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Figure 1. Expression changes of Caspase-3 cleavage and PARP-1induced by low-dose LPS (5mg/kg) were both suppressed by propofol (*$P < 0.05$).

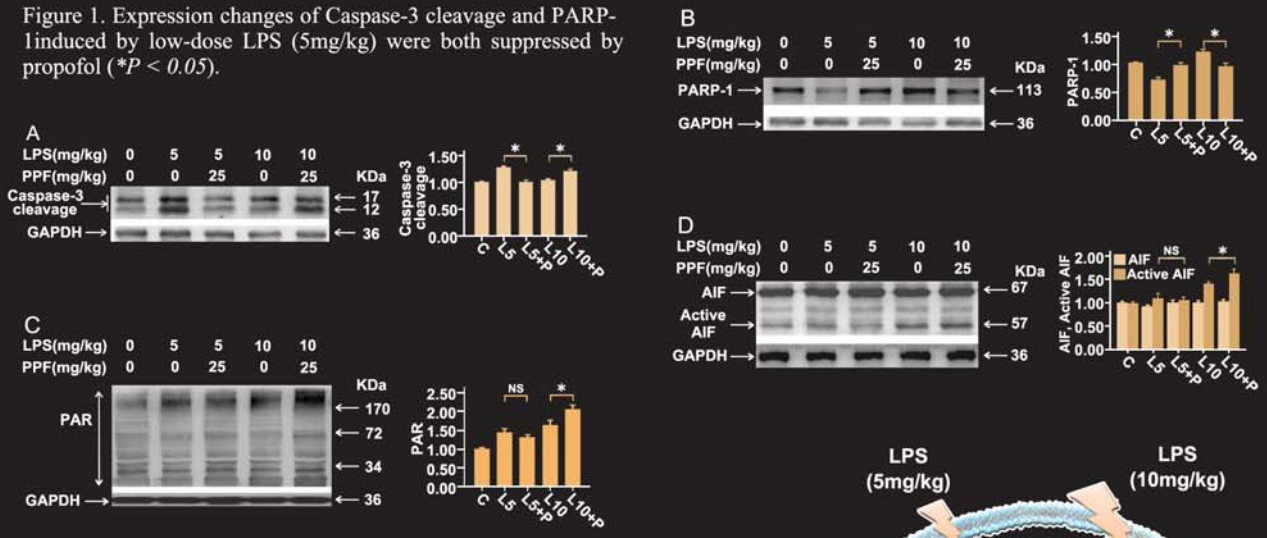
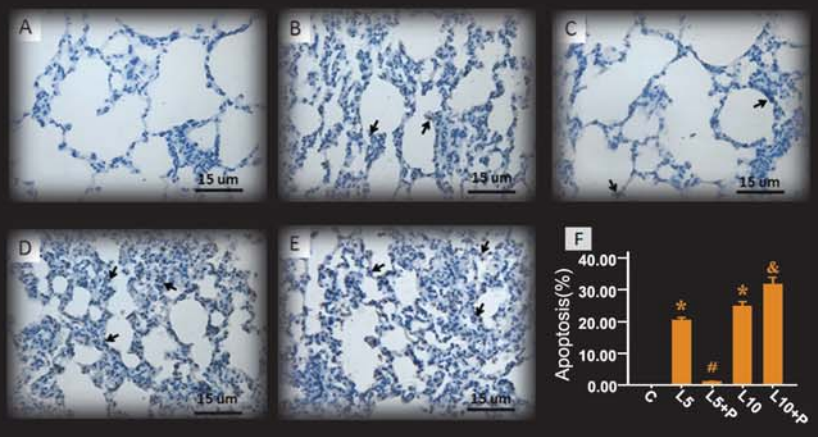


Figure 2. There were significantly fewer apoptotic epithelial cells in the group of L5+P (5.00±0.58)% than those in the group of L5 (20.44±0.42)% (*$P < 0.05$).



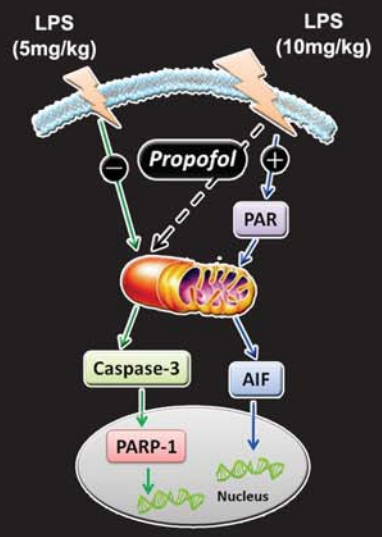


Figure 5. Cartoon shows different effects of propofol on the Caspase-3 and the AIF apoptotic patterns.

Propofol inhibited the increase of Caspase-3 cleavage in the 5 mg/kg LPS-inducible lung injury, but activated Caspase-3 and promoted AIF in the 10 mg/kg LPS-inducible lung injury.

Figure related to "Propofol Attenuates Alveolar Epithelial Cell Apoptosis Induced by Low, But not High, Dose of Lipopolysaccharide in Rats" by Li-jie Jia, Han Lu, Fu-jun Zhang, Yan Luo, Bu-wei Yu, et.al, pp.252.

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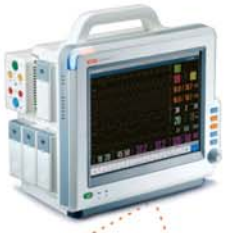

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地址：上海市茂名南路205号瑞金大厦1411室　邮编：200025
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总部：香港
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上海
上海市金都路3266号莘庄工业(科技)园1幢3层
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Fax：021-54429643
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新加坡
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新达第二大厦33-02楼
Tel：(65)68269931
Fax：(65)68269897
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	10.0	15-20	150-200	10-20	4-6
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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
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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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Headquarter: Hong Kong
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E-mail: fam_Singapore@medicalinfo.cn

Shanghai(Lian Luo Chu)
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Fax: 021-54429643
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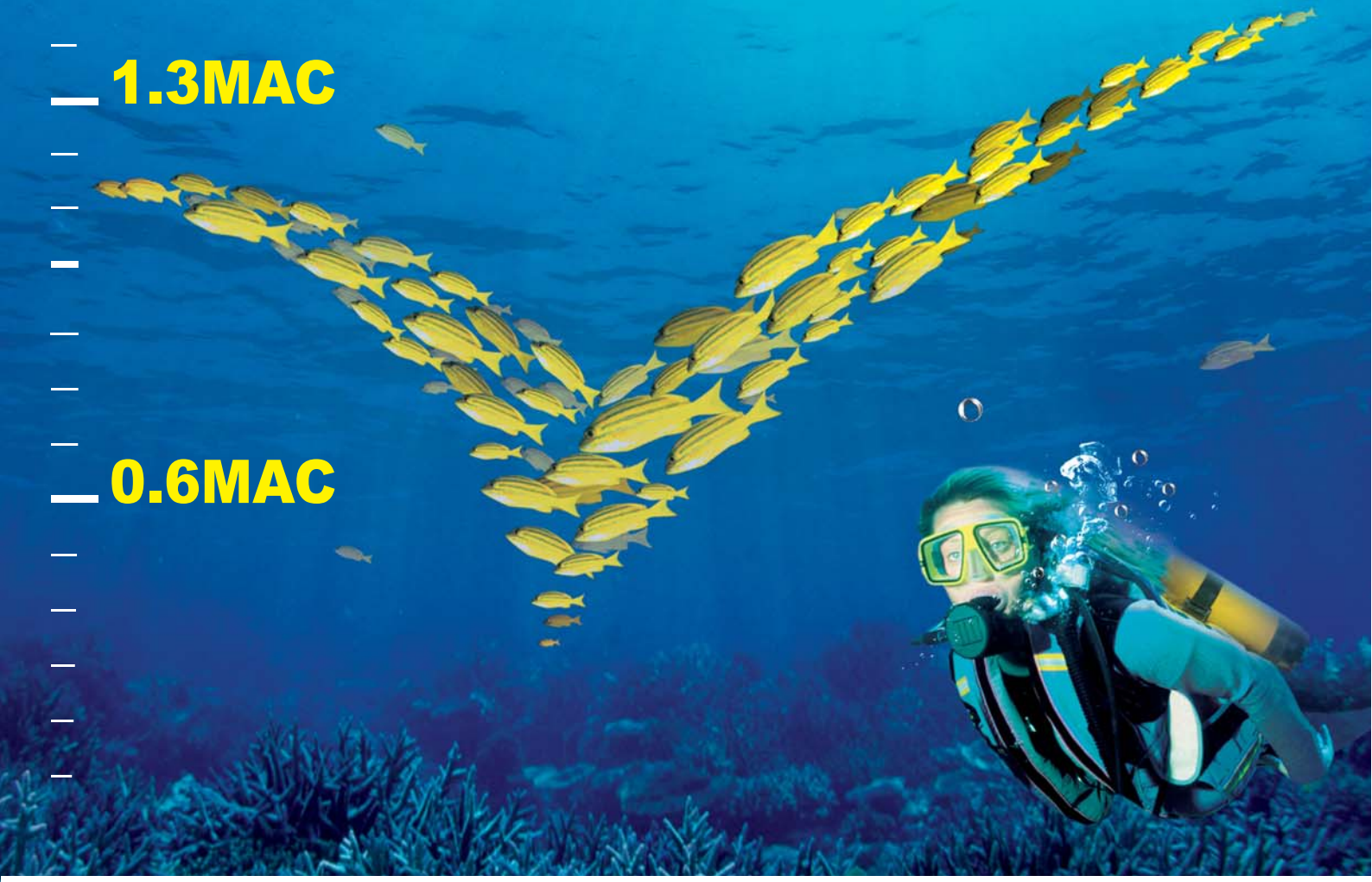

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5.Technical Communications

6.Clinical Experience

7.Letters to the editors

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Arrange all articles in the following order.

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Propofol Attenuates Alveolar Epithelial Cell Apoptosis Induced by Low, but not High, Dose of Lipopolysaccharide in Rats

Li-jie Jia[1], Han Lu[1], Fu-jun Zhang[1], Wen-yuan Wang[1], Bin Liu[2], Qing-sheng Xue[1], Yan Luo[1], Rong Dong[1], Dong-mei Qu[1], Sheng-wu You[1], Bu-wei Yu[1]

1.Department of Anesthesiology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin Er Road, Shanghai 200025, P.R. China

2.Department of Pathophysiology, Key Laboratory of Cell Differentiation and Apoptosis of National Ministry of Education, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 280 South Chongqing Road, Shanghai 200025, P.R. China

Abstract

Pulmonary cell apoptosis is essential for the pathogenesis of acute lung injury and the apoptotic pathways of LPS-inducible lung injury were changeable. Propofol has been reported to play discrepant roles in apoptosis and lung injury, while the underlying mechanism remains elusive. The present study was designed to detect effects of propofol on the Cysteine-aspartic acid protease 3 (Caspase-3)-dependent and the apoptosis inducing factor (AIF)-dependent apoptotic patterns using rat models treated by doses of lipopolysaccharide (LPS). We fund that Six hours after treatment, propofol inhibited the increase of Caspase-3 cleavage in the 5 mg/kg LPS-inducible lung injury, but activated Caspase-3 and promoted AIF in the 10 mg/kg LPS-inducible lung injury. Accordingly, propofol attenuated alveolar epithelial cell apoptosis in the low-dose-LPS model but exacerbated apoptosis in the high-dose-LPS model. Furthermore, propofol alleviated lung injury and reduced 24-hour mortality under the stress of low, but not high, dose of LPS. These results appear to raise a possible unitary interpretation for understanding the conflicting findings of propofol in previous reports.

Key Words:Propofol; Apoptosis; Lung injury; Cysteine-aspartic acid protease 3; Poly (ADP-ribose) polymerase-1; Apoptosis inducing factor; Poly (ADP-ribose) polymer; Lipopolysaccharide

Corresponding Author: Bu-wei Yu, E-mail: yubuwei@yahoo.com.cn

Introduction

Multiple organ dysfunction syndrome (MODS) is a serious condition resulting from severe infection, injury and shock. During the development of MODS, lung is the most vulnerable organ to be damaged [1]. Despite recent advances, the incidence and mortality of acute lung injury (ALI)/ acute respiratory dysfunction syndrome (ARDS) are still high and there are still lots of difficulties for its clinical treatment [2].

Propofol (2,6-diisopropylphenol) is an intravenous anesthetic with characteristics of rapid onset and offset of drug effect. This hypnotic agent has been widely used for intensive care unit (ICU) sedation as well [3]. Besides, it has been reported that propofol alleviates cell apoptosis and tissue injury in ALI/ARDS and MODS [4-8]. However, there are also some differential reports that propofol induces apoptosis and exacerbates damage [9-11]. These contradictory findings concerning apoptosis imply that propofol might have some worries when employed in the treatment of critical illness.

Apoptosis is an evolutionarily conserved "cell suicide" program, and has drawn increasing attention in accumulating evidences with regard to the pathogenesis of ALI [12, 13]. Our previous research demonstrated that, with increases of the dose of LPS and the severity of tissue damage, the apoptotic mechanisms of LPS-inducible lung injury were changeable, and that either Cysteine-aspartic acid protease 3 (Caspase-3)

or apoptosis inducing factor (AIF) was the primary mediator involved.

On these backgrounds, we hypothesized that propofol might play discrepant roles in different apoptotic pathways and this may relate to previous conflicting reports of propofol. The present study was therefore conducted to investigate effects of propofol on the Caspase-3-dependent and the AIF-dependent apoptotic patterns in lung injury evoked by two doses of LPS first, then to examine the apoptosis, tissue injury and survival rate reversed by propofol.

Materials and methods

Animals

After obtaining Institutional Animal Care and Use Committee approval (Shanghai Jiao Tong University School of Medicine, Shanghai, China), 75 adult male Sprague-Dawley rats weighing 220-250g were purchased from SLAC Laboratory Animal (Shanghai, China). Animals were housed in a temperature-controlled (22 ± 1℃) room, with food and water available ad libitum. They were maintained throughout the experiments on a 12-hour light-dark cycle (lights on at 8:00 AM). Every effort was made to minimize suffering of animals.

Experimental protocol

Administration of LPS in animals has gained common application as an experimental model of lung injury. Considering the level of LPS influenced apoptotic pattern in our previous study, two doses of LPS were introduced to the present study as stimulators. Rats were randomly assigned to one of five groups (n =5): ①group C (1ml saline); ②group L5 (LPS 5mg/kg); ③group L5+P (LPS 5mg/kg and propofol 25mg/kg); ④group L10 (LPS 10 mg/kg); and ⑤group L10+P (LPS 10mg/kg and propofol 25mg/kg). Animals were anesthetized by sevoflurane. Subsequently, LPS (Escherichia coli LPS serotype 055:B5; Sigma Chemical Co., USA; 5 or 10mg/kg) dissolved immediately before use in 1ml saline or 1ml saline was injected in a tail vein. Rats in the groups of L5+P and L10+P were treated with LPS (5 and 10mg/kg, respectivly) as stated above, and immediately, propofol (J&K Scientific Ltd., China; 25mg/kg) was treated intraperitoneally, which was previously dissolved in 10% Dimethyl Sulfoxide (Sigma Chemical Co., USA) in saline to the final concentration of 10 mg/ml. Every rat was transferred to its cage with free access to water and food.

Six hours later, animals were anesthetized with sodium pentobarbital (50mg/kg, injected intraperitoneally). After the forepaw righting reflex lost, the thoracic cavity was opened, exposing heart and lungs. Using blunt clamps, the upper lobe of the right lung was excluded from instillation procedure. Then the animal was perfused with 200ml phosphate-buffered saline, and then lungs were quickly removed and processed for the following experiments.

Animals were excluded from data analysis if they died before the end of the period of six hours. Every group was stopped after 5 animals had been enrolled.

Western blotting

The left lobe of lungs was homogenated in a protein extraction reagent containing inhibitors (Beyotime Institute of Biotechnology, China). Protein concentrations were determined by the BCA method. Fifty micrograms of protein extracts from each sample were loaded on SDS-polyacrylamide gels and subsequently transferred onto a PVDF membrane by electrophoresis. Membranes were blocked in Tris-buffered saline with 0.1% Tween 20 (TBST) containing 5% nonfat milk for 1 hour at room temperature. Appropriate primary antibodies (Anti-Caspase-3 form Sigma Chemical Co., USA, 1:1000; Anti-PARP-1 from Santa Cruz Biotechnology Inc., Santa Cruz, USA, 1:1000; Anti-PAR from Trevigen Inc., USA, 1:2000; and Anti-AIF from Millipore Inc., USA, 1:1000) were incubated overnight at 4℃ and washed at room temperature for 15 minutes with three changes of TBST. Appropriate horseradish peroxidase-labeled secondary antibodies were added to TBST and the membranes were incubated at room temperature for 1 hour followed by three washes in TBST (10 minutes each time). The images were visualized by luminescent image analyzer LAS-4000 (Fujifilm, Japan).

Apoptosis analysis

The assessment of lung apoptosis was performed

by the terminal deoxynucleotidyl transferase dUTP-mediated nick-end labeling (TUNEL) staining. The lower lobe of the right lung was fixed in 4% phosphate-buffered Paraformaldehyde for 3 days. The fixed tissue was then dehydrated and embedded in paraffin. Each paraffin section was cut serially into 4μm-thick slices. Apoptosis was detected using TUNEL Assay Kit (Roche, Indianapolis, USA) and the percentage of apoptotic cells was calculated.

Histological examination

The paraffin section had been embedded as above. Each paraffin section was cut serially into 4μm-thick slices which were stained with hematoxylin-eosin, and examined under light microscopy. The severity of tissue injury was assessed by a pathologist blinded to the study groups. According to an amended method reported in document [6,7,14], tissue injury was briefly graded on a scale of 0-3 (0, absent and appears normal; 1, light; 2, moderate; 3, strong) for interstitial edema, neutrophils infiltration and hemorrhage. A mean score for the three categories was calculated.

Lung wet-to-dry weight (W/D) ratio

The upper lobe of the right lung that had been excluded from perfusion procedure was weighed, desiccated (60℃ for 48 hours) to invariant, and weighed again. The lung W/D ratio was calculated.

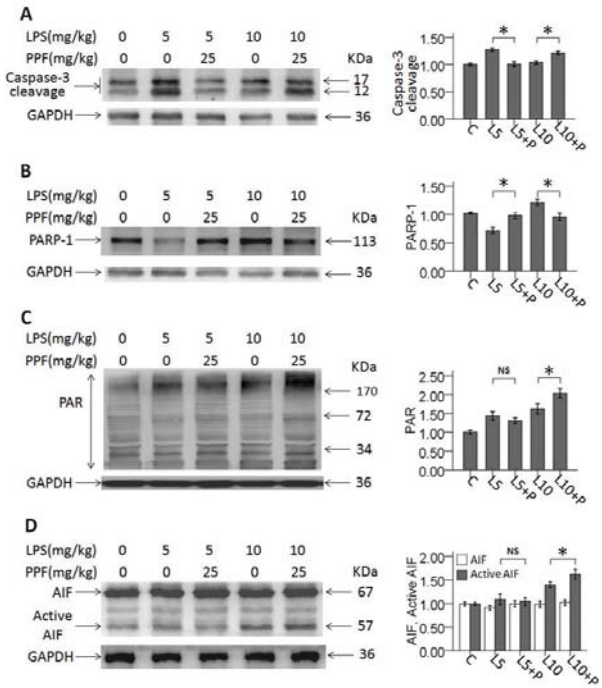
Survival rate

Animals were randomly assigned to the groups of C, L5, L5+P, L10 or L10+P, respectively (n=10), and treated as stated above. The rat was then transferred to its cage with free access to water and food and checked hourly for continuous24 hours after LPS administration.

