员会
联 系 人：苏老师
电　　话：029--84775343/13193384460
邮　　箱：zhongqinghui2012@163.com

第二届全国胸科麻醉会议暨国际胸科麻醉论坛会
时　　间：2012年6月30日-7月1日
地　　点：北京
主办单位：卫生部中日友好医院
联 系 人：王老师
电　　话：15300094072
邮　　箱：medical585@163.com

全球华人药学家大会
时　　间：2012年7月1日
地　　点：北京市
主办单位：中国药学会
联 系 人：Mr. Ziye Zhang
电　　话：86 10 58699276-822
传　　真：86 10 58699272
邮　　箱：gcpsc@cpa.org.cn
会议网站：http://www.gcpsc-cn.org/

全国第三次麻醉药理学术会议
时　　间：2012年7月6～8日
地　　点：西安
主办单位：中国药理学会麻醉药理学
　　专业委员会
联 系 人：高昌俊
电　　话：15996913556
邮　　箱：gaocj74@163.com

2012年广东省医学会麻醉学学术会议
时　　间：2012年8月
地　　点：广东省梅州市
主办单位：广东省医学会麻醉学分会
联 系 人：徐世元
电　　话：020-61643298
邮　　箱：1712952690@qq.com

第二届盛京急重症诊治论坛
时　　间：2012年8月3～4日
地　　点：沈阳市
主办单位：中国医科大学附属盛京医院
联 系 人：李丽妍
电　　话：024-23892620
邮　　箱：sjlt@sj-hospital.org

中国心脏大会国际心血管麻醉会议
暨第八届国际华人心血管麻醉论坛
时　　间：2012年8月9-12日
地　　点：北京国家会议中心
主办单位：中华医学会
联 系 人：会务组
电　　话：010-88398489
邮　　箱：lilytea96@126.com

2012年浙江省麻醉学学术年会
时　　间：2012年8月10-12日
地　　点：杭州
主办单位：浙江省医学会麻醉学分会
联 系 人：冯智英
电　　话：0571-87236169
邮　　箱：anesanal@gmail.com

2012北京国际疼痛论坛
暨第六届中国临床疼痛学术会议
时　　间：2012年8月17日-20日
地　　点：北京国际会议中心
主办单位：世界疼痛医师协会
联 系 人：会务组
电　　话：010-59046396
邮　　箱：wspc@mediwelcome.com

2012年中华医学会全国麻醉学术年会
时　　间：2012年8月30—9月2日
地　　点：重庆
主办单位：中华医学会麻醉学分会
联 系 人：白雪
电　　话：010-85158614
邮　　箱：csa2012@live.cn

国际会议信息

2012年欧洲麻醉学协会大会
时　　间：2012年06月09-12日
地　　点：法国巴黎
主办单位：欧洲麻醉协会
联 系 人：王老师
电　　话：15300094072
邮　　箱：medical585@163.com

第59届日本麻醉科学会年会
时　　间：2012年6月7-9日
地　　点：日本神户 国际会议中心
主办单位：日本麻醉科学会
　　奈良县立医科大学
电　　话：010-81458365/676113239

国内展会信息

2012年香港医疗展
时　　间：2012年5月7-9日
地　　点：香港会议展览中心
主办单位：香港贸发局
联 系 人：潘婷 小姐
电　　话：010-67619211
邮　　箱：panting_expo@126.com

2012第十届中国（上海）国际医疗器械展览会
时　　间：2012年6月7日-9日
地　　点：中国上海世博会主题馆
主办单位：中国医促会
联 系 人：贺洋
电　　话：021-54175087

2012中国（上海）临床检验设备及用品展览会
时　　间：2012年6月7日-9日
地　　点：上海
主办单位：中国医促会
联 系 人：吴俊
电　　话：13062800785
邮　　箱：wujunexpo@yahoo.cn

CMEH 2012第十一届中国（北京）医疗器械展览会
时　　间：2012年9月26日—28日
地　　点：北京中国国际展览中心
主办单位：北京医学会
联 系 人：吴俊
电　　话：13062800785
邮　　箱：wujunexpo@yahoo.cn

2012（上海）世界抗衰老医学大会
暨再生生物科技博览会
时　　间：2012年10月18日-20日
地　　点：上海世博展览馆
　　（上海市国展路1099号）
主办单位：WAAAM世界抗衰老医学会
联 系 人：刘 浩
电　　话：15921612613
邮　　箱：shmrzlh@163.com

国际展会信息

2012南非国际医疗器械展览会
-AFRICA HEALTH
时　　间：2012年5月9-11日
地　　点：南非- 约翰内斯堡
主办单位：英福曼会展集团南非公司
　　informa exhibitions
联 系 人：韩笑笑小姐姐
电　　话：13718173925

巴西医疗展/HOSPITALAR医疗展
时　　间：2012年5月22-25日
地　　点：巴西圣保罗ExpoNorte展览中心
主办单位：巴西医促会
联 系 人：金　露
电　　话：021-55315333