Statistical analysis

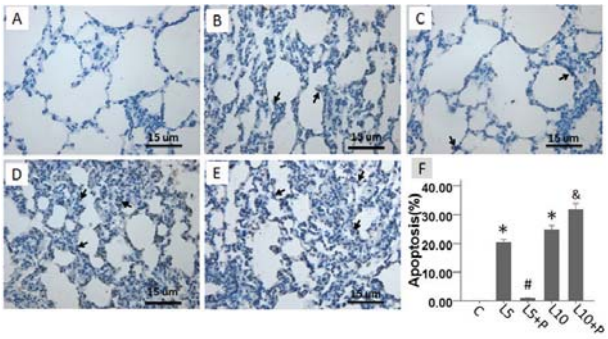
The normality of data was evaluated, and all

Figure 1: Effects of propofol on Caspase-3-PARP-1 and PAR-AIF apoptotic mechanisms



Rats were injected with saline, LPS (5 and 10mg/kg) in group C, L5 and L10 respectively. Propofol (PPF) was applied immediately to rats administrated with LPS (5 and 10mg/kg) in group L5+P and L10+P respectively. Six hours after treatment, expressions of Caspase-3 (A), PARP-1 (B), PAR (C) and AIF (D) were evaluated by western blotting. The experiments were repeated three times. Histograms and bars showed the quantified data (the ratio to expression of the integral marker, Mean ± SEM, n=5). *$P < 0.05$, NS represents non-significant.

Figure 2: Effects of propofol on apoptosis



Rats were injected with saline, LPS (5 and 10 mg/kg) in group C (A), L5 (B) and L10 (D) respectively. Propofol was applied immediately to rats administrated with LPS (5 and 10 mg/kg) in group L5+P (C) and L10+P (E) respectively. Six hours after exposure, lung apoptosis was determined by TUNEL assay. The apoptotic cells showed a dark-brown nucleus (indicated by arrow). Representative lung sections of each group were shown (original magnification 400×). The apoptotic percentage of each group was calculated and shown in F (Mean ± SEM, n=5). *$P < 0.05$, NS represents non-significant.

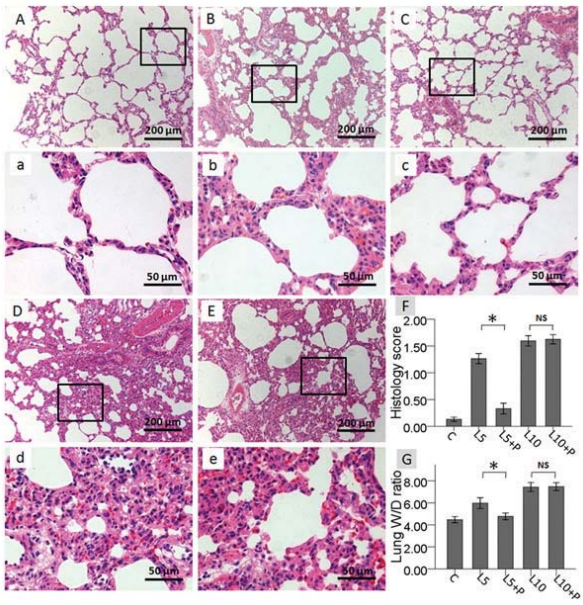
normally distributed variables were expressed as (Mean ± SEM). Comparisons between groups were made using one-way analysis of variance, and subsequently verified by Student-Newman-Kuels post hoc test. Survival analysis was carried out using the method of Kaplan and Meier, and comparisons between groups were made using the log-rank test. Statistical significance was accepted at $P < 0.05$.

Results

Effects of propofol on Caspase-3-PARP-1 and PAR-AIF apoptotic mechanisms

Expression changes of Caspase-3 cleavage and PARP-1induced by low-dose LPS (5mg/kg) were both suppressed by propofol (*$P<0.05$, Fig. 1A and B). In addition, level of active Caspase-3 was significantly higher in group L10+P compared with that in group L10 (*$P<0.05$, Fig. 1A). And PARP-1 expression of group L10+P was significantly lower than that of group L10 (*$P<0.05$, Fig. 1B). We then detected PAR-AIF apoptotic mechanism. Neither PAR conjugation nor active AIF was obviously changed by propofol in the low-dose LPS model. However, treatment of propofol in the high-dose LPS (10mg/kg) model led to a great increase in PAR conjugation compared with only treatment of high-dose LPS (*$P<0.05$, Fig. 1C). And so was the active AIF (*$P<0.05$, Fig. 1D). We did not detect perceptible changes in primary AIF expression induced by propofol.

Figure 3: Effects of propofol on lung tissue injury

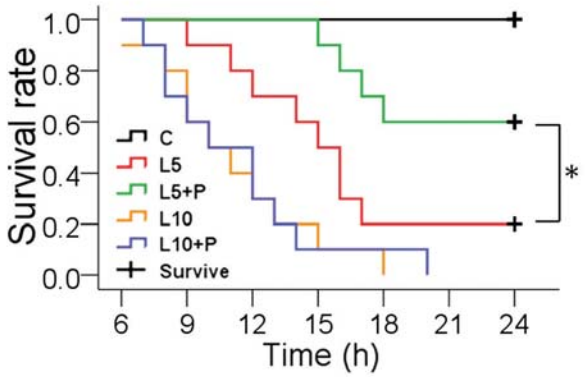


Rats were injected with saline, LPS (5 and 10 mg/kg) in group C (A and a), L5 (B and b) and L10 (D and d) respectively. Propofol was applied immediately to rats administrated with LPS (5 and 10mg/kg) in group L5+P (C and c) and L10+P (E and e) respectively. Six hours after exposure, the sections were stained with hematoxylin-eosin for morphological evaluation. The severity of tissue injury was graded on a scale of 0-3 (0, absent and appears normal; 1, light; 2, moderate; 3, strong) for interstitial edema, neutrophils infiltration and hemorrhage. A mean score for these three categories was calculated and shown in F (Mean ± SEM, n=5). (G) The lung wet-to-dry weight (W/D) ratio was determined (Mean ± SEM, n=5). Representative lung sections of each group were shown (A-E, original magnification 100×; a-e, original magnification 400×). *$P < 0.05$, NS represents non-significant.

Effects of propofol on apoptosis

We observed characteristic dark-brown nuclei in TUNEL-positive cells in the experimental groups, and almost all the apoptosis occurred in alveolar epithelial cells (indicated by arrow in Fig. 2). The apoptotic percentage of control group was (0.43±0.16)%. There

Figure 4: Survival rate



Rats were injected with saline, LPS (5 and 10 mg/kg) in group C, L5 and L10 respectively (n=10). Propofol was applied to rats administrated with LPS (5 and 10 mg/kg) in group L5+P and L10+P respectively (n=10). Animals were checked hourly for continuous24 hours after LPS administration, and the 24-hour survival rate was calculated. All saline-treated control animals survived. Survival rates of group L5 and group L5+P were 20% and 60% respectively. The survival rates of the groups treated with only high-dose LPS and high-dose LPS plus propofol were both zero. *$P < 0.05$.

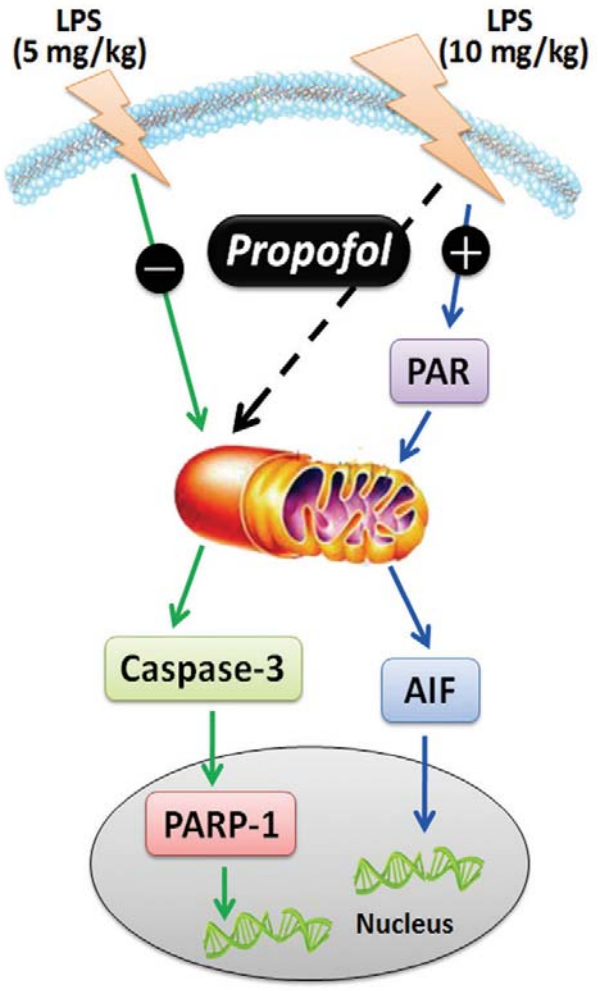
were significantly fewer apoptotic epithelial cells in the group of L5+P (5.00±0.58)% than in the group of L5 (20.44±0.42)% (*P<0.05, Fig. 2F). In contrast, the apoptotic percentage in the group treated with high-dose LPS and propofol (24.73±0.78)% was significantly more than that in the group administrated with only high-dose LPS (31.73±1.09)% (*P<0.05, Fig. 2F).

Effects of propofol on lung tissue injury

No pathological changes were observed in group C (Fig. 3A and a). Six hours after injection of low-dose LPS, the lung was markedly atelectatic, and there were interstitial edema, neutrophils infiltration and hemorrhage (Fig. 3B and b). All of these morphological changes were substantially attenuated by propofol (Fig. 3C and c). Much more serious injury was observed in the model administrated high dose of LPS (Fig. 3D and d). However, there were few effects of propofol on pulmonary tissue injury challenged by high-dose LPS (Fig.3E and e). Histology score is an acceptable quantitative analysis of morphology [6,7]. Histology score of the control group was (0.13±0.02). The score of group L5+P (0.33±0.05) was significantly lower than that of group L5 (1.26±0.05) (*P<0.05, Fig. 3F). Histology score of group L10+P was (1.63±0.04) and was not obviously different from that of group L10(1.60±0.05).

Lung W/D ratio is an approximate reflection of extravascular lung water. As shown in Fig. 3G, the control W/D ratio was (4.47±0.14). The W/D ratio in the group of L5+P (4.77±0.16) was significantly lower compared with that in the group of L5 (5.98±0.24) (*P<0.05, Fig. 3G). However, the W/D ratio of group L10+P (7.48±0.18) was different from that of group L10(7.43±0.20) with no statistic significance.

Figure 5: Cartoon showing different effects of propofol on the Caspase-3 and the AIF apoptotic patterns



Green arrows and blue arrows denoted the Caspase-3-PARP-1 and the PAR-AIF apoptotic patterns respectively. Black rondures and dashed arrow denoted effects of propofol.

Survival rate

Rat survival rate was analyzed 24 hours after the exposure of LPS. At this time point, only 2 of 10 rats survived in group L5. In contrast, 6 of 10 rats receiving propofol when injected with low-dose LPS survived, yielding a statistically significant increase in survival rate (*P<0.05, Fig. 4). None of 10 rats survived in the groups treated with only high-dose LPS or high-dose LPS plus propofol. All saline-treated control animals survived.

Discussion

Despite a mighty advance in knowledge regarding ALI, its incidence and mortality are still high and there are lots of difficulties for treatment [2, 15, 16]. Accumulating evidence has suggested the apoptosis of alveolar epithelial cells plays an important role in the pathogenesis of lung injury [12, 13, 17, 18]. Mitochondrion, perturbed under lung injury stress, is the primary organelle to mediate intrinsic apoptotic pathways [17, 19]. Both Caspase family

and AIF are considered to play essential roles in the intrinsic apoptotic process [20, 21]. Caspase-3, existing as a dominant executant in the execution-phase of apoptosis, proteolytically degrades a host of proteins (e.g. poly (ADP-ribose) polymerase-1, PARP-1), and consequently carries out the cell death program [22]. Meanwhile, there is a Caspase-independent intrinsic apoptotic pathway mediated by AIF [17]. Active AIF translocating in nucleus causes chromatin condensation and large-scale fragments of DNA [20]. And poly (ADP-ribose) polymer (PAR) is a pivotal upstream signal for activating AIF [23]. Another important issue is that there are gender-specific differences between Caspase-3-PARP-1 and PAR-AIF apoptotic patterns [24-26]. In this context, we studied male subjects only.

Propofol has gained general acceptance in the ICU for sedation purposes [3, 27]. In addition, it has been found that propofol has potent radical scavenging activity similar to the endogenous antioxidant vitamin E and is capable of modulating the host's inflammatory response [3]. Its antioxidant and anti-inflammatory properties could reduce cell apoptosis, attenuate tissue injury and have beneficial effects in ALI/ARDS and MODS [4-7, 28, 29]. However, there are still different views that propofol induces apoptosis through increasing oxidative stress, exciting nociceptors and changing signaling transduction pathways, and consequently exacerbates damage [9-11]. Therefore, it is worried about the application of propofol to critical illness, and a possible unitary interpretation is inexistent.

In this study, we first analyzed effects of propofol on the two intrinsic apoptotic patterns in LPS-inducible lung injury (Fig. 5). According to our previous study, intraperitoneal administration of propofol (25 mg/kg) courses some sedative effects on rats without strongly inhibition of circulation [30]. Here we found that Caspase-3 cleavage was inhibited by propofol in the low-dose-LPS model. In contrast, propofol activated Caspase-3 and promoted active AIF in the high-dose-LPS model. Accordingly, propofol attenuated alveolar epithelial cells apoptosis induced by low-dose LPS, but exacerbated apoptosis in the high-dose-LPS model in our experimental conditions. This interesting phenomenon may be attributed to differential adaptive immune response generated by levels of stimulators (e.g. the endotoxin) [31, 32]. Although the exact mechanism has not been completely understood, the data herein, to a certain extent, explains previous conflicting findings.

To fully appreciate the results, the following points must be considered. Being a substrate of Caspase-3, PARP-1 is initially identified as an abundant nuclear enzyme that participates in maintenance of genome integrity [33]. And PARP-1can not perform its function when cleaved by Caspase-3, resulting in an increased cleavage between nucleosomes and apoptosis [22, 34]. A negative correlation has been found between the PARP-1 expression and the Caspase-3 activation, therefore the former is usually used for an indicator of the latter [22, 34]. We confirmed this negative correlation in this study. In addition, PARP-1 is the canonical representative of PARP super-family to catalyze to form PAR polymer [35]. However, it was not shown that PAR reacted in parallel with PARP-1 in our research. Some reports demonstrate that the appearances of DNA breaks could up-regulate PARP [36]. At the same time, the enzyme poly (ADP-ribose) glycohydrolase (PARG), activated under stress, contributes to the turnover of PAR to free ADP-ribose [37]. Therefore we speculated that, when PARP-1 had been cleaved by Caspase-3, PARG and/or other family of PARP might predominate in the formation of PAR. This proposal may account for the variances in our experimental models partly, but need to be further defined.

In our low-dose-LPS models, propofol substantially alleviated lung tissue injury, whereas, there were still forty percent of the animals died 24 hours after propofol administration. It implies that, other therapeutic measures must be applied to the treatment of ALI/ARDS. It is possible that, other organs could be involved in septic-inducible models. Another, in the high-dose-LPS models, propofol facilitated apoptosis, however, tissue injury was not significantly changed after propofol treatment. Although the 24-hour survival rate were both zero, it is not unreasonable to assume that pathological changes are gradual and sustained processes, and often occur after cellular injury.

In addition, apoptosis of peripheral blood lymphocytes has been found in a murine model of ALI

after LPS challenge [38], and propofol also have some functions to lymphocytes [39]. In order to remove this interference to the analysis of pulmonary cell apoptosis, we instilled the lungs with phosphate-buffered saline before tissue collection. Meanwhile, to avoid an impact of instillation on the lung W/D ratio, we used blunt clamps to exclude the upper lobe of the right lung from perfusion procedure [40]. Moreover, systemic administration of LPS could induce ALI/ARDS in rats [4-6, 28, 29]. Compared to a model of intratracheal instillation of LPS, this indirect lung injury model is more relevant to clinical ALI/ARDS which is a frequent complication of critical illness [2, 15]. And compared to the cecal ligation puncture model, LPS-inducible model is more controllable and more stable.

Finally, it needs to be regarded as a limitation in our study that we just found the changes of apoptotic patterns after propofol application. Although this is an interesting finding, it could be better to apply genetic interventions or pharmacological blockers to further investigate effects of propofol on the specific apoptotic signaling pathway.

Conclusions

Our results demonstrated that, propofol performed distinct roles in the Caspase-3 and AIF apoptotic patterns that altered in LPS-inducible lung injury. Accordingly, propofol attenuated alveolar epithelial cell apoptosis, alleviated tissue injury, and reduced mortality induced by low, but not high, dose of LPS. This proposed mechanism partly explains the contradictory effects of propofol on injury, and may imply some clues on its clinical application in critical illness.

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The authors declare that they have no competing interests.

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Relationship between Cerebral Hyperperfusion and Postoperative Cognitive Dysfunction in the Elderly

Cheng Liu[1], *Lin-tao Qu*[2], *Hong-bing Xiang*[1]

1. Department of Anesthesiology and Pain Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, PR China

2. Department of Anesthesiology, Yale University School of Medicine, New Haven, 06510, USA

Abstract

Postoperative cognitive dysfunction (POCD) commonly occurs after cardiac surgery. An increase in systemic blood flow could contribute to left ventricular assist device (LVAD)-related neurologic dysfunction (ND) in patients with end-stage heart failure. There are striking similarities between POCD and LVAD-related ND. We hypothesized that the mechanism of POCD observed in some patients after surgery, which is similar to the restoration of normal cardiac output in LVAD patients might result in cerebral dysfunction. Cerebral hyperperfusion during operation is a potent factor in the pathogenesis of POCD, and promotes the development of POCD in elderly surgical patients. Some measures against cerebral hyperperfusion should be considered as a new pathway to prevention of POCD.

Key Words: Cerebral hyperperfusion; POCD; Cardiac surgery

Corresponding Author: Hong-bing Xiang, E-mail: xhbtj2004@163.com

Background

Many scholars investigated whether an increase in systemic blood flow could contribute to left ventricular assist device (LVAD)-related neurologic dysfunction (ND) in patients with end-stage heart failure[1-4]. Deng et al[2]. reported that postoperative serious neurologic complications were in 14% of 655 recipients with LVAD at 60 international centers. Lietz et al[3]. found that cerebral hyperperfusion was possible in recipients of mechanical circulatory support with postoperative neurologic dysfunction, and reduction of LVAD flow in 16 of the 19 symptomatic patients led to improvement of postoperative neurologic symptoms in 14 (87%) patients in a retrospective review. LVAD-related ND is associated with a decline in performance of activities of elderly patients and can cause substantial damage to family and/or to social support systems.

Postoperative cognitive dysfunction (POCD) commonly occurs after cardiac surgery[5,6]. The incidence of POCD in the first week after major surgery is 23% in patients between 60 and 69 years of age and 29% in patients older than 70[7,8]. Cognitive dysfunction was still present in 14% of patients over 70 at three month after surgery. POCD is a postoperative memory or thinking impairment that has been corroborated by neuropsychological testing[9,10]. Severe POCD is apparent even without neuropsychological testing[6].

Though the manner in which cerebral hyperperfusion can contribute to postoperative ND in LVAD recipients could not be definitively explained in many observational studies, an association between

an increase of blood flow after LVAD implantation and the development of ND had been found[3]. Pathophysiological mechanisms of POCD are multifactorial in origin, but its exact aetiology remains unclear.

The hypothesis

We hypothesize that cerebral hyperperfusion during operation is a potent factor in the pathogenesis of POCD, and promotes the development of POCD in elderly surgical patients. Some measures against cerebral hyperperfusion should be considered as a new pathway to prevention of POCD.

Evaluation and discussion of the hypothesis

Although there are differences between POCD and LVAD-related ND, there are also striking similarities: to commonly occur after cardiac surgery; elderly patients; the reduction of cerebral flow before surgery compared with the special stage of intra-surgery or after surgery; to reflect microembolic brain injury[6,11,12]. These findings have implications for the information provided that the mechanism of POCD observed in some patients after surgery, which is similar to the restoration of normal cardiac output in LVAD patients might result in cerebral dysfunction. Otherwise, the increment of cerebral flow during general anaesthesia, leading to reperfusion injure of brain6, promotes the inflammatory response to surgery, so this is consistent with an interesting hypothesis that inflammation contributes to cognitive decline in the elderly[13-16].

This hypothesis has some implications for the pathogenesis and treatment of POCD. Because cerebral hyperperfusion during operation might be a potentially preventable and/or reversible condition, we think that there is necessary to observe a relationship between cerebral hyperperfusion and postoperative cognitive dysfunction in the elderly in prospective studies, including direct measurements of cerebral blood flow[17,18] and formal neurologic and neurocognitive evaluation, to better understand the role of cerebral hyperperfusion during operation in POCD after surgery and anesthesia. Otherwise, perioperative physicians should be familiar with management of general anaesthesia and the prevention of postoperative cognitive dysfunction[9].

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邵刘佳子 王保国

北京三博脑科医院

首都医科大学第十一临床医学院 麻醉科，北京100093

摘要

创伤性颅脑损伤作为临床常见疾病，具有高致死率及高致残率的特点，严重威胁国民生命和健康，而其早期诊断、病情分级及预后判断则是降低创伤性颅脑损伤后致死率及致残率的关键。生物标志物作为预警评估分子在多种临床疾病中展示了广泛的应用前景，也是目前颅脑创伤领域的研究热点。近年来，研究发现多种与创伤性颅脑损伤的早期诊断、病情分级及预后判断相关的潜在的生物标志物，但令人遗憾的是目前尚无一种生物标志物被广泛应用于临床实践。未来创伤性颅脑损伤特异性的生物标志物势必会给颅脑外伤诊治体系带来极大的发展。

关键词：创伤性颅脑损伤；生物标志物；诊断；预后

责任作者与联系方式：王保国，E-mail：wbgttyy@sina.com

生物标志物在创伤性颅脑损伤中的现代研究进展

The Role of Biomarkers in the Traumatic Brain Injury

Liu-jiazi Shao, Bao-guo Wang

Department of Anesthesiology, Beijing Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Abstract

As a common disease in the clinic, traumatic brain injury (TBI) severely threats people's health because of its high mortality and morbidity. And the early diagnosis, classification and outcome predication of the TBI is the key to reduce the mortality. Biomarkers have been widely used as a predictor in a variety of diseases such as myocardial infarction, and the researches of the application of biomarkers in the TBI are carried out around the world. In recent years, many potential biomarkers have been demonstrated to be related to the early diagnosis, classification and outcome predication of the TBI. Unfortunately, no biomarkers are available in the clinical practice of TBI. In the future, it is definite that TBI-specific biomarkers will lead to a great improvement in the current system of TBI.

Key Words: Traumatic brain injury; Biomarker; Diagnosis; Outcome

Corresponding Author: Bao-guo Wang, E-mail: wbgttyy@sina.com

创伤性颅脑损伤（Traumatic brain injury; TBI）目前已成为全球青少年伤病致死的首位病因[1]。随着国民经济和交通的发展，我国颅脑外伤发生率和因颅脑外伤致死致残的伤员也逐年大幅增加。近年来，虽然TBI的总体死亡率有所下降，但仍高居创伤致死率的首位，同时存活的患者中有10%的轻度损伤患者会遗留永久性残疾，而中度和重度损伤患者中神经功能障碍更是高达66%和100%，由此造成的经济损失每年高达数百亿之多[2]。创伤性颅脑损伤显然已经成为严重的社会经济问题，并引起了国内外医学界的高度关注，其造成的高死亡率和高致残率也促使我们对TBI现行的诊断方法、病情分级及预后判断体系进行反思，探索更为有效的诊治评估模式。生物标志物的出现为临床医生提供了一个崭新的选择，其在医学领域各种疾病中的研究也得到了迅速开展，并取得了一定的成绩，已经成为目前国内外研究的热点。本文就生物标志物在创伤性颅脑损伤中的应用研究进展作一综述。

一、TBI现行诊治评估体系的局限性

目前创伤性颅脑损伤的诊断主要依赖于患者颅脑损伤的病史和神经影像学检查。就前者而言，轻型颅脑损伤不易引起患者的重视，患者多在出现严重症状后就诊，延误了相关诊治，而重型颅脑损伤则多导致患者意识水平出现改变，表现为嗜睡、昏迷等，对医务人员了解受伤经过、推断损伤机制造成了一定困难，不利于给予个体化治疗。针对TBI，目前临床上常用的神经影像学检查有CT、MRI及单电子发射CT扫描等。神经影像学检查在一定程度上为颅脑损伤的诊断及伤情判定提供了依据，并且不受患者意识水平等临床因素的干扰，但是CT图像对弥漫性脑损伤的分辨率很低，同时由于MRI设备的稀有性，临床工作中尚难以做到外伤后早期行MRI检查，而单电子发射CT扫描虽可用于检测外伤后局部脑血流的

异常，但对器质性的病变毫无用处[3]。其它因素如较高的检测费用，多次CT扫描可能造成放射性损伤等都限制了临床上影像学检查的开展。

正确的评估TBI损伤程度及预后有利于对就诊患者实行个体化治疗。目前国际上通行的脑外伤后病情分级及预后评估的核心标准仍然是Teasdale G等人于1974年根据患者睁眼、言语及运动三项功能制定的Glasgow昏迷评分（Glasgow coma scale;GCS）。根据GCS可将TBI患者分成三型：轻型（GCS：13-15），中型（GCS：9-12）及重型（GCS：≤8）。临床上一般认为GCS分数越低，患者预后越差。随着Glasgow昏迷评分在临床的广泛开展，其局限性也越来越受到临床医生的重视。例如临床上轻中型颅脑损伤约占TBI的90%，在急性期仍有发生颅内出血和弥漫性轴索损伤的风险，同时相当部分轻中型患者虽然没有睁眼、言语及运动功能障碍，但有明显的心理及认知功能损伤，对此GCS评分均未能显示，如果单纯依靠GCS评估病情，容易对病情严重性估计不足，造成漏诊，导致延迟治疗[4,5]。同时亦有研究表明重型颅脑损伤患者损伤早期由于使用镇静药物或者酒精中毒（致伤因素）等原因，采用GCS评估病情并不合适，可能会高估患者的损伤程度，引发过度治疗[6]。

TBI现行诊治评估体系的局限性得到了临床工作者的广泛认可，并促使美国国立卫生研究院（National Institutes of Health; NIH）于2008年专门召开会议研究此项议题，会上明确指出“迫切需要引入新的方法（如生物标志物等）对颅脑外伤现行的诊断、分级及预后评估系统进行彻底的改造，让临床医生能够据此迅速做出正确评估，进而给予患者个体化治疗，改善患者的预后，从而减少整个社会及家庭的负担”[7]。

二、生物标志物在TBI中运用的可行性

目前生物标志物已经成功运用于脑组织以外的其它系统疾病的快速诊断、病情分级及预后评估中，如cTnT、cTnI已经成为急性心肌梗死诊断的“金标准”，应用血清肌酐水平评价肾功能等。生物标志物作为预警评估分子在临床疾病中展示了广泛的应用前景，促使颅脑外伤领域的研究人员希望能够找到一种或者数种针对TBI的特异性标志物，但令人遗憾的是目前尚无一种生物标记物被应用于颅脑损伤的诊断，病情分级和预后评估[8]。

理想的生物标志物通常认为需要符合以下三个方面的条件：（1）取材方便，检测简单快捷；（2）对颅脑外伤有高度的敏感性和特异性；（2）能够在一定程度上反映颅脑外伤的病理生理机制。

颅脑外伤后，神经细胞受损，细胞蛋白及降解产物外流入细胞外夜(Extracellular fluid;ECF)，继而经过体液平衡途径与蛛网膜下腔的脑脊液（Cerebrospinal fluid;CSF）沟通或者通过破损的血脑屏障(Blood-brain barrier,BBB)进入血液循环，最终经过各种代谢途径被清除。在这条生物标志物的代谢通路中，在不同的水平点如脑组织、脑脊液及血液等采集样本，使之成为研究TBI的特殊窗口。当然不同的样本来源各有优缺点：（1）脑组织：对于了解TBI后标记物的变化情况，脑组织取材是最直接的方式。但如前所述，临床上轻中型颅脑损伤占TBI 的90%，此类病人通过获取脑组织检测对TBI进行分级与预后评估显得十分不切实际。（2）脑脊液：动物CSF取材方便，但临床患者取材相对困难，重型TBI患者通常通过颅内压监测导管获取CSF而轻中型的TBI患者只能通过腰穿留取CSF，不利于反复获取样本。（3）血液：无论是动物还是临床患者均能简单方便的留取血样标本，无疑是生物标志物最佳的样本来源，但血液中生物标志物含量相对较低，对检测技术的要求较高。

三、潜在的TBI特征性生物标志物

近年来随着蛋白组学技术在颅脑外伤领域的运用，研究人员通过分析比对脑外伤与正常对照组的蛋白谱，发现了大量的脑外伤后差异性表达蛋白[9]，这群数目纵多的差异性表达的蛋白为临床上寻找TBI特征性生物标志物提供了巨大的线索[10]。以蛋白组学和系统生物学为导向探索TBI后特征性生物标志物是目前大量的动物及临床研究中所采取的研究策略[11,12]，这些结果表明以下6种分子基本符合了理想生物标志物的条件，有可能成为TBI特征性的标志物。

（1）泛素C末端水解酶L1(Ubiquitin carboxy-terminal hydrolase L1; UCH-L1)：又称为神经元特异性基因产物9.5，是目前已知的与中枢神经系统(Central nervous system;CNS)最相关的蛋白分子，主要表达于神经元胞体。目前已经证实UCH-L1在多种神经系统退行性疾病中发生突变和多形性改变[13]。最近TBI动物模型研究亦证实伤后大鼠血清和脑脊液中UCH-L1含量明显升高[14]。（2）S-100：一种主要存在于星形胶质细胞胞浆中的低亲和力钙离子结合蛋白。中枢神经系统组织间液中S-100含量的升高被认为是星形胶质细胞损伤和死亡的标志，而由于星形胶质细胞参与了BBB的组成，因此有学者认为S-100含量的升高亦是血脑屏障遭到破坏的标志之一[15,16]。（3）血管内皮单核细胞激活肽II(Endothelial monocyte activating polypeptide-II;EMAP-II)：研究发现在自身性免疫炎症机能损伤、脊椎损伤、病毒介导的神经系统炎症反应、海马趾损伤及TBI等疾病中，巨噬细胞和小胶质细胞能够特异性产生EMAP-II[17]。基于这些发现，EMAP-II被认为是脑内小胶质细胞的一个分子标记[18]。（4）II-膜收缩蛋白降解产物（II-Spectrin breakdown products;SBDPs）：CNS神经元的轴突和突触前末梢含有丰富的II-膜收缩蛋白，当TBI发生后，II-膜收缩蛋白可经calpain 途径和caspase-3途径特异性降解为145kDa和120kDa两种片段，考虑到calpain 途径是导致坏死的主要通路而caspase-3途径则是介导凋亡的主要通路，因此认为SBDPs不但可以作为TBI的潜在的标志物，其具体亚型亦可指示神经元损伤的方式[19]。（5）髓鞘碱性蛋白（Myelin basic protein;MBP）：一种由CNS内少突胶质细胞合成的膜蛋白，是CNS髓鞘的主要组成部分。当脑组织受损或者发生脱髓鞘疾病时，MBP被大量释放入CSF和血液，因此使之成为

一个潜在的生物标志物，特异性较好。（6）微管相关蛋白2（Microtubule-associated protein-2;MAP-2）：MAP-2是神经元细胞骨架的重要组成成分，主要分布于神经元树突，对维持神经元内环境的稳定起着重要的作用，当发生TBI后，MAP-2含量明显下降[20]。

针对上述潜在的分子标记物在脑外伤领域的运用，目前国际上已开展部分临床研究验证其可行性，但多采用重型颅脑损伤患者的急性期样本进行单个标志物的研究，如上所述，每个标志物反映的临床意义不同，同时不同的标志物在脑内的表达时间谱亦不同。而采用重型颅脑损伤患者的标本进行检测，研究结果对占90%的轻中型颅脑损伤患者而言相对缺乏指导意义，因此在未来的研究中如果联合检测多种潜在的生物标志物，在急性期及亚急性期留取轻、中、重型脑损伤患者或者动物模型的相应标本进行研究，将更有利于找出与TBI诊断、病情分级及预后评估最为相关的血清生物标志物。

四、结语

TBI后生物标志物的寻找已经成为颅脑外伤领域的研究热点。简单快捷而又稳定可靠的生物标志物势必会极大地促进现行TBI诊治体系的发展，为脑外伤后的早期诊断、病情分级及预后评定提供指导意义，最终达到“一血而知TBI全貌”的目的。

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2012年河北省麻醉学术年会

河北省医学会麻醉学分会及河北省医师协会麻醉学医师分会定于2012年9月14～16日在河北省廊坊市召开“2012年河北省麻醉学术年会”，会议将以知识更新讲座、学术报告和临床病例讨论相结合的形式进行学术交流。现将会议征文有关事项通知如下：

一、征文内容及分类：

1、麻醉学科建设与管理；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、输血与血液保护；7、气道管理；8、特殊病例报告；9、麻醉相关新技术、新业务；10、其他。

二、征文要求：

1、凡报送参加会议交流的论文，请提交电子版论文摘要一份（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。

2、格式要求：要求Word文档、4号字体，文稿顺序为题目、单位、邮编、作者姓名、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、投稿方式：邮箱：hbsmzxh@163.com

5、截稿日期：2012年7月31日。

6、本次会议将授予省级继教Ⅰ类学分。

7、有关会议具体时间、地点等事宜另行通知。

三、联系方式：

联系人：李　超　13831110738

刘　雅　13832300822

李慧超　13832320664

邮箱：hbsmzxh@163.com

Protective Effect of PNU-120596, a Selective alpha7 Nicotinic Acetylcholine Receptor Positive Allosteric Modulator, on Myocardial Ischemia-reperfusion Injury in Rats

Hui Li , Zong-ze Zhang , Jia Zhan , Xiang-hu He , Xue-min Song , Yan-lin Wang

Department of Anesthesiology, Zhongnan Hospital of Wuhan University, Wuhan 430071, Hubei, PR China

Abstract

The cholinergic anti-inflammatory pathway (CAP) has been found to exert a protective role in myocardial ischemia-reperfusion injury (MIRI). Alpha7 nicotinic acetylcholine receptor (α7nAChR) is a regulator of CAP, however, little information is available on effect of α7nAChR on MIRI. In the present study, we hypothesized that 1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxanol-3-yl)-urea (PNU-120596), a potent positive allosteric modulator of α7nAChR, could play a protective role on MIRI. Fifty-five rats were randomly assigned into four groups: Sham group, ischemia-reperfusion group, PNU-120596 group, α-bungarotoxin group. Compared with ischemia-reperfusion group, PNU-120596 treatment markedly decreased infarct size, ultrastructural damage, serum creatine kinase and lactate dehydrogenase. Serum proinflammatory cytokines production, myocardium endothelial activation and neutrophil infiltration, myocardium malondialdehyde were also significantly decreased, accompanied by increased superoxide dismutase production, in PNU-120596 group compared with ischemia-reperfusion group. Meanwhile, we observed a significant inhibition of Nuclear factor-κB activation in PNU-120596 group compared with ischemia-reperfusion group. Pretreatment of α7nAChR-selective antagonist α-bungarotoxin, abolished all the protective effects of PNU-120596 in MIRI. In conclusion, PNU might have a protective effect against MIRI. Its action mechanisms might be involved in the inhibition of inflammatory responses, attenuation of lipid peroxidation and suppression of NF-κB activity.

Key Words: PNU-120596; Myocardial reperfusion injury; Inflammation; Alpha7 nicotinic acetylcholine receptor; Cytokines

Corresponding Author: Yan-lin Wang, E-mail: wyl0342@gmail.com

INTRODUCTION

Myocardial ischemia-reperfusion injury (MIRI) is a common clinic event that occurs in mechanical or pharmacological treatment of myocardial infarction and counteracts the beneficial effects of restoration of blood flow[1].

Inflammatory reaction has been demonstrated to play a crucial role in reperfusion-induced myocardial damage, promoting cell death and impairing pump function[2]. Recently, a novel anti-inflammatory mechanism termed 'the cholinergic anti-inflammatory pathway (CAP)' has attracted many researchers' attention[3]. It is a fast and integrated anti-inflammatory pathway, which is composed of vagus nerve and its principal neurotransmitter acetylcholine[4]. Nicotinic acetylcholine receptor alpha7 subunit (α7nAChR) has been proven to be an essential regulator for the anti-inflammatory function of CAP[5]. Although there is accumulating evidence that vagus nerve stimulation or acetylcholine protects against MIRI[6,7], little has been reported on the effect of α7nAChR in MIRI. Moreover, the present approaches activating CAP is not optimal, because of the suffering brought by vagus nerve stimulation and side effects by nonselective cholinergic agents[4]. We hypothesized that a more targeted pharmacological intervention would be better. 1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxanol-3-yl)-urea (PNU-120596), a potent α7nAChR-selective positive allosteric modulator[9,10], could enhance responsiveness of α7nAChRs to nicotinic agents and slow down desensitization of α7nAChRs, and consequently, reinforce the endogenous cholinergic neurotransmission[11]. This study is designed to observe the effect of PNU-120596 in a rat model of MIRI, together with investigating its possible mechanism.

METHODS

Animals and groups

Adult male Sprague Dawley rats (body weight: 225-

275g) were supplied by department of laboratory animal center of Wuhan University, China. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health, and the protocol was approved by the ethical committee of Wuhan University.

Fifty-five rats were randomly assigned into four groups. Sham group (SHAM) (n=10), sham operated animals. Myocardial ischemia-reperfusion group (IR) (n=15), animals were subjected to 30 min of left anterior descending coronary artery (LAD) occlusion followed by 2h of reperfusion. PNU-120596 group (PNU) (n=15), animals were treated intravenously with 1mg/kg PNU-120596 (dissolved in 5% dimethyl sulfoxide and 5% Solutol in PBS) 30min before LAD occlusion. α-bungarotoxin group (BGT) (n=15), animals were pretreated intravenously with 1μg/kg α-bungarotoxin (dissolved in PBS) 15min before PNU-120596 administration. PNU-120596 was purchased from Sigma-Aldrich (Sigma, St. Louis, MO, USA) and α -bungarotoxin from Invitrogen (Invitrogen, Carlsbad, CA, USA).