2012美国医疗展
时　　间：2012年8月10-12日
地　　点：美国佛罗里达州迈阿密
主办单位：FIME国际医疗展览公司
联 系 人：潘婷 小姐
电　　话：010-67619211/67660511

新加坡国际医疗器械设备及医院用品展览会
时　　间：2012年9月12-14日
地　　点：新加坡
主办单位：德国杜塞尔多夫展览公司
联 系 人：李敬小姐
电　　话：13718173925

2012年第十届阿根廷国际医疗展
EXPO MEDICAL 2012
时　　间：2012年9月26-28日
地　　点：阿根廷
主办单位：阿根廷医疗协会
联 系 人：黄亮
电　　话：13824796832
邮　　箱：hkhuizhan@vip.163.com

2012年慕尼黑上海分析生化展
时　　间：2012年10月16-18日
地　　点：上海新国际博览中心N1、N2馆
主办单位：德国慕尼黑国际博览集团
联 系 人：洪燕
电　　话：021-20205527
邮　　箱：hong.yan@mmi-shanghai.com

2012美国亚特兰大国际医疗居家护理保健展
时　　间：2012年10月16日—18日
地　　点：佐治亚世界会议中心
主办单位：尼尔森商业传媒公司
联 系 人：余慧
电　　话：021-60490443
邮箱：1435354139@qq.com

第二十一届乌克兰国际医疗医药展
时　　间：2012年10月23-26日
地　　点：基辅国际展览中心
主办单位：英国国际贸易与展览有限公司
联 系 人：金露
电　　话：021-55315333
邮　　箱：sales-3@dongsinexpo.com

2012年第二十二届俄罗斯医疗、诊断、实验室及制药、康复展览会
时　　间：2012年12月6-10日
地　　点：俄罗斯莫斯科国际展览中心
主办单位：俄罗斯莫斯科展览公司
联 系 人：任丽
电　　话：010-67660511
邮　　箱：angieren@126.com

E-Mali δ lyelectron@yahoo.com.cn
famttyy@sina.com

读者服务表

Reader Service

姓名：_____ 性别：□男 □女
生日：____年__月__日 工作单位：_____
职称：_____ 部门：_____
通讯地址：_____ 电话：_____
邮编：_____移动电话：_____
电子邮件：_____ 传真：_____
毕业院校：_____
学历：□专科 □本科 □硕士 □博士 □博士后
曾发表文章：□是 □否
(名称：_____ 刊物：_____)
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：_____
电话：_____ 电话：_____

本人欲获赠阅《麻醉与监护论坛》杂志，双月刊，从2012年____月至2012年12月刊，共____套(每期邮寄服务费美金3元或人民币20元，全年美金18元或人民币120元)，总计共_____元。

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耐乐品®

（盐酸罗哌卡因注射液）

原创品牌，品质卓越

第一个纯左旋长效酰胺类局麻药
无菌聚丙烯安瓿，效期长达三年
原创品牌，瑞典原装进口，品质值得信赖

简短处方资料 [Naropin_V(2)]

【适应症】 外科手术麻醉
——硬膜外麻醉，包括剖宫产术
——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，
如术后或附道分娩镇痛
——区域阻滞

【用法用量】

	浓度 (mg/ml)	容量 (ml)	总剂量 (mg)	起效时间 (分)	持续时间 (小时)
外科手术麻醉					
腰椎硬膜外给药外科手术	7.5	15-25	113-188	10-20	3-5
	10.0	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	5.0	3-5	15-25	1-5	1-2
区域阻滞 (例如末梢神经阻滞和浸润麻醉)	7.5	1-30	7.5-225	1-15	2-6
急性疼痛控制					
腰椎硬膜外给药单次给药量	2.0	10-20	20-40	10-15	0.5-1.5
腰椎硬膜外给药追加剂量(足量)	2.0	10-15	20-30	n/a	n/a
腰椎硬膜外给药持续滴注	2.0	6-14ml/h	12-28mg/h	n/a	n/a
胸椎硬膜外给药持续滴注	2.0	4-8ml/h	8-16mg/h	n/a	n/a
区域阻滞 (例如末梢神经阻滞和浸润麻醉)	2.0	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）

【禁忌症】对本品或本品中任何成分或对同类药品过敏者禁用

【注意事项】有些局部麻醉如头颈部区域的注射，严重不良反应的发生率较高。

对于有 II 度或 III 度房室传导阻滞的患者要慎用，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上佳的患者，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

本广告仅供医学药学专业人士阅读

广告批准文号“苏药广审（文）第　　号”

进口药品注册证号 H20100104 H20100105

ANA-1202-NA-0047 有效期至2013年2月

AstraZeneca
阿斯利康
携手为生命护航

阿斯利康无锡贸易有限公司（总部）地址：上海市南京西路1168号中信泰富广场43楼　邮政编码：200041 电话：（86-21）52564555　传真：（86-21）52984834
ADD: 43/F.CITIC SQUARE,1168 Nan Jing Xi Road,Shanghai 200041,China TEL:（86-21）52564555　FAX:（86-21）52984834