Myocardial ischemia-reperfusion injury model

All rats were anesthetized by intraperitoneal injection of 1% pentobarbital Sodium (40mg/kg), and then mechanically ventilated with room air. Right femoral vein was cannulated for fluid or drug delivery. Electrocardiogram, heart rate and mean arterial blood pressure were continuously monitored. A left thoracotomy was performed and heart was exposed. A 5-0 silk suture was placed around the proximal part of LAD, and a small vinyl tube was used to form a snare for reversible LAD occlusion. LAD was occluded for 30 min and reperfused for 2h. Myocardial ischemia was confirmed by ST segment elevation, QRS complex widening and the color changes of area-at-risk (AAR). In SHAM group, the same procedure was performed without LAD occlusion. After 2h of reperfusion, blood samples and hearts were collected for further examinations. Five hearts in each group except SHAM group were used for determination of infarct size; five hearts in each group were used for transmission electron microscopy (TEM) examination and immunohistochemistry assay; five hearts in each group were used for Western blot analysis and measurement of superoxide dismutase (SOD), malondialdehyde (MDA) and myeloperoxidase (MPO). The animal experimental protocol was outlined in Figure 1.

Measurement of myocardial infarct size

Myocardial infarct size was measured by evans blue/ triphenyl tetrazolium chloride (TTC) staining as previously described[12]. Briefly, LAD was reoccluded at the end of reperfusion and 1ml of 2% evans blue dye was injected. The heart was excised and transected parallel to the atrioventricular goove and cut into 2-mm thick slices.

Figure 1 General outline of the experiment. *expect SHAM group. IR, ischemia-reperfusion; PNU, PNU-120596; BGT, α-bungarotoxin; CK, creatine kinase; LDH, lactate dehydrogenase; TNF-alpha, tumor necrosis factor-alpha; IL-6, interleukin-6; TEM, transmission electron microscopy; IHC, immunohistochemistry; SOD, superoxide dismutase; MDA, malondialdehyde; MPO, myeloperoxidase.

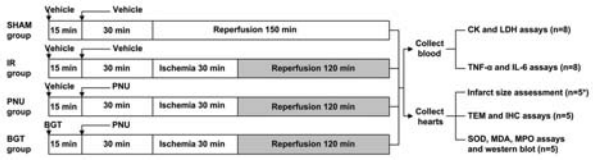
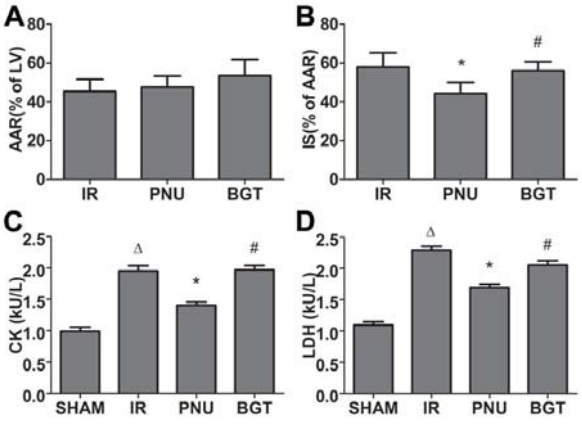


Figure 2 PNU-120596 attenuates IR-induced myocardial damage. (A) Area at risk (AAR) was expressed as percentages of LV (left ventricular) mass (n=5). AAR was comparable among groups. (B) Infarct size (IS) was expressed as percentages of AAR mass (n=5). Compared with IR group, $^{*}P < 0.05$; compared with PNU group, $^{\#}P < 0.05$. (C)(D) Serum levels of creatine kinase (CK) and lactate dehydrogenase (LDH)(n=8). Compared with SHAM group, $^{\Delta}P<0.05$; compared with IR group, $^{*}P<0.05$; compared with PNU group, $^{\#}P<0.05$.



The slices were then incubated in 1% TTC PBS solution at 37°C for 30min. Infarct area (absence of staining), non-infarcted AAR (red staining), and non-ischemic portion of left ventricular (LV) (blue staining) were dissected and weighed after storage overnight in 10% formaldehyde. AAR was expressed as a percentage of the LV mass (AAR/LV). Myocardial infarct size (IS) was expressed as a percentage of the AAR mass (IS/AAR).

Ultrastructure observation

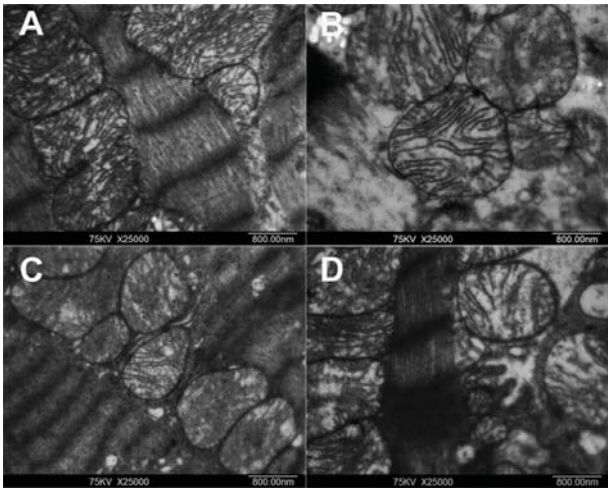
TEM was used to observe ultrastructure of hearts. The hearts were cut into 1-mm thick slices, and fixed in 4% glutaraldehyde and embedded in Epon resin. Then ultrathin sections were cut and counter-stained with uranyl acetate and lead citrate, and examined with a Hitachi H-600 transmission electron microscope (Hitachi, Tokyo, Japan).

Measurement of serum creatine kinase (CK) and lactate dehydrogenase (LDH)

CK and LDH activities were measured spectrophotometrically. Blood samples were centrifuged for 10 min at 3000 rpm at 4°C, and serum was collected and assayed according to the instructions of commercial kits (Jiancheng biologic project company, Nanjing, China). Results were expressed as U/L.

Measurement of serum proinflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)

Figure 3 Ultrastructure of myocardium (n=5). A, SHAM group; B, IR group; C, PNU group; D, BGT group. Scale bars represent 800nm.



Serum concentrations of immunoreactive TNF-α and IL-6 were determined with sandwich ELISA kits (R&D, Minneapolis, USA) according to the manufacturer's protocols. Briefly, blood samples were centrifuged, and supernatant was collected and reacted with the assay reagents in TNF-α and IL-6 kits respectively, and analyzed spectrophotometrically at 450 nm. The levels of TNF-α and IL-6 were expressed as pg/ml.

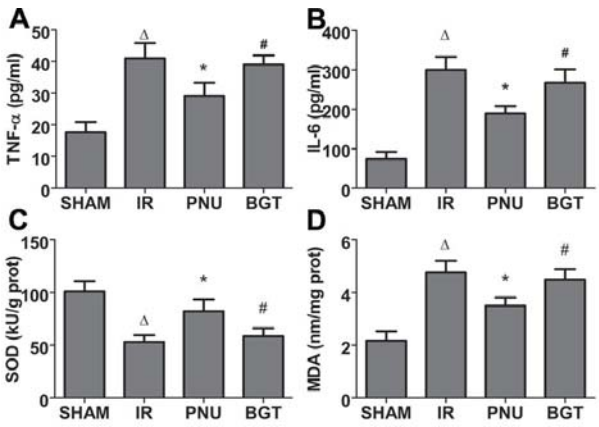
Measurement of SOD, MDA and MPO in myocardium

Cardiac tissue samples were homogenized in 0.9% saline solution and supernatant was collected for assays of SOD activities, MDA contents and MPO activities. They were determined spectrophotometrically by colorimetric assays using commercial kits (Jiancheng). SOD activity was expressed as kU/g protein. MDA content was expressed as nm/mg protein. MPO activity was expressed as U/mg wet tissue.

Expression of intercellular adhesion molecule-1 (ICAM-1)

ICAM-1 is a cell surface glycoprotein expressed by activated endothelial cells [13]. We tested ICAM-1 expression to detect endothelial cell activation by

Figure 4 Changes of serum cytokines levels and myocardium SOD activities and MDA contents. A, B, Changes of serum TNF- and IL-6 levels (n=8). Compared with SHAM group, $^{\Delta}P < 0.05$; compared with IR group, $^{*}P < 0.05$; compared with PNU group, $^{\#}P < 0.05$." C, D, Changes of myocardium SOD activities and MDA contents (n=5). Compared with SHAM group, $^{\Delta}P < 0.05$; compared with IR group, $^{*}P < 0.05$; compared with PNU group, $^{\#}P < 0.05$.



immunohistochemical staining. Briefly, the ischemic regions of hearts were embedded in paraffin after fixation with 4% paraformaldehyde and were cut into 4-μm sections. These sections were incubated for 24h with mouse anti-ICAM-1 antibody at 1:100 dilution (Santa Cruz Biotechnology, Santa Cruz, CA, USA) followed by a rabbit anti-mouse secondary antibody at 1:1000 dilution (Santa Cruz). Avidine-biotin-peroxidase complex was used for signal amplification and diaminobenzidine (DAB) substrate was used to develop color. Intensity of ICAM-1 staining was measured by determining integrated optical densities of DAB-stained cells using Image-Pro plus software (Media Cybernetics, Silver Spring, MD, USA).

Expression of Nuclear Factor-κB (NF-κB) p65

NF-κB p65 expression was determined by western blot analysis. Cardiac tissues were homogenized, nuclear proteins were extracted, and protein concentrations was measured by a BCA protein assay kit (Beyotime, Shanghai, China). Proteins were separated by 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and then transferred to a nitrocellulose membrane. The membrane was blocked in 5% non-fat milk for 1 h. Afterwards, the membrane was incubated with goat polyclonal antibody against NF-κB p65 (1:100 dilution, Santa Cruz) or mouse polyclonal anti-β-actin (1:1000 dilution, Santa Cruz) and with a rabbit anti-goat secondary antibody (1:1000 dilution, Santa Cruz) for 1h at room temperature. The immunoreactive bands were visualized with enhanced chemiluminescence (Beyotime).

Statistical analysis

Data were expressed as mean ± SD and compared by a one-way ANOVA, followed by a Bonferroni post hoc analysis. Statistical analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL) and P<0.05 was considered as statistically significant.

RESULTS

Myocardial infarct size

No differences were observed in AAR among the three groups (P>0.05), indicating that a comparable degree of ischemic jeopardy existed (Figure 2A). PNU-120596 administration significantly decreased myocardial infarct size compared with IR group (P < 0.05), and α-bungarotoxin pretreatment abolished the reducement effect of PNU-120596 on infarct size (P<0.05) (Figure 2B).

Figure 5 Changes of intercellular adhesion molecule-1 (ICAM-1) expression on vascular endothelial cells and MPO activities in myocardium (n=5). (A) Immunohistochemical staining of ICAM-1 in myocardium. Brown staining indicates the positive expression of ICAM-1. a, SHAM group; b, IR group; c, PNU group; d, BGT group. Scale bars represent 100μm. (B) The quantitative analysis of ICAM-1. Compared with SHAM group, $^{\Delta}P < 0.05$; compared with IR group, $^{*}P<0.05$; compared with PNU group, $^{\#}P<0.05$. (C) The MPO acitivities of the myocardium. Compared with SHAM group, $^{\Delta}P<0.05$; compared with IR group, $^{*}P<0.05$; compared with PNU group, $^{\#}P<0.05$.

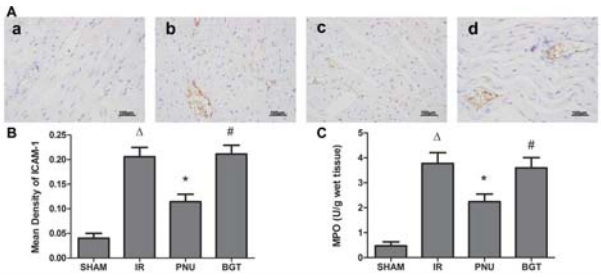
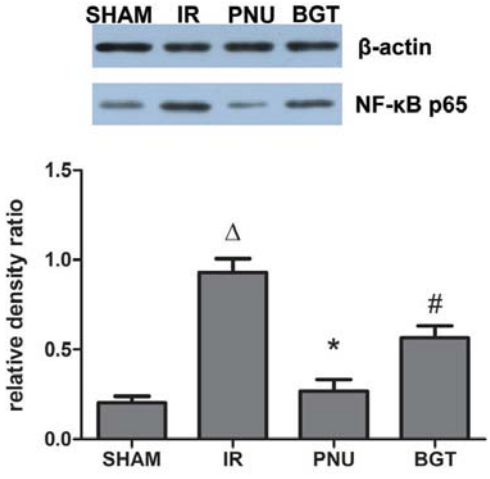


Figure 6 Effects of PNU-120596 on Nuclear Factor-κB (NF-κB) activity (n=5). Western blotting analysis of NF-κB p65 protein in myocardium. The relative desity was calcutated as the ratio of NF-κB p65 expression to -actin expression. Compared with SHAM group, $^{\Delta}P < 0.05$; compared with IR group, $^{*}P < 0.05$; compared with PNU group, $^{\#}P < 0.05$.



Serum CK and LDH concentrations

Levels of CK and LDH were significantly increased in IR group compared with SHAM group (P<0.05). Compared with IR group, PNU-120596 administration significantly reduced the levels of the two markers (P<0.05). α-bungarotoxin pretreatment abolished the effects of PNU-120596 (P < 0.05) (Figure 2C, Figure 2D).

Ultrastructure observation

In SHAM group, cardiac muscle fibers were arranged regularly, with clear and integrated structures of mitochondria. In IR group and BGT group, cardiac muscle fibers were arranged in an irregular way and some were dissolved, muscle striations were obscure, with mitochondrion swollen, vacuolar degeneration, cristea destruction and dissolved. Compared with IR group and BGT group, pathological changes in PNU group were lighter (Figure 3).

Concentrations of TNF-α and IL-6

Levels of TNF-α and IL-6 were significantly increased in IR group compared with SHAM group (P<0.05). Compared with IR group, PNU-120596 administration significantly reduced the levels of the two cytokines (P<0.05). α-bungarotoxin pretreatment abolished the effects of PNU-120596 (P<0.05) (Figure 4A, Figure 4B).

Changes of SOD activities, MPO activities, and MDA contents in myocardium

Compared with SHAM group, SOD activities were markedly decreased, while MDA contents and MPO activities were increased in IR group (P<0.05). Compared with IR group, PNU-120596 administration increased SOD activities, and decreased MDA contents and MPO activities (P<0.05). However, α-bungarotoxin pretreatment abolished the effects of PNU-120596 (P<0.05) (Figure 4C, Figure 4D and Figure 5C).

ICAM-1 expression on endothelial cells

ICAM-1expression was significantly increased in IR group compared with SHAM group (P<0.05). PNU-120596 reduced ICAM-1 expression in myocardium compared with IR group (P<0.05), however, this effect was abolished by α-bungarotoxin (P<0.05) (Figure 5A, Figure 5B).

NF-κB activity

Compared with Sham group, NF-κB activity was markedly elevated in IR group (P<0.05). PNU-120596 inhibited activation of NF-κB (P<0.05), and α-bungarotoxin pretreatment abolished the inhibitory effect of PNU-120596 (P<0.05) (Figure 6).

DISCUSSION

In the present study, we made several observations. Above all, PNU-120596 possessed cardioprotective properties against MIRI. Second, the protection of PNU-120596 might be related to suppression of inflammation and oxidative stress. Third, the anti-inflammation and anti-oxidation might be correlated with inhibition of NF-κB activation through CAP.

CAP is a physiological mechanism through which efferent signals in vagus nerve could modulate inflammatory status[3]. Previous researches have demonstrated that vagus nerve stimulation and some acetylcholine receptor agonists exert protective effects against MIRI in vivo and in vitro[6,7,14-16]. 7nAChR is the critical regulator of CAP[5], however, little information is available on the effects of 7nAChR in MIRI. PNU-120596 is a potent modulator of 7nAChR, and it can dramatically enhance responsiveness of 7nAChR to endogenous cholinergic agonists and slow down 7nAChR desensitization[11]. It may be used as an alternative to vagus nerve stimulation or exogenous cholinergic agonists. McLean et al[17]. studied the pharmacokinetics of PNU-120596 in rats after administration of 10mg/kg(s. c.) and found that PNU120596 was well absorbed, rapidly distributed. We also carried out preliminary experiments to grope the optimum dose, and the dose of PNU120596 we have chosen seemed to have preferable effects to other doses in MIRI rats.

Our study showed that PNU-120596 exerted cardioprotective properties characterized by reducing infarct size, attenuating serum CK and LDH activities and attenuating myocardial ultrastructural damage compared with that of IR group. These effects can be abolished by selective-7nAChR antagonist α-bungarotoxin, suggesting that 7nAChR may be a target of cardioprotection.

We also observed that PNU-120596 could significantly inhibit the production of proinflammatory cytokines TNF- and IL-6, attenuate endothelial cells activation and neutrophils recruitment, and modulate redox state. There is strong evidence that proinflammatory cytokines, neutrophils and reactive oxygen species play important roles

in myocardial damage caused by IR[1]. TNF- is a critical early cytokine that can cause direct myocardial toxicity and induce further inflammatory signaling[18]. Neutrophils can not only induce mechanical obstruction of capillary vessels, but also release cytotoxic agents[19]. Reactive oxygen species can lead to cellular damage through direct damage to membranes and indirect activation of pro-apoptotic pathway[20]. Interventions that target these mediators have revealed cardioprotective effects in MIRI[21-23]. Previous studies indicate that vagus nerve stimulation or cholinergic agonists could suppress production of proinflammatory cytokines and reactive oxygen species, and attenuate endothelial cell activation and neutrophil recruitment[24-26]. Consequently, we hypothesized that PNU-120596 might exert cardioprotective effects by anti-inflammation and anti-oxidation.

NF-κB is a 'fast-acting' redox-sensitive transcription factor that regulates the expression of many genes involved in ischemia and reperfusion injury[27]. Activated NF-κB promotes proinflammatory cytokines production, leukocyte recruitment and complement activation, ultimately contributing to myocardial damage[3,27,28]. It is proven that CAP suppresses proinflammatory cytokines production through inhibiting NF-κB activity in sepsis[29]. In our study, we observed that NF-κB activity was inhibited by PNU-120596. We presumed that PNU-120596 might exert anti-inflammation and anti-oxidation through inhibition of NF-κB.

However, as we all know, inflammation not only plays a role in acute extension of injury, but also in myocardial healing process[30]. In our study, we only observed the early effects of PNU-120596 after 2h of reperfusion, more studies are needed to clarify the long-term effect of PNU-120596 in MIRI.

CONCLUSION

In conclusion, our study showed that a selective 7nAChR modulator PNU-120596, exerted a cardioprotective effect in a rat model of MIRI, possibly owing to attenuation of endothelial activation, neutrophil infiltration, cytokine secretion and oxidative stress.

Acknowledgements

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Effect of Sevoflurane Preconditioning-Postconditioning on Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase during Myocardial Ischemia-Reperfusion in Rats

Yue Liu, Zhen-ming Dong

Department of Anesthesiology, the Second Affiliated Hospital to Hebei Medical University, Shijiazhuang, Hebei Province, 050000, China

Abstract

Objective: The purpose of this study was to investigate the protective mechanisms of sevoflurane preconditioning combined with sevoflurane postconditioning against acute myocardial ischemia-reperfusion (I/R) injury.

Methods: Seventy-five healthy male Wistar rats weighing 250-280 g were randomly divided into 5 groups (n=15 each): sham operation group (S group), I/R group, sevoflurane preconditioning group (Spre group) and sevoflurane postconditioning group (Spo group) and sevoflurane preconditioning combined with sevoflurane postconditioning group (Spre+Spo group). Myocardial I/R were produced by occlusion of anterior descending branch of left coronary artery for 30 min followed by 2 h reperfusion in anesthetized rats. In group S the anterior descending branch was only exposed but not ligated. In I/R group, oxygen 2 L/min was inhaled during operation and no other treatments were performed before and after ischemia and reperfusion. Group Spre received 15 min inhalation of 2.5% sevoflurane and 15 min wash-out 30 min before occlusion. Group Spo received 5 min inhalation of 2.5% sevoflurane 1 min before reperfusion. Group Spre+Spo received 15 min inhalation of 2.5% sevoflurane and 15 min wash-out 30 min before occlusion, and received 5 min inhalation of 2.5% sevoflurane 1 min before reperfusion.

At 2 h of reperfusion blood samples were taken from the left carotid artery to determine the concentrations of serum lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI). Five rats in each group were selected to measure the area at risk and infarct size. Another five rats in each group were sacrificed and hearts removed, the ultrastructure of myocardium was observed using transmission electron microscope. The myocardial tissues of the remaining 5 rats in the ischemic area were taken and centrifuged for determination of the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase.

Results: Compared with group S, the concentrations of CK-MB and LDH and cTnI were significantly increased and the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes were significantly decreased in I/R group ($P < 0.05$ or 0.01). Compared with group I/R, the concentrations of CK-MB and LDH and cTnI and myocardial infarct size were significantly decreased and the concentrations of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes were significantly increased in Spre, Spo and Spre + Spo groups ($P < 0.05$ or 0.01). Compared with Spo and Spre groups, the concentrations of CK-MB and LDH and cTnI and myocardial infarct size were significantly decreased and Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes were significantly increased in Spre+Spo group ($P < 0.05$). There was no significant difference between Spre and Spo groups ($P > 0.05$).

Myofibrils aligned, mitochondrial membrane integrity and relative intact mitochondria were seen in group S. The disordered myofibrils, mitochondrial swelling, incomplete mitochondrial membrane and mitochondrial cristae disappeared were observed in group I/R. Inter-myofibrillar edema, mitochondrial membrane integrity and part of mitochondrial cristae disappeared were seen in Spre group. Myofibrillar edema, mitochondrial membrane integrity, mitochondrial moderate edema and partial mitochondrial cristae disappeared were also seen in group Spo. Inter-myofibrillar edema, mitochondrial localized edema, mitochondrial membrane integrity and partial mitochondrial cristae disappeared in group Spre +Spo.

Conclusions: Sevoflurane preconditioning combined with postconditioning reduces myocardial I/R injury in rats through increasing the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase. .

Key words:Sodium-potassium-exchanging ATPase; $Ca^{2+}Mg^{2+}$ ATPase; Myocardial reperfusion injury; Preconditioning; Postcondioning; Sevoflurane

Corresponding Author: Zhen-ming Dong, E-mail: hbmzzk@163.com

Introduction

Myocardial ischemia-reperfusion injury is a common pathophysiological process in clinical anesthesia. Energy metabolism dysfunction is the initial stage, and calcium overload is the principal[1].Therefore, the myocytes could be protected through reducing the intracellular calcium overload when reperfusion[2]. Whereas the mechanisms of the intracellular calcium overload in myocytes with reperfusion injury is related with the inhibition of the avtivities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase.

Na^+-K^+-ATPase actively transports Na+ and K^+ transmembrane and hydrolyzes ATP to supply energy and

maintain action potential and myocardial excitability. If the activities of Na^+-K^+-ATPase was suppressed Ca^{2+} influx would be increased by the exchange of Na^+ and Ca^{2+}. Ca^{2+}-Mg^{2+}-ATPase can take Ca^{2+} from cytoplasmic actively into sarcoplasmic reticulum and transport Ca^{2+} across the membrane out of the cell. It is a lipotropic protein to control the concentration of the intracellular Ca^{2+} whose activity is regulated by Na^+-K^+-ATPase. The two enzymes are important for intracellular ions balance and myocardial excitation-contraction coupling[3].

This study is to evaluate the effect of sevoflurane preconditioning combined with sevoflurane postconditioning on Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase during myocardial ischemia-reperfusion in rats. To investigate the protective mechanisms of sevoflurane preconditioning combined with sevoflurane postconditioning against acute myocardial ischemia-reperfusion (I/R) injury.

Table 1: Changes in the activities of LDH, CK-MB and concentration of cTnI in serum of rats in each group (n=10, x±s)

Group	CK-MB(U/L)	LDH(U/L)	cTnI（ng/ml）
group S	385±72	428±43	0.62±0.18
group I/R	957±69**	864±55**	2.66±1.00**△△
group Spre	731±89**△△	695±68**△△	1.38±0.85**△△
group Spo	801±78**△△	724±79**△△	1.46±0.76**△△
Group Spre+po	607±101**△△★	615±62**△△★	1.01±0.62**△△★

Compared with group S, **P<0.01
Compared with group I/R, △△P<0.01
Compared with group Spre and group Spo, ★P<0.05

Table 2: Changes in IS and AAR of rats in four groups (%, n=10, x±s)

Group	AAR	IS
group I/R	50.9±1.8	50.3±4.8
group Spre	50.0±3.3	29.6±3.3△
group Spo	51. 4±1. 8	28. 9±3. 2△
groupSpre+Spo	51. 0±3. 5	22. 7±4. 0△△★

Compared with group I/R, △P<0.05 △△P<0.01
Compared with group Spre and group Spo, ★P<0.05

Table 3: The activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocardial tissues in rats in each group(μmol Pi·h^{-1}·mg^{-1} prot，n=5,±s)

group	Na^+-K^+-ATPase(μmol Pi/mg prot/h)	Ca^{2+}-Mg^{2+}-ATPase(μmol Pi/mg prot/h)
group S	1.59±0.18	1.52±0.17
group I/R	0.70±0.23**	0.81±0.19**
group Spre	1.13±0.13*△	1.08±0.11*△
group Spo	1.10±0.12*△	1.07±0.11*△
group Spo+pre	1.41±0.14*△★	1.36±0.08*△★

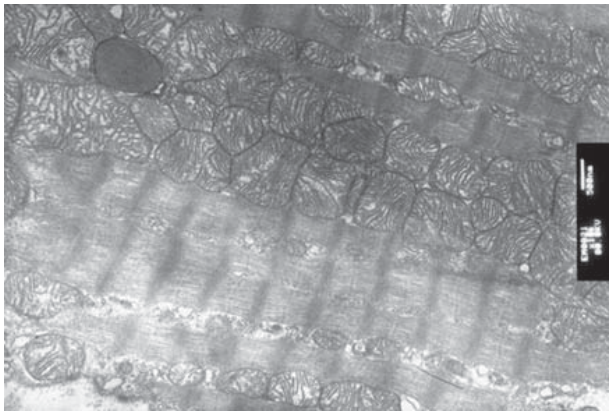
Compared with group S, *P<0.05**P<0.01
Compared with group I/R, △P<0.05
Comparison among group Spre, Spo and Spo + pre, ★P<0.05

Materials and Methods

The experiment procedures and protocols used in this study were reviewed and approved by the Institutional Animal Care and Use Committee.

Seventy-five healthy male Wistar rats weighing 250-280g, obtained from Laboratory animal center in Hebei province, China, were used for study and given 45mg/kg of 3% pentobarbital sodium. After each rat was anesthetized and no longer responsive to noxious stimulus to the tail, a median thoracotomy was performed. All hearts were allowed to stabilize for at least 20 minutes. All the rats were randomly divided into 5 groups (n=15 each): sham operation group (S group), I/R group, sevoflurane preconditioning group (Spre group) and sevoflurane postconditioning group (Spo group) and sevoflurane preconditioning combined with sevoflurane postconditioning group (Spre+Spo group). Myocardial I/R was induced by making a snare with the passage of a 6-0 polypropylene occlusion of anterior descending branch of left coronary artery for 30 min followed by 2 h reperfusion in anesthetized rats. In group S the anterior descending branch was only exposed but not ligated. In I/R group, oxygen 2 L/min was inhaled during operation and no other treatments were performed before and after ischemia and reperfusion. Group Spre received 15 min inhalation of 2.5% sevoflurane and 15 min wash-out 30 min before occlusion. Group Spo received 5 min inhalation of 2.5% sevoflurane 1 min before reperfusion. Group Spre+Spo received 15 min inhalation of 2.5% sevoflurane and 15 min wash-out 30

Fig.1 (×12 000)
Group S: Myocardial fibrils aligned, mitochondrial cristae were clear and structure was complete.



min before occlusion, and received 5 min inhalation of 2.5% sevoflurane 1 min before reperfusion.

At 2 h of reperfusion blood samples were taken from the left carotid artery to determine the concentrations of serum lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI). Five rats in each group were selected to measure the area at risk and infarct size. Another five rats in each group were sacrificed and hearts removed, the ultrastructure of myocardium was observed using transmission electron microscope. The myocardial tissues of the remaining 5 rats in the ischemic area were taken and centrifuged for determination of the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase.

Calculation

①Definition: ATP enzyme in per mg tissue protein per hour decomposing ATP to produce l μ mol inorganic phosphorus is one ATP enzyme activity unit. That is μmol Pi/mg prot/h.

②Formula: ATP enzyme activity in tissues (μ mol Pi/mg prot/h) = (OD value of sample tube - OD value of contrast tube) ÷OD value of standard tube × standard tube concentration (0.5μmol/ml) x sample diluted times in reaction system (2.5) x 6note ÷ homogenate protein concentration (mg prot/ml)

Note: water bath time was 10 min; enzyme activity definition was for 1 h, multiply by 6.

Statistical Analysis

Data were stored electronically and analyzed by use of SAS software, version 8.1(SAS Institute Cary, NC). Data was presented as mean ± standard deviation.1-way analysis of variance was used to analyze the differences among groups. Comparisons between groups were performed Using Dunnett's t test. Differences were considered to be statistically significant when p values were < 0.05.

Results

Compared with group S, the concentrations of CK-MB and LDH and cTnI in group I/R were significantly increased ($P < 0.05$ or 0.01). Compared with group I/R, the concentrations of CK-MB and LDH and cTnI were significantly decreased in Spre and Spo groups ($P < 0.05$ or 0.01). The concentrations of CK-MB and LDH and cTnI were significantly decreased in group Spre + Spo than in Spre and Spo groups ($P < 0.05$) (Table 1).

There was no significant difference in the area at risk among all groups（$P>0.05$）. The myocardial infarct size was significantly decreased in Spre, Spo and Spre + Spo groups than in group I/R ($P < 0.05$ or 0.01), and in Spre + Spo group than in Spre and Spo groups ($P < 0.05$) (Table 2).

Myofibrils aligned, mitochondrial membrane integrity and relative intact mitochondria were seen in group S. The disordered myofibrils, mitochondrial swelling, incomplete mitochondrial membrane and mitochondrial cristae disappeared were observed in group I/R. Inter-myofibrillar edema, mitochondrial membrane integrity and part of

Fig.2 (×20 000)

Group I/R: Myocardial fibrils were disordered arranged, mitochondrial moderate swelling, the mitochondrial membrane incomplete, local cristae disappeared, arranged disorderly.

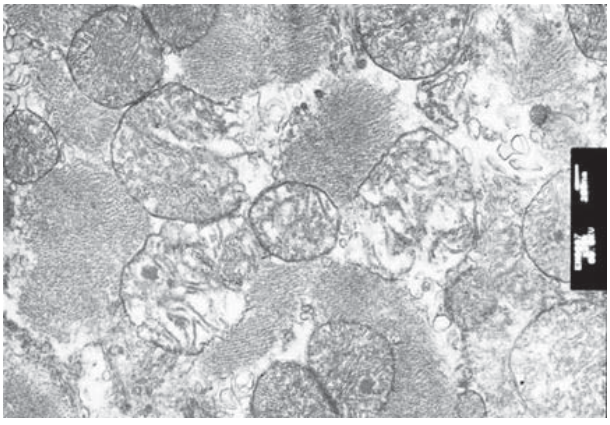
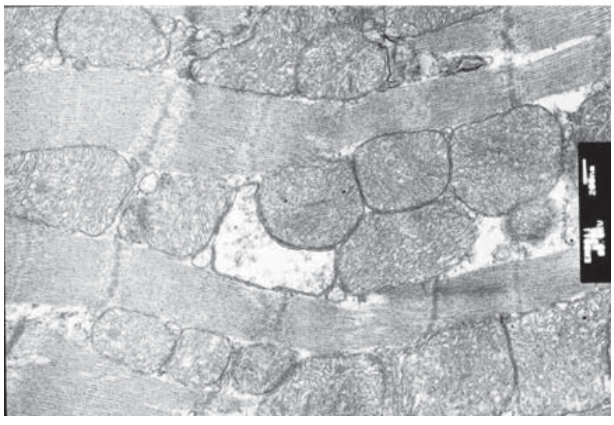


Fig.3 (×20 000)

Group Spre: Myocardial fibrils gap oedema, mitochondrial fibrils crest disappeared.



mitochondrial cristae disappeared were seen in Spre group. Myofibrillar edema, mitochondrial membrane integrity, mitochondrial moderate edema and partial mitochondrial cristae disappeared were also seen in group Spo.

Inter-myofibrillar edema, mitochondrial localized edema, mitochondrial membrane integrity and partial mitochondrial cristae disappeared can be seen in group Spre +Spo（Figure 1～5）.

Compared with group S, the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes were significantly decreased in I/R group. Compared with I/R group, the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes were significantly increased in Spo and Spre groups ($P<0.05$). Compared with Spo and Spre groups, the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes were significantly increased in Spre+Spo group ($P<0.05$). There was no significant difference between Spre and Spo groups ($P> 0.05$) (Table 3).

Discussion

In the study, the rats were taken as research object because rat's cardiovascular system growth is consistent and almost no variation. Their cardiovascular system distribution is similar to human being's and so little myocardial collateral circulation as to be more liable to reperfusion injury. There are so many experimental materials about rat's physiology, biochemics, morphology, pharmacology, and other aspects as to easy to be studied and compared. Otherwise the lower price is favorable for large number of repeated experiments. Purebred rat of inbreeding so there is little variation in cardiovascular anatomy and physiology.

The development of reperfusion injury is associated with ischemia period. Reperfusion injury would not develop if ischemia period was too long or short. There would be more liability of arrhythmia when the coronary flow recovered 5~10 minutes after the coronary artery was occluded. There would be less when ischemia period was shorter than 2 minutes or longer than 20 minutes. Because of the coronary artery in rat is very small, if the occlusion period was more than 30 min the coronary artery would be inaccessible forever and myocardial infarct size would be increased so as to affect the accuracy of the experiment. Otherwise the myocardial ischemia-reperfusion injury commonly occurs within 30 min of ischemia, if more than 30 min, the incidence of myocardial reperfusion injury would drop.

Stable myocardial ischemia-reperfusion injury[4] can be induced by sixty minutes of reperfusion for rats. So according to reference 5 and the beforehand experimental, the model was made for 30min ischemia and 2h of reperfusion.

The study showed that the myocardial enzymes and infarct size in I/R group were increased compared with group S, which indicated the model of ischemia-reperfusion injury was made successfully.

Fig.4 (×20 000)

Group Spo: Myocardial fibrils were edema, the mitochondrial membrane integrity, mitochondria moderate edema, mitochondrial cristae partly disappeared.

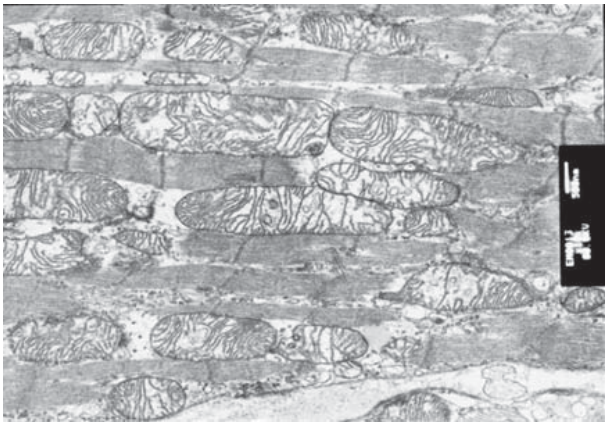
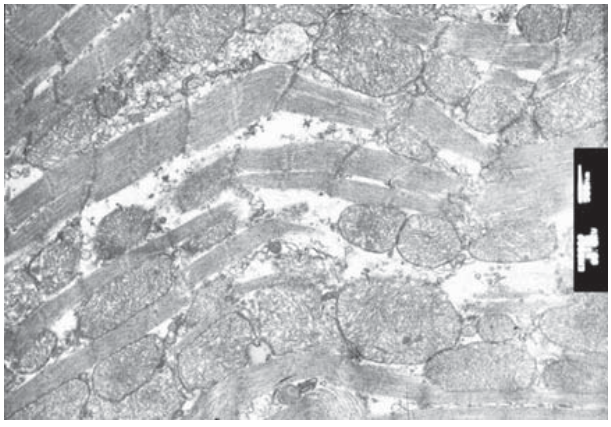


Fig.5 (×20 000)

Group Spre+Spo: Myocardial fibrils were edema, local mitochondria were mildly edema, the mitochondrial membrane integrity, and mitochondrial cristae partly disappeared.



Deyhimy et.al[6] reported 2.5% sevoflurane postcondtioning reduced the myocardial infarct size which showed the appropriate sevoflurane concentration was very important to protect against the myocardial reperfusion injury.

Piriou et.al[7] reported that 3.7% sevoflurane preconditioning had no effect on myocardial ischemia-reperfusion injury. Okusa et.al8 reported that sevoflurane preconditioning washed-out time should be no longer than 60min; the myocardial protection would be lost instead.

A previous report showed the protection of postconditioning was only induced at the time of reperfusion started, if intervented 1min after reperfusion there would be no myocardial protection[9,10]; whereas there was no similar duration of start or maintaining[11,12,13].

The study based on Redel et.al[13] and the beforehand experiment was made to inhale sevoflurane 1min before reperfusion in order to make expired end-tidal concentration of sevoflurane reach 2.5% at the start of reperfusion.

The concentrations of myocardial enzymes and infarct size were decreased in Spre group, Spo group and Spre +Spo compared with group I/R in this study. And sevoflurane preconditioning combined with postconditioning was better. It showed that whatever sevoflurane preconditioning or sevoflurane postconditioning both can protect the myocardium against ischemia-reperfusion injury and both the treatments had the similar effect. But sevoflurane preconditioning combined with postconditioning was the best.

Volatile anesthetics can reduce myocardial oxygen intake, oxygen consumption and increase the ratio of oxygen supply and demand in favor of storage more energy for myocardium. Volatile anesthetics can inhibit the heart rate to a certain extent maybe it is correlated to the volatile anesthetics' similar function to calcium channel blockers and beta blockers so as to affect the concentration of intracellular calcium[14].

The research before had shown that sevoflurane postconditioning can promote the metabolism of energy recovery. It is possible that sevoflurane could reduce the release of adenosine, inosine, lactic acid, purine and then provide the raw material for energy recovery[15].Another research had shown that sevoflurane postconditioning can inhibit the mitochondrial permeability transition hole16 so as to improve the mitochondrial function and produce more ATP. Sevoflurane postconditioning could promote more ATP through the above mechanisms to improve the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes which inhibited the intracellular calcium overload, furthermore reduced the myocardial ischemia-reperfusion injury.

The study showed that sevoflurane preconditioning combined with postconditioning reduced the myocardial ischemia-reperfusion injury. It is possible that the activitivities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes and energy metabalism disfunction was improved,that inhibited the intracellular Calcium overload further.

In conclusion sevoflurane preconditioning combined with postconditioning can reduce myocardial ischemia-reperfusion injury through improving the activities of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase in myocytes.

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Comparison of C_{50} for Propofol-Remifentanil Target-Controlled Infusion and Bispectral Index at Loss of Consciousness and Response to Painful Stimulus in Elderly and Young Patients

Ning Yang, Ming-zhang Zuo

Department of Anesthesiology of Beijing Hospital, Beijing, 100730, China

Abstract

Background: In this prospective randomized study, we compared the predicted blood and effect-site C_{50} for propofol and remifentanil target-controlled infusion and the Bispectral Index (BIS) values at loss of consciousness (LOC) and response to a standard noxious painful stimulus in elderly and young patients respectively. We hypothesized that the elderly patients will require lower target concentration of both propofol and remifentanil at above two clinical end-points.

Methods: There were 80 ASA physical status I ~ II unpremedicated patients enrolled in this study, they were divided into elderly group (age≥65yrs, n=40) and adult group (aged 18–64 yrs, n = 40). Propofol was initially given to a predicted blood concentration of 1.2μg/mL and thereafter increased by 0.3μg/mL every 30 s until Observer's Assessment of Alertness and Sedation score was 1. The propofol level was kept constant, and remifentanil was given to provide a predict blood concentration of 2.0 ng/mL, and then increased by 0.3 ng/mL every 30 s until loss of response to a tetanic stimulus. BIS (version 3.22, BIS Quattro sensor) was also recorded.

Results: In elderly group, the propofol effect-site C_{50} at LOC of was 1.51(1.48–1.55)μg/mL, was significantly lower than that of young group, which was 2.16 (1.17–2.51) μg/mL, the remifentanil effect-site C_{50} at loss of response to painful stimulus was 3.5(3.3~3.5) ng/ml^{-1} in elderly patients, was similar with 3.7(3.6~3.8) ng/ml^{-1} in young patients. Fifty percent of patients lost consciousness at a BIS value of 57.3(56.4~58.1), was similar with that of young group, which was 58.5 (57.6~59.5).

Conclusion: In elderly patients, the predicted blood and effect-site concentrations of propofol at LOC was lower than that of young patients. BIS values at LOC and predicted blood and effect-site concentrations of remifentanil at loss of response to painful stimulus were similar between two groups.

Key Words: Propofol-remifentanil; Bispectral index; Painful stimulus

Corresponding Author: Ming-zhang Zuo, E-mail: zuozuo2000cn@yahoo.com.cn

Introduction

Intravenous anesthesia with propofol, especially target-controlled infusion systems (TCI) are commonly used in clinical practice, and became widely used in elderly patients. There were many investigations about pharmocodynamic or pharmacokinetic data of propofol and remifentanil in adult, healthy Caucasians and as well as Chinese patients[1]. However, there is few published pharmocodynamic data of propofol and remifentanil when they were used by target-controlled infusion in elderly patients. Therefore, we designed this prospective clinical study to determine the predicted effect-site concentration of propofol at LOC and predicted effect remifentanil concentration required for no response to a standard noxious painful stimulus in elderly patients.

Methods

After Institutional Ethics Committee approval and individual written informed consent, 80 patients were enrolled. They were divided into 2 groups: young (<65yr, n=40) and elderly (≥65, n=40). Exclusion criteria included recent administration of sedative or opioid drugs, body weight<80% of >120% of ideal weight, age<18yr, and impairment of cardiac, respiratory, hepatic or renal function, known allergy to propofol or its lipid emulsion, general anesthesia 7 days before surgery, history of mental disorders , and American Society of Anesthesiologists (ASA) physical status Ⅲ or over. After the insertion of

a 20G venous canula, patients received Ringer's lactate solution 10mL/kg. BIS was monitored with a BIS XP (A-2000, Aspect Medical System, USA, software version 3.22, BIS Quattro sensor). Noninvasive arterial blood pressure, SpO_2, electrocardiogram, and tidal volume were monitored routinely.

A TCI of propofol (Diprivan 1% AstraZeneca Corp with a pre-filled syringe) was administered using the Diprifusor TM (software version 2.0, Graseby 3500 Syringe Pump, Smiths Medical, Watford, UK), which uses the Marsh pharmacokinetic model. Remifentanil was administered using a microcomputer-controlled pump (SLGO High-tech Development CO, Beijing, China), which uses the Minto pharmacokinetic model. These systems display both the predicted blood concentration and the effect-site concentration. The propofol infusion was started so as to provide a blood concentration of 1.2ug/mL and increase by 0.3ug/mL every 30s until the Observer's Assessment of Alertness and Sedation was 1, i.e., no response. This point was defined as LOC. BIS and predicted blood and effect-site propofol concentrations were recorded at this point. This predicted blood propofol concentration was kept stable for 3min and then remifentanil TCI begun. The predicted blood remifentanil concentration was started at 2.0ng/mL and increased by 0.3ng/mL every 30s until no purposeful movement was observed after a tetanic stimulus (50Hz, 80mA, 0.25ms pulses for 4s)[2], which was applied to the wrist using a peripheral nerve stimulator. Twisting or jerking the head was considered a purposeful movement, but twitching or grimacing was not[3]. This point was defined as "no response to a painful stimulus." BIS and remifentanil concentrations were recorded and thereafter surgery proceeded as per normal. The protocol was same in both young and elderly group.

Data are expressed as mean (±SD). SPSS (version 13.0, SPSS American) statistical software was used to perform statistical analysis. P-value <0.05 was considered as statistically significant. One-way analysis of variance and two-sample t test were used to compare values at baseline, LOC, and loss of response to noxious stimulation after testing continuous data (heart rate [HR], mean arterial blood pressure [MAP], and SpO_2) for normality. A quantal response model (probit analysis) was used to calculate C_{05}, C_{50} and C_{95} (concentrations associated with 5%, 50% and 95% probabilities, respectively) at each end point based on predicted blood and effect-site concentrations of the two drugs. An identical method was applied to calculate C_{05}, C_{50} and C_{95} at each end point of BIS.

Results

The mean (SD) age was 70(±4) yr in elderly patients and 42(±9) yr in young patients. Their characteristics are shown in Table 1. In both age groups, HR and MAP decreased during the infusion of propofol and decreased sharply during the infusion of remifentanil, the changes were obviously in elderly group, and were significantly more than that in young group (Table 2). Induction of anesthesia was smooth in all patients.

Most patients had respiratory depression before they

Table 1: Patients Characteristics

Variables	Young patients	Elderly patients
Weight(kg)	42(9)	70(4)[a]
Male/Female	19/33	25/27
Height(cm)	164(7)	164(8)

Data are mean (SD).
Young group:n = 40. Elderly group: n = 40.
a Compared with young patients P < 0.05.

Table 2: Cardiovascular Response

Variables	Group	Baseline	Loss of consciousness	No response to titanic stimulus
HR(bpm)	Young	79.7(12.8)	73.4(8.8) a	60.8(8.4) b
	Elderly	81.4(13.1)	73.4(9.2) c	64.0(7.3) d
MAP(mmHg)	Young	99.8(14.3)	78.7(11.5) e	71.9(11.3) f
	Elderly	107.4(13.9) g	89.9(12.3) h	77.2(11.6)i

Mean (SD). Young group:n = 40. Elderly group: n = 40.
HR: heart rate; MAP: mean arterial blood pressure.
a Compared with baseline P = 0.000.
b Compared with baseline P = 0.000, Compared with loss of consciousness P = 0.000.
c Compared with baseline P = 0.000.
d Compared with baseline P = 0.000. Compared with loss of consciousness P = 0.007.
e Compared with baseline P = 0.000.
f Compared with baseline P = 0.000. Compared with loss of consciousness P = 0.000.
g Compared with young group P = 0.018.
h Compared with the point of loss of consciousness P = 0.000. Compared with young group P = 0.000.
I Compared with baseline P = 0.000.Compared with loss of consciousness P = 0.000. Compared with young group P = 0.043.

lost response to a painful stimulus. A facemask was used to deliver oxygen to all patients.

The effect-site propofol concentrations associated with a 50% probability of LOC was 1.5(1.5~1.6)μg/mL in elderly patients, was significantly lower than 2.2(2.1~2.3)g/mL in young patients (Table 3). The effect-site remifentanil concentrations associated with a 50% probability of at nonreponse to tetanic stimulus was 3.5(3.3~3.5)ng/mL in elderly patients, was similar with 3.7(3.6~3.8)ng/mL in young patients (Table 4). The BIS associated with a 50% probability of LOC was 57.3(56.4~58.1) in elderly patients, 55.2(54.0~56.3) in young patients (Table 3), and the BIS associated with a 50% probability of no response to painful stimulus was 66.8(66.0~67.6) in elderly patients, 62.4(61.5~63.2) in young patients (Table 4), there were no difference between elderly and young groups about the BIS associated with LOC and nonresponse to painful stimulus.

The effect-site propofol concentrations associated with 5% and 95% probability of LOC were 1.0(0.9~1.1) and 2.0(1.9~2.1)μg/mL in elderly patients, 1.6(1.4~1.7) and 2.9(2.7~3.3)μg/mL in young patients, respectively (Table 3, Fig.1). The effect-site remifentanil concentrations associated with 5% and 95% probability of nonresponse to tetanic stimulus were 1.8(1.5~2.1) ng/mL and 5.4(5.2~5.6) ng/mL in elderly patients, were lower than 2.3(2.1~2.5) ng/mL and 5.9(5.6~6.2) ng/mL in young patients, respectively (Table 4, Fig. 2). 5% and 95% patients lost consciousness at BIS values of 77.2(75.3~79.4) and 37.3(35.1~39.2) in elderly patients, at 79.1(76.1~82.9) and 38.5(36.6~40.2) in young patients. The BIS values associated with 5% and 95% probability of nonresponse to tetanus stimulus were of 85.6(83.8~87.6) and 48.0(46.0~50.0) in elderly patients, at 78.7(76.8~80.9) and 46.0(43.6~48.0) in young patients. The BIS values associated with nonresponse to painful stimulus were higher than that at LOC ($P<0.05$). The probabilities of LOC and nonresponse to the tetanic stimulus versus BIS in both groups are shown in Figure 3 and Figure 4, respectively.

Table 3: Propofol Concentrations and Bispectral Index (BIS) Values at Loss of Consciousness

Fraction not responding	Group	Predicted blood conentration (μg/mL)	Effect-site conentration (μg/mL)	BIS
C_{05}	Young	3.2(3.0~3.3)	1.6(1.4~1.7)	79.1(76.1~82.9)
	Elderly	2.5(2.3~2.6) a	1.0(0.9~1.1) b	77.2(75.3~79.4)
C_{50}	Young	4.0(3.9~4.1)	2.2(2.1~2.3)	55.2(54.0~56.3)
	Elderly	3.1(3.1~3.2) c	1.5(1.5~1.6) d	57.3(56.4~58.1)
C_{95}	Young	5.0(4.8~5.3)	2.9(2.7~3.3)	38.5(36.6~40.2)
	Elderly	3.8(3.7~3.9) e	2.0(1.9~2.1) f	37.3(35.1~39.2)

Values in parentheses are 95% confidence intervals.
Young group:n = 40. Elderly group: n = 40.
BIS = bispectral index.
a Compared with young group P = 0.000.
b Compared with young group P = 0.000.
c Compared with young group P = 0.000.
d Compared with young group P = 0.000.
e Compared with young group P = 0.000.
f Compared with young group P = 0.000.

Discussion

Previous clinical studies reported that predicted blood and effect-site propofol and remifentanil concentrations and values of BIS, based on Caucasian data, are also useful for predicting whether a Chinese patient is unconscious and unresponsive to painful stimulus (population aged from 18 to 65 yr)[1]. In this study, we continued to investigate and compare predicted blood and effect-site concentrations of propofol and remifentanil , values of BIS at two clinical end-points——loss of consciousness (LOC) and no response to painful stimulus in elderly and young Chinese patients.

Although age-related changes in the pharmacology of propofol are now well demonstrated, age is not taken into account by the Marsh pharmacokinetic model incorporated in the Diprifusor device[4]. But it has been

Table 4: Remifentanil Concentrations and Bispectral Index (BIS) Values at no response to Tetanic Stimulus

Fraction not responding	Group	Predicted blood conentration (μg/mL)	Effect-site conentration (μg/mL)	BIS
C_{05}	Young	3.1(2.8~3.4)	2.3(2.1~2.5)	78.7(76.8~80.9)
	Elderly	2.9(2.6~3.1)	1.8(1.5~2.1)	85.6(83.8~87.6)
C_{50}	Young	4.8(4.7~5.0)	3.7(3.6~3.8)	62.4(61.5~63.2)
	Elderly	4.8(4.7~4.9)	3.5(3.3~3.5)	66.8(66.0~67.6)
C_{95}	Young	6.5(6.3~6.8)	5.9(5.6~6.2)	46.0(43.6~48.0)
	Elderly	6.8(6.6~7.1)	5.4(5.2~5.6)	48.0(46.0~50.0)

Values in parentheses are 95% confidence intervals.
Young group:n = 40. Elderly group: n = 40.
BIS = bispectral index.

reported that TCI propofol with Marsh parameters could be applied to Chinese elderly patients safely and efficiently[5]. For remifentanil, we used the TCI system made by SLGO Corporation, which is widely used in China. The remifentanil model uses the Minto pharmacokinetic model, which has been demonstrated as adequately accurate in predicting plasma and effect-site concentrations of remifentanil[6,7].

Elderly patients are reported to be more sensitive to propofol than are young patients[4,8,9]. However, there was few study determining the C_{50} of propofol and remifentanil that elderly patients required during TCI at LOC and painful stimulus in either Caucasian or Chinese populations. The effect-site EC_{50} and EC_{95} of propofol at loss of consciousness have been shown to be 2.8 and 4.1 μg/ml in adult Caucasian populations[2]. However, in a study by Xu et al, effect-site EC_{50} and EC_{95} of propofol at loss of consciousness were 2.2 and 3.2 μg/ml in the Chinese adult populations (aged≤65yr). As results of our study, the C_{50} and C_{95} for effect-site propofol concentration at LOC was 1.5μg/mL and 2.0μg/mL in elderly patients, 2.1μg/mL and 2.8μg/mL in young patients respectively, the results of our study were similar to those of Liu et al, which showed that Ce of propofol with (1.9±0.3)μg/mL may make the elderly patients unconscious[10]. Therefore, compared to previous studies we found that effect-site concentration required for unconsciousness was obviously lower in Chinese than Caucasian population, and was significantly lower in elderly patients than young patients. It has been proved by Kirkpatrick and Schuttler et al. that central volume (V_1) and elimination clearance (CL_1) of propofol reduced in elderly patients, and was linearly decreased with age for the patients older than 60years[11,12]. Because the plasma concentration of propofol was not measured in all studies above, it is impossible to know whether these inconsistent results were due to pharmacokinetic or pharmacodynamic differences among the populations of different races and age.

Tetanic stimulation of the ulnar nerve has the advantage of ease of performance, repeatability, re-producibility and is frequently used in lieu of skin incision[13-15].

Unique features of remifentanil are its rapid clearance and rapid ke0, resulting in a rapid onset and offset of drug effect. It is tempting to speculate that these characteristics will make remifentanil an easy drug to titrate, and that clinicians will not need to consider that patient covariates including age when choosing a dosing regimen. Previous studies have reported conflicting findings concerning the influence of age and gender on the pharmacokinetics of opioids. Minto et al considered that it is for pharmacodynamic reasons (the 50% reduction in EC_{50} in the elderly) that remifentanil bolus doses should be halved in the elderly, although there are no pharmacokinetic grounds for recommending reduced bolus doses in the elderly[7]. In contrast , Xu et al found predicted effect-site concentration of propofol was required lower in older patients than that in young patients, but there were no age-related difference between young and older patients[16]. Results of our study demonstrated that effect-site C_{50} and C_{95} of remifentanil at nonresponse to painful stimulus was 3.5ng/mL and 5.4ng/mL in elderly, that was similar with 3.7ng/mL and 5.9ng/mL in young group. The reason which probably can explain why no significant difference was found between groups as to the predicted effect-site remifentanil concentrations required is that because we chose the Minto pharmacokinetic model, which does take into account some co-variables such as height, weight and age. We compared the hemodynamic changes after TCI remifentanil for both young and elderly patients and found that MAP and HR decreased more sharply in elderly than in young patients, suggesting that we still need to titrate the remifentanil dose according to elderly individual.

Several investigators have studied the sensitivity of BIS as a measure of sedation and anesthesia in adult and elderly patients receiving propofol infusions[17-19]. It has been shown to be a useful monitor of propofol sedation and anesthesia. Barakat et al. identified that the changes of both the sedation score and BIS index correlated better with the predicted Ce in using the Marsh model than in using the Schnider model. Two previous studies have evaluated the BIS values at LOC when TCI propofol is

used[1,2]. The C_{50} and C_{95} of BIS were 71 and 53 respectively in Caucasians[2], whereas the values were 58 and 39 respectively in Chinese[1], which is similar to our results. We noted that the predicted blood and effect-site propofol concentrations in our Chinese population were lower than that in Caucasians at LOC. Our results therefore suggested that the correlation between the predicted blood or effect-site propofol concentrations and BIS in Chinese patients differ from that in Caucasians[16,18-20] and that the standard BIS values to predict the depth of hypnosis may not be suitable for Chinese patients. A different range of BIS values and propofol TCI concentrations should be used in clinical practice in elderly patients.

From our study, there was no difference found about BIS between young and elderly groups at both LOC and nonresponse to painful stimulus clinical end points. But the MAP and HR decreased significantly during TCI infusing propofol at LOC, before achieving no response to tetanic stimulus MAP and HR further decreased due to administration of remifentanil, the hemodynamic changes was greater in elderly than that of young patients. Therefore, during anesthesia induction using TCI propofol combined with remifentanil, we should modify the target concentration or the TCI technique, such as stepwise (two stepwise or three stepwise) technique[21-23] or a step-by-step technique, can result in stable hemodynamic, especially for the elderly patients, or in those with the cardiovascular diseases[21].

The BIS_{50} at loss of response to tetanic stimulation was higher than the BIS_{50} at LOC. This might be because we measured the BIS after we applied the stimulation. Recording BIS before the stimulation is applied would have been better. However, this method did not work well as the interval between the two stages of drugs administration was too short for BIS stabilization.

In conclusion, the findings from our study suggest that an adjustment of propofol targeted concentration in elderly patients should be applied; a lower plasma concentration of propofol should be best selected with the plasma-controlled TCI technique. This should be particularly necessary when the anaesthetist does not have access to BIS monitoring. It seems that aged people will not significantly decrease the plasma concentration of remifentanil requirement, and it's safe to titrate both propofol and remifentanil properly according to BIS and hemodynamic changes during anaesthesia induction using target-controlled infusion in elderly patients.

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Effects of Different Target Concentrations of Propofol on the S-100β Protein in Patients Undergoing Cardiopulmonary Bypass

Gang Ma, Jin-hua Chen, Li-qin Deng, Jin-hai Meng

Department of Anesthesiology, General Hospital of Ningxia Medical University, Yinchuan, 750004, Ningxia Hui Autonomous Region, China

Abstract

Background: The aim of this study was to investigate the effects of different target plasma concentrations of propofol on the level of cerebral injury by serum S-100β protein and Mini-Mental State Examination (MMSE) score in patients undergoing mitral valve replacement (MVR) with cardiopulmonary bypass (CPB).

Materials and Methods: Forty five patients, scheduled for MVR with CPB, were selected and randomly divided into three groups (n=15 each), each groups receive a target-controlled infusion (TCI) of propofol with target concentrations of 1.8μg/ml (Group-L), 2.4μg/ml (Group-M) or 3.2μg/ml (Group-H). The propofol target concentrations of all patients were unchanged throughout surgery. Blood samples from the internal jugular vein were collected immediately before skin incision (Pre-incision)、at the cessation of CPB (CPB-cessation)、at 2 (Post-CPB 2h)、4 (Post-CPB 4h) h after CPB for measurement of the plasma S-100β protein level. MMSE were measured on the day before operation, 24 and 48 hours after operation.

Results: Plasma S-100β protein, biochemical marker of brain damage, at all time points after separation from CPB were higher among three groups of patients, there were significant difference compared with the preoperative ($P<0.05$); Group-L group increased more significantly, there was significant difference compared with the Group-H group ($P<0.05$). MMSE score were lower at 24 and 48 hours after surgery of three groups, and there was significant difference compared with preoperation. There were no significant differences among three groups ($P> 0.05$).

Conclusion: In the range of clinical commonly used concentrations, administration of a large dose of propofol during CPB attenuates biochemical marker of brain damage as compared with small-dose propofol anesthesia. But there were no difference in MMSE score.

Key Words: Cerebral protection; Propofol; Target-controlled infusion; Cardiac surgery

Corresponding Author: Jin-hai Meng, E-mail: mengjinhai2616@163.com

Introduction

Despite advances in anesthesia, cardiopulmonary bypass (CPB) and surgical techniques, central nervous system complications continue to be a major cause of morbidity and mortality after cardiac surgical procedures[1]. As many as 79% patients have the neuropsychological dysfunction after CPB during the early postoperative period[2]. It has been reported that S-100 β protein is early biochemical marker of cerebral injury during cardiac operations[3,4]. The appearance of S-100 β in serum indicates that the neuronal damaged and the permeability of the blood-brain barrier increased[5]. The serum concentration of S-100 β protein could reflect the degree of neuronal damage[6]. The Mini-Mental State Examination (MMSE) is a screening tool for detecting changes in cognitive skills[7]. The range of scores is 0 to 30, with increasing scores indicating better performance.

Propofol is a general anesthetic which is widely used for induction and maintenance of anesthesia during cardiac surgery and in postoperative sedation[8]. Besides its classical anesthetic effect, a growing number of evidences indicated that propofol exerted a variety of non-anesthetic effects, such as antioxidant, anxiolytic, and immunomodulatory effects[9]. It has also been shown to protect the brain in a variety of experimental and clinical pharmacology models[10]. Several mechanisms, including the reduction in cerebral metabolism, redistributing cerebral blood flow as well as the inhibition of mitochondrial swelling, were implicated in propofol-induced neuroprotection[10,11,12]. Moreover, target-controlled-infusion(TCI) of anesthetics, such as propofol has been shown not only to improve intraoperative hemodynamic stability, but also to facilitates rapid arousal and early tracheal extubation after cardiac surgery[13,14].

A clinical study has presented that the protective effect of propofol on myocardial cellular damage is dose dependent[15]. However; it remains unclear that, in the range of clinical commonly used concentrations, weather different dose of propofol has a different clinical protective effect against cerebral injury in on-pump surgery patients. Based on the previously described available laboratory and clinical evidence, the authors of this study hypothesized that large dose of propofol would induce cerebral protective effects in patients undergoing cardiac surgery with CPB.

The purpose of this study was to examine the comparative effects of different target concentrations of propofol on release of cerebral injury marker such as S-100 β protein, and MMSE scores in patients undergoing mitral valve replacement (MVR) with CPB.

Methods

After institutional ethics review board approval, 45 consecutive patients scheduled for MVR under moderate hypothermia CPB gave written informed consent were enrolled in this double-blind clinical trial. Patients were included if they had an American Society of Anesthesiologists (ASA) status of II or III and an age between 18 and 60 years. Patient exclusion criteria included: 1) a preoperative history of liver or kidney dysfunction, peripheral vascular disease, diabetes mellitus, or arterial hypertension; 2) Patients with ischemic cerebrovascular disease; 3) a history of an acute or evolving myocardial infarction or presented with a left ventricular ejection fraction(LVEF) which less than 50%; 4) Obesity (body mass index>30 $kg \cdot m^{-2}$); 5) Patients with moderate or severe atherosclerotic lesions in the ascending aorta or carotid artery stenosis confirmed by preoperative ultrasonography; 6) recent usage of propofol. Patients requires re-exploration after operation, necessitating large dose pharmacological support (Phenylephrine>100μg, iv, and/or epinephrine>0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to maintain hemodynamic stability (mean arterial pressure (MAP)>60mmHg), total CPB time>115 min were also excluded from the study.

Patients were assigned (according to randomization envelopes) to the 3 groups (n=15, each): the Large-dose propofol (Group-H), Middle-dose propofol (Group-M), or Small-dose propofol (Group-L) groups. The randomization scheme provided an equal number of patients from each study group.

Before the surgery, the principal investigator and/or coinvestigators reviewed the study with the patients in their room and obtained informed consent. In the operating room, patients received routine monitoring (Zeus 4.n, Dräger, Germany), including 5-lead electrocardiogram, pulse oximetry, capnography, as well as nasopharyngeal and rectal temperature monitoring. Systemic arterial blood pressure was measured via radial artery catheterization. After induction of anesthesia, a central venous catheter was inserted for monitoring central venous pressure and fluids management. Baseline readings of hemodynamics were taken 5-10 min after radial artery cannulation had been completed. Hemodynamics was continuously monitored for 24 h after CPB.

Induction of anesthesia was performed with target-controlled infusion ("Diprifusor"TCI system, AstraZeneca, watword, USA) of propofol (Diprivan, AstraZeneca, Corden Pharma S.P.A, Italy). All patients received an infused scheme of several steps: starting from a target plasma concentration (Cp) of 1.0μg/ml that was increased stepwised by 0.5μg/ml until a final target Cp was achieved (Group-L:1.8μg/ml, Group-M:2.4μg/ml, Group-H:3.2μg/ml), the interval between the two steps was 3 minutes. After loss of consciousness, cisatracurium 0.2mg/kg and fentanyl 10~15μg/kg were infused in all groups. Oxygen was given by facemask ventilation, the trachea was intubated and the lungs were ventilated with oxygen-enriched air (fraction of inspired oxygen=0.6) to an end-tidal carbon dioxide partial pressure of 35-45mmHg. The propofol target Cp of all patients was unchanged throughout the surgery. Intermittent iv boluses of fentanyl 10~15μg/kg accorded to blood pressure and heart rate at the following time point: before the skin incision, before the onset of CPB, after separation from CPB, for a total doses of 40-50μg/kg; All patients received infusion of cisatracurium at 0.1mg $\cdot kg^{-1} \cdot h^{-1}$ throughout the surgery.

Surgery was conducted on all patients via a standard median sternotomy approach. Porcine heparin was administered at a dose of 300 IU/kg and supplemented when required to maintain activated coagulation time at least 480 sec during CPB. Heparin was neutralized with 1 mg of protamine/100 IU of heparin administered after separation from CPB. The extracorporal circuit was primed with 1L lactated Ringer's solution and 0.5 L colloid (Voluven, Fresenius Kabi, Beijing China), Body temperature was cooled to 30-32 °C on CPB (moderate hypothermia). All patients were treated with intermittent antegrade infusion of cooled high potassium blood cardioplegia during continuous aortic cross-clamping (ACC). Using a nonpulsatile flow rate of 1.8-2.8 $L \cdot m^{-2} \cdot min^{-1}$(TERUMO Advanced Perfusion system 1, Terumo Cardiovascular systems corporation, USA)and a membrane oxygenator (Medtronic.Inc, USA). Phenylephrine (iv, 20-100ug) and/or epinephrine ($<0.1 \mu g \cdot kg^{-1} \cdot min^{-1}$) were used to restore systemic vascular resistance, MAP was maintained at a target range of 60 to 80 mmHg. Patients were warmed to a bladder temperature of 37°C before separated from CPB. Hematocrit was maintained at more than 25% on CPB, with the addition of blood as necessary. Blood remaining in the CPB circuit was collected and infused to the patient 4 h after CPB. Insulin therapy was initiated in the operation to treat serum blood glucose levels higher than 150 mg/dl.

Hemodynamic (pre- or post-CPB) management aimed

to keep MAP at 60-100 mmHg. Hypertension was treated with additional bolus dose of fentanyl 0.2-0.3 mg, and/or with nitroglycerin (0.1-0.5μg·kg^{-1}·min^{-1}). Hypotension was treated with fluid intake (including crystalloids, colloids, and blood products) or vasoactive drugs administration (Phenylephrine iv, 20-100ug or concomitant use of epinephrine, <0.1μg·kg^{-1}·min^{-1}). The dosage of vasoactive drugs, fluid intake (including crystalloids, colloids, and blood products), output (urine and blood loss) were recorded when the operation finished.

As the surgeons started to skin closure, 0.08 mg·kg^{-1} bolus dose of midazolam was given intravenously and infusion of propofol was stopped. After the operation, all patients were admitted to the surgical intensive care unit (ICU) and monitored there. The patients were tracheally extubated when they were able to sustain adequate spontaneous respiration and required minimal oxygen support, as reflected by normal arterial blood gas levels. The patients were then discharged from ICU when they were hemodynamically stable with blood gas variables within normal range without the need of inotropic or oxygen support. Tracheal extubation time and length of ICU stay were recorded. MMSE scores were measured on the day before operation (Pre-operative), 24hours (Post-operative 24h) and 48hours (Post-operative 48h) after operation.

For all patients, Hemodynamic measurements were measured and recorded at the following times: before induction of anesthesia (Pre-indu), before skin incision (Pre-incision), after sternotomy (sternotomy), at the cessation of CPB(CPB-cessation), at 1(Post-CPB 1h)、2(Post-CPB 2h)、4(Post-CPB 4h)h after CPB. At Pre-indu、CPB-cessation、Post-CPB 2h, radial artery blood were sampled to analyze the blood gas analysis. Central venous blood were sampled at Pre-incision、CPB-cessation、Post-CPB 2h、Post-CPB 4h for the measurements of S-100β protein, as well as blood glucose, lactic acid. The blood samples were centrifuged at 1,000 g for 15 minutes and the serum samples were stored at - 80°C until analysis. Patients were followed up with a interview for intraoperative awareness on the first and third post-operative day.

The serum levels of S-100β protein were measured by using commercial enzyme-linked immunosorbent assay kits (Research & Diagnostics Systems, Inc, America), witch based on the sandwich model enzyme-linked immunosorbent assay. The lower detection limits were 0.06μg/ml and 0.8μg/ml respectively, for plasma S-100β protein. Plasma samples were coded. In addition, the laboratory investigator was blinded regarding treatment regimen. Similarly, all hemodynamic data were collected by trained observers who were not authors of this study and who were blinded to the anesthetic regimen used.

All continuous data are expressed as means ± standard deviation. All data were tested for normality using the Shapiro-Wilk normality test and were determined to have a normal distribution. Homogeneity of variance was tested using Bartlett's test. After confirmation of equal variance among the groups by the Bartlett test, 1-way analysis of variance (ANOVA) was used. Hemodynamic、plasma S-100β protein and MMSE score changes over time from baseline within each group were determined by repeated-measures ANOVA. Differences between the groups at each timepoint were evaluated by 1-way ANOVA and a post hoc Tukey test. Chi-square test was used to compare non-numerical data Differences in values were considered significant at $P<0.05$. All calculations were performed using SPSS for windows (SPSS, version 11.0, Chicago, IL, USA) software.

Results

A total of 45 patients initially were enrolled in the study. One patient in each group was excluded: one patient in the Group-H subsequently was excluded because of an intraoperative event of blood loss necessitating secondary surgery; Two patients in the Group-L、Group-M withdrew from the study because of long time of CPB.

Table 1: Clinical Characteristics

	Group-L(n=14)	Group-M(n=14)	Group-H(n=14)
Male / Female	7/7	8/6	6/8
MVR/AVR	6/8	9/5	7/7
NYHA class(Ⅱ/Ⅲ)	7/7	7/7	6/8
Age(yrs)	46.67±8.22	47.87±8.59	49.07±12.65
Weight(kg)	60.07±9.17	61.01±8.39	61.38±8.63
Height(cm)	165.67±8.06	166.8±9.61	166.33±8.22
Preoperative LVEF(%)	54.54±7.46	58.86±6.55	58.66±5.94
The total time of CPB(min)	100.00±12.97	98.07±11.48	102.36±12.38
The time of ACC(min)	73.29±16.62	72.79±14.18	73.21±14.79
fentanyl dosage(mg)	2.52±0.82	2.41±0.76	2.51±0.59
epinephrine dosage(μg/kg)	3.37±2.40	3.53±2.04	5.60±1.31*#
Phenylephrine dosage(μg)	137.14±48.89	148.57±31.10	237.14±83.70Δ▲
Nitroglycerin dosage (μg/kg)	4.14±1.79	4.84±2.07	3.64±1.15
Time of extubation(h)	10.26±2.52	10.73±2.68	10.20±2.62

NOTE: Data are shown as mean ± standard deviation. Abbreviation: MVR, Mitral valve replacement; NYHA, New York Heart Association; AVR, Aortic valve replacement; LVEF, Left ventricular eject infarction; CPB, Cardiopulmonary bypass; ACC, Aorta cross-clamp. * $P<0.05$ versus Group-L, Δ$P<0.01$ versus Group-L; #$P<0.05$ versus Group-M, ▲$P<0.01$ versus Group –M.

There are no surgical deaths occurred. None of the patients reported intraoperative recall during the interview on postoperative days 1 and 3. No overt neurological injury was detected in any patients.

Clinical characteristics of 42 patients are summarized in Table 1. The age, gender, weight, height, preoperative LVEF, total time of CPB, time of ACC, perioperative fentanyl and nitroglycerin dosage, nasopharyngeal temperature, and tracheal extubation time and length of ICU stay showed no significant difference among the three groups (Table 1).

No differences in hemodynamic parameters (including HR, MAP, and CVP), blood gas (including PH, BE, PO_2, $PaCO_2$), blood glucose, lactic acid were identified among groups of patients throughout the observation interval (data not shown). However, perioperative phenylephrine and epinephrine dosage in the Group-H were significantly more than those of the Group-L and Group-M ($p < 0.05$, Table 1).

Baseline plasma levels of S-100 β protein did not differ among groups. Plasma S-100 β protein increased significantly after CPB in all groups. Application of large-dose propofol during CPB(Group-H) significantly attenuated the increase in plasma S-100 β protein as compared with Group-L($P<0.05$). but there were no significant intergroup differences between Group-L and Group-M、Group-M and Group-H(Fig. 2).

MMSE score were lower at 24 and 48 hours after surgery of three groups, and there was significant difference compared with preoperation. There were no significant differences among three groups (Fig. 3).

Discussion

The principal finding of this clinical study is that the application of propofol in a large dosing regimen during perioperative attenuated indice of brain injury. But there were no difference in MMSE score among groups, and the consumption of pressor agent were more if the patients receiving large dose propofol treatment.

Central nervous system complications continue to be a major cause of morbidity and mortality after cardiac surgical procedures, sequelae can be as mild as postoperative cognitive dysfunction and as severe as stroke[1,2]. There are many factors may be associated with the occurrence of brain damage and outcome after cardiac surgery, such as old age, diabetes mellitus, preoperative cerebrovascular complications, CPB time, intraoperative hypotension[5]. In this study, patient characteristics and surgery related events are the most common reasons for possible complications. Patient characteristics were similar in three groups, as were MAP, CPB time, and fentanyl dosage. This suggested that the differences in brain function between groups were not caused by differences in patient characteristics and intraoperative events but seemed instead to be related to the choice of the propofol dosage.

Total intravenous anesthesia using propofol combined with opioid has been proposed as a safe anesthetic procedure for patients undergoing cardiac surgery, even in those with substantially impaired left ventricular function[8,16]. Multiple clinical trials have demonstrated that the performance of TCI of propofol for cardiac surgery

Figure 1 Variations of perioperative MAP. Data are shown as mean ± standard deviation. Abbreviation: Pre-indu, before induction of anesthesia; Pre-incision, before skin incision; sternotomy, after sternotomy, CPB-cessation, at the cessation of CPB, Post-CPB 1 h, 1 h after CPB; Post-CPB 2h, 2 h after CPB; Post-CPB 4h, 4 h after CPB.

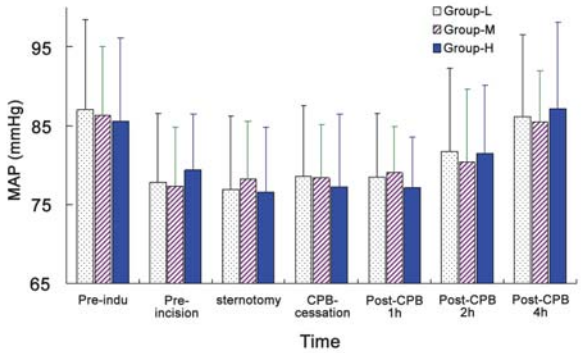
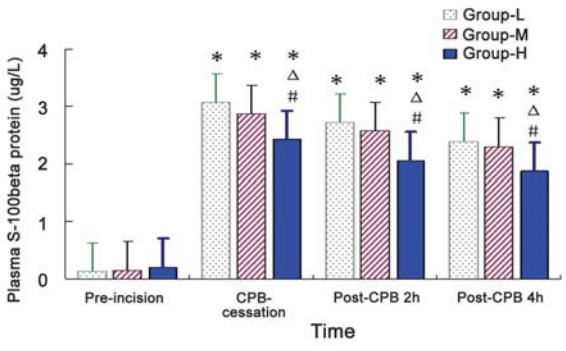


Figure 2 Variations of perioperative plasma levels of S-100β protein. Data are shown as mean ± standard deviation. *P＜0.05 versus Pre-incision; ΔP＜0.05 versus Group-L; #P＜0.05 versus Group-M. Abbreviation: Pre-incision, before skin incision; CPB-cessation, at the cessation of CPB; Post-CPB 2h, 2 h after CPB; Post-CPB 4h, 4 h after CPB.

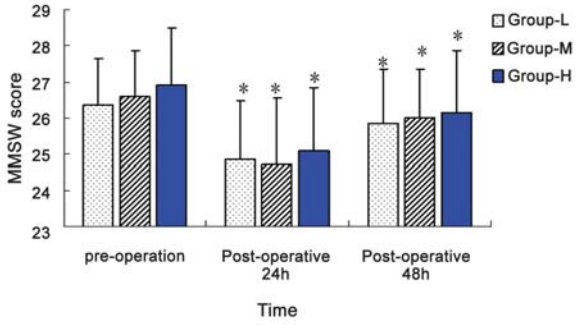


under CPB is safety and reasonable[13,14,17]. The optimal dose to maximize critical organ protection and minimum side effect is not clearly established for propofol, and clinical dose varies widely in the literatures[18,19,20]. The propofol anesthesia protocol and dose gradient being studied in this study were chosen on the basis of previous reports and preliminary experiment.

There was no significant difference among groups for MAP during perioperative. But we found that Large-dose propofol group need more vasoactive agent to keep MAP higher than 60 mm Hg. propofol anesthesia is often results in transient hypotension, which is mainly mediated with the decrease in sympathetic activity, direct vascular smooth muscle relaxation and direct negative inotropic effects[21,22]. and such effects are dose-dependent fashion[21,23]. After a change in management, such as fluids, blood transfusion or vasoactive drugs, haemodynamic unstable can be reversed easily. Our study confirmed that the target plasma concentration of propofol in 1.8μg/ml and 2.4μg/ml are effective and safe with stable hemodynamics, It is consistent with the other reports[13,24]. However, there is a marked variability in cardiovascular sensitivity to propofol among patients, This variability may induce the serious side effect of hypotension, especially in elderly and hypertensive patients[24,25,26,27]. So, Propofol infusion rate should be adjusted according to depth of anesthesia and surgical procedure of individuals.

It has been reported that S-100β protein is the early marker for cerebral injury during cardiac operations[3,4]. Its released after onset of CPB and its level correlated with the duration of CPB, deep circulatory arrest and aortic cross-clamping[28,29]. We measured serum levels of S-100β protein interval 2h after CPB to examine the effects of anesthetic management on cerebral injury. We found that S-100β protein level increased after CPB in all patients. This suggests that both neuronal damage and increased permeability of the blood-brain barrier in patients undergoing cardiac surgery with CPB[5].

Figure 3 Variations of MMSE. Data are shown as mean ± standard deviation. *P<0.05 versus Pre-operation. Abbreviation: the day before operation (Pre-operative), 24hours (Post-operative 24h) and 48hours(Post-operative 48 h) after operation.



Propofol is known to have potential anti-inflammatory effects and antioxidant activity[30,31]. It has been proven to provide cardiac and brain protective effects for patients underwent cardiac surgery[15,32]. large dose of propofol have an advantage in attenuates postoperative myocardial cellular damage as compared with small dose propofol anesthesia during CPB[15]. But in the scope of clinical commonly used doses, if the large dose of propofol have an advantage in neuroprotection during the clinical setting, such as CPB, is not clearly established. In the present study, we also found that application of large dose propofol is preferable to Group-L in attenuated the increase in plasma S-100β protein in patients underwent MVR with CPB. In the scope of clinically commonly used dose, the large-dose protective effect is more obvious. This indicates that propofol's brain protection, as determined by the surrogate measures of brain injury in this study, is dose dependent. It is consistent with the animal experimental[11,33,34]. These effects were attributed to its ability to improve cerebral oxygenation[35]、reducing oxidative injury[36]、reduce inflammation and oxidative stress[37]. After separation from CPB, there were no significant difference compared with Group-L and Group-M、Group-M and Group-H, May be associated with a group of propofol target concentration difference is low, cerebral protection effect of the difference is not observed in our study.

But Berns M et al.[38] reported that high dose propofol triggers short-term neuroprotection and long-term neurodegeneration in primary neuronal cultures from rat embryos. CHEN Gang et al.[39] demonstrated that propofol aggravates the damage to cognitive function while it attenuates the chronic cerebral ischemia-induced injury in aged rats, especially the high dose. Neuropsychological testing, such as MMSE, is accepted as one of the best methods for assessing changes in intellectual function after operation[7]. In contrast to a previous study[39], we observed that patients in the group-L had no advantage in neurocognitive test scores than patients in

the group-H and group-M.

Our study indicated that large dose of propofol attenuates biochemical markers of brain damage as compared with small-dose propofol anesthesia, but no effects on MMSE score. Though propofol protect the brain in several mechanisms, including the reduction in cerebral metabolism, redistributing cerebral blood flow as well as the inhibition of mitochondrial swelling[10,11,12] But propofol affects the retention mechanism of the memory in a dose-dependent manner, Subhypnotic dose of propofol may affect the sub-cellular process of the memory consolidation[40]. Low dose may contribute to propofol-induced deficits in memory following propofol anesthesia[41]. So, in the whole effects, large dose of propofol may weaken or aggravate cognitive function impairment.

This study has at least two limitations. First, only one biochemical markers (S-100 β protein) and one neurocognitive test (MMSE) were measured to assess cerebral injury. It is unknown whether this observed is correlated with improved long-term function outcome. Second, the number of patients we recruited was low. Further research is needed more sample size to compare these parameters among the three groups.

Conclusion

We conclude that, using S-100 β protein levels as marker of cerebral injury, large dose propofol (Cp 3.2μg/ml) appears to offer advantage over smaller dose propofol(Cp 1.8μg/ml) for brain protection during CPB in this study. But there are no difference in MMSE score were identified among groups, anesthetized with the target plasma concentration of propfol in 1.8μg/ml or 2.4μg/ml are effective and safe with stable hemodynamics for cardiac surgical patients.

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许德奖[1,2] 杨威[1] 赵国栋[1]

1.广东省医学科学院，广东省人民医院，麻醉科，广东广州 510080

2.汕头大学医学院，广东汕头 515041

摘要

目的：探讨应激性胃溃疡中Th1/Th2细胞和Th17/Treg细胞平衡的变化及凯时干预作用的影响。方法：40只雄性SD大鼠随机分为5组：正常对照组（N组）、应激组（S组）、脂微球空载体10μg/kg组（L组）、凯时低剂量1μg/kg组（M组）和凯时高剂量10μg/kg组（P组）。经上述药物预处理后，制作应激性胃溃疡模型。造模完成后采集外周血分离淋巴细胞及血浆，采用荧光定量PCR方法分析Th1/Th2/Th17/Treg细胞相对应的转录因子T-bet/Gata-3/RORγt/Foxp3 mRNA的表达量，采用试剂盒检测血浆中的SOD活性及MDA浓度，并评价胃溃疡指数（Ulcer Index，UI）及制作病理切片。结果：与N组比，S组UI加重，血浆MDA含量增高，SOD活性降低（p<0.05），Gata-3 mRNA表达上调（p<0.05）；RORγt与Foxp3 mRNA表达均下调（p<0.05）。而T-bet/Gata-3比值下降（p<0.05）。与S组比，P组UI减轻，血浆MDA含量降低，SOD活性升高（p<0.05），Gata-3 mRNA表达下调（p<0.05），Foxp3 mRNA表达上调（p<0.05）。结论：应激性胃溃疡的发生发展可能与Th1/Th2细胞和Th17/Treg细胞失衡有关。凯时具有抗氧化作用，且能减少应激性胃溃疡的发生，并在急性应激早期可能有保护机体免疫功能的作用。

关键词：应激性溃疡；Th1/Th2平衡；Th17/Treg平衡；前列腺素E1

责任作者及联系方式：赵国栋，E-mail：shyzhao@163.com

应激性胃溃疡中Th1/Th2细胞与Th17/Treg细胞平衡的变化及凯时的干预作用研究

Effects of Lipo-PGE1 on the Th1/Th2 and Th17/Treg Cell Balance in Stress-induced Ulcer

De-jiang Xu [1,2], Wei Yang [1], Guo-dong Zhao [1]

1.Department of Anesthesiology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China

2.Medical College of Shantou University, Shantou 515041, China

Abstract

Objective: To detect the effects of lipo-PGE1 on the Th1/Th2 and Th17/Treg cell balance in stress-induced ulcer.

Methods: Forty male Sprague Dawley rats were randomly divided into the control (Group N), model (Group S), lipid microspheres 10μg/kg (Group L), Lipo-PGE1 1μg/kg (Group M) and Lipo-PGE1 10μg/kg (Group P). After pretreatment, rats were subjected to water-immersion and restraint stress. Later, peripheral blood was obtained and lymphocyte and plasma was separated. The mRNA of Specific transcription factors T-bet/Gata-3/RORγt/Foxp3 which represented Th1/Th2/Th17/Treg cell, were detected with RT-PCR. The activity of superoxide dismutase (SOD) and the levels of malondialdehyde (MDA) were assayed. Besides, ulcer index (UI) assessment and pathological sections of the stomach were carried out.

Results: Compared with Group N, the UI and the levels of MDA of Group S were higher, while the activity of SOD was lower($p<0.05$). The mRNA of Gata-3 raised while the mRNA of RORγt and Foxp3 decreased ($p<0.05$). Compared with Group S, the UI and the levels of MDA of Group P were lower, while the activity of SOD was higher($p<0.05$). The mRNA of Gata-3 was down-regulated while the mRNA of Foxp3 was up-regulated($p<0.05$).

Conclusion: The development of stress-induced ulcer may be related to the imbalances of Th1 / Th2 cells and Th17 / Treg cells. Lipo-PGE1 could be an antioxidant and could decrease the occurrence of stress ulcer. It might protect the immunologic function at the early acute stress procedure.

Key Words: Stress-induced ulcer; Th1/Th2 cell balance; Th17/Treg cell balance; Prostaglandin E1

Corresponding Author: Guo-dong Zhao, E-mail: shyzhao@163.com

一、引言

临床上，应激性胃溃疡是一种常见的危重病并发症。目前，应激性胃溃疡发生机理尚不完全明了，但普遍认为是机体对各种应激性刺激的非特异性防御反应，是中枢神经系统、内分泌系统和免疫系统相互作用的结果。近年来，研究者越来越关注应激对免疫系统的作用研究。T淋巴细胞作为免疫系统的重要组成部分，一直是临床和科研关注的热点，近年来尤以Th1/Th2细胞平衡与Th17/Treg细胞平衡的研究为热，这两个平衡的打破，可能与疾病的发生发展有关。有研究表明，在应激状态下，机体的免疫功能是受抑制的。而应激性溃疡时Th1/Th2细胞平衡与Th17/Treg细胞平衡的变化还不清楚。另外，脂微球载体前列腺素E1（Lipo-PGE1，商品

名：凯时）具有改善病灶周围炎症反应功能，但它与T淋巴细胞亚群之间的平衡是否有关系目前尚不得而知。因此，本实验通过制作大鼠束缚浸水应激胃溃疡模型，来观察应激性胃溃疡时外周血中Th1/Th2细胞与Th17/Treg细胞相关特异性转录因子mRNA的变化，并观察脂微球载体前列腺素E1的干预作用，以期阐释应激性胃溃疡与这两个细胞平衡之间的关系，也为临床防治应激性相关疾病提供理论和实验基础。

二、材料与方法

1. 材料

SPF级雄性SD大鼠40只，体重200-250g（由广东省动物中心提供）。动物在广东省人民医院医学研究中心动物房饲养一周以适应环境，饲养条件为恒温恒湿，食物和水自由摄食，每日光暗环境各12小时。大鼠淋巴细胞分离液由天津灏洋生物科技公司（TBD公司）生产。荧光定量PCR所用试剂均为宝生物工程（大连）有限公司（Takara公司）提供，引物由上海捷瑞生物工程有限公司设计并合成（序列见表1）。超氧化物歧化酶（SOD）测定试剂盒和丙二醛（MDA）测定试剂盒由南京建成生物工程研究所提供。脂微球载体前列腺素E1（批号：2271K）及脂微球空载体（批号：20110327）由北京泰德制药公司生产。

2. 方法

大鼠经禁食不禁水24小时后随机分为正常组（N组）、应激组（S组）、脂微球空载体组（L组）、小剂量凯时组（M组）和大剂量凯时组（P组）共5组（n=8），L组、M组、P组大鼠用大鼠固定器固定后分别经尾静脉给予脂微球空载体10μg/kg、凯时1μg/kg、凯时10μg/kg溶于0.4ml生理盐水，S组给予0.4ml生理盐水，N组不予任何处理。10min后将大鼠垂直浸入（21±1℃）水中，水面约平胸骨剑突水平，持续浸泡3.5h。大鼠应激完毕后予氯胺酮100mg/kg,安定60mg/kg麻醉后，剑突下正中切口，轻轻拨开肠组织，暴露下腔静脉，5ml注射器缓慢抽取大鼠静脉血4ml，置于EDTA抗凝管中。结扎大鼠胃贲幽门，取胃后于腺胃区注入10ml 4%的甲醛，再置于4% 的甲醛浸泡20min。沿胃大弯切开，干净纱布轻轻擦拭血污，展开胃，在10×的显微镜下观察胃黏膜损伤情况，按Guth法[1]计算胃黏膜溃疡指数（UI）：损伤长度≤1mm（包括糜烂点）为1分；1～2mm记2分；～3mm记3分；～4mm记4分；＞4mm记5分，当宽度＞2mm者记分加倍。累计得分即为溃疡指数。计算完毕后胃组织继续泡在4%甲醛过夜，进一步做病理切片。

所获得4ml外周血中，取2ml离心后取上清进行SOD和MDA检测，检测步骤严格按照说明书进行。另2ml外周血进行淋巴细胞分离后加入400μl Trizol 进行总RNA提取。所获得RNA经紫外分光光度计检测并计算OD260/OD280值在1.8～2.0之间，提示RNA纯度较高。cDNA的合成按照试剂盒（Takara:DRR036A）说明书进行，取600ng RNA反转录为20μl cDNA体系，-20℃冰箱保存。荧光定量PCR反应（Takara:DRR820A）采用SYBR Green I法，反应体系如下：反应体系20μl,2×SYBR® Premix Ex Taq™ 10μl,10μmol/L上下游引物各0.8μl,cDNA 2μl,灭菌蒸馏水6.4μl。反应条件为：94℃预变性2min,94℃变性25s,59℃退火25s,72℃延伸25s,循环大于39次，收集荧光，分析熔解曲线。每个体系两个复孔测试，取平均值为Ct值，按照$2^{-\Delta\Delta Ct}$法[2]进行基因相对定量表达计算。统计分析：实验数据用均数±标准差（x±s）表示,应用SPSS13.0统计软件进行统计分析，两组间比较用t检验，多组间比较用方差分析。P＜0.05表示差异有统计学意义。

表1 PCR引物序列

Table1 Primers sequences for PCR

gene name	sense(5'→3')	antisense(5'→3')
T-bet	CCCACTGGATGCGACAGGAAG	CCTCTGGCTCACCGTCATTCAC
Gata-3	GAGGAACGCTAACGGAGAC	TTTGCTAGACATCTTACGGTTTC
RORγt	GAAGTCGTCCTCGTCAGAATG TG	TTGCAGATGCTCCACTCTCCTC
Foxp3	CACACCTCCTCTTCTTCCTTGAAC	AGACTCCAGTGGCAGCAGTAG

表2 各组溃疡指数、血浆中丙二醛含量及超氧化物歧化酶活性

Table2 Ulcer Index, MDA and SOD (x±s)

GROUP	UI	MDA(nmol/ml)	SOD(U/ml)
N	0.75±0.62	4.16±0.43	289.0±8.06
S	55.88±3.76#	6.21±0.54#	224.1±10.32#
L	56.75±5.11	5.25±0.41	249.5±5.761
M	47.38±2.56	4.75±0.28*	295.1±10.49*
P	41.13±3.13*	4.50±0.36*	276.7±14.50*

Notes: compared with Group N, #p＜0.05；compared with Group S, *p＜0.05.

三、结果

1. 各组UI及病理切片比较

正常对照组胃黏膜基本无损伤，应激后UI明显增加（p＜0.05），而凯时预处理的大鼠比无凯时给药组的UI减少，尤其在P组表现更为明显（p＜0.05），见表2。N组大鼠胃黏膜肉眼下光滑完整，呈粉红色，未见溃疡、糜烂及明显的出血点。镜下胃黏膜层、肌层完整连续，腺体排列紧密，未见炎性细胞浸润；S组胃黏膜充血明显，全胃可见散在点状及条状出血，镜下黏膜断裂缺损，腺体排列紊乱，炎症细胞如单核细胞及中性粒细胞大量浸润，并可见黏膜血管血流瘀滞；L组与S组大抵一致；M组仍可见散在溃疡出血灶，镜下黏膜稍有脱落凹陷，腺体可见稍有炎性细胞浸润；P组散在点状出血点，黏膜破损明显比S组减轻，镜下也只见黏膜少许脱落，腺体少量炎性细胞浸润，如图1。

2. 各组血浆MDA含量及SOD活性比较

与N组相比，S组MDA明显升高，SOD降低，差异有统计学意义（p＜0.05）；与S组相比，凯时预先用药组（M组与P组）MDA下降，SOD显著升高（p＜0.05），如表2。

3. 应激3.5h后Th1/Th2细胞与Th17/Treg细胞平衡的改变

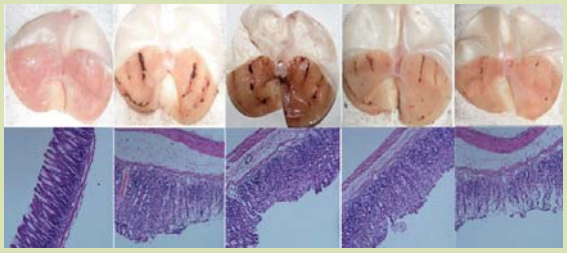
与N组对比，S组T-bet mRNA表达量下降，但无统计学差异。Gata-3mRNA表达上调（p＜0.05）；RORγt与Foxp3 mRNA表达均下调（p＜0.05）。而T-bet/Gata-3比值下降（p＜0.05），RORγt/Foxp3比值无明显变化，如图2。

4. 凯时预处理对Th1/Th2细胞与Th17/Treg细胞平衡的影响

由图2可见，与S组比较，P组Gata-3mRNA表达下调（p＜

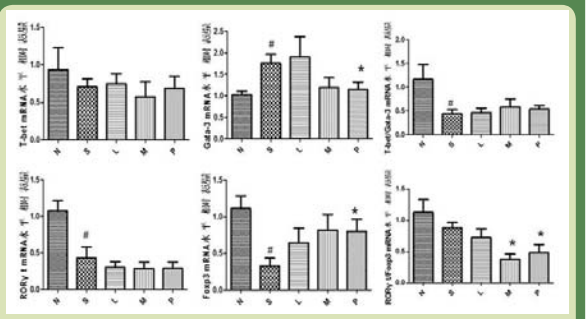
0.05），Foxp3mRNA表达上调（p＜0.05），而T-bet与RORγt mRNA表达水平无明显变化。另外，RORγt/Foxp3比值降低有统计学意义（p＜0.05），而T-bet/Gata-3比值无明显变化。

图1 各组胃组织肉眼观及病理切片（200×）
Fig.1 The whole view and the pathologic slice(200×) of the stomach



Notes: from left to right: Group N、Group S、Group L、Group M、Group P.

图2 Th1/Th2细胞与Th17/Treg细胞相关特异转录因子mRNA相对表达量
Fig.2 The Expression of Th1/Th2 cell and Th17/Treg cell related specific transcription factors



Notes: compared with Group N, #p＜0.05; compared with Group S, *p＜0.05.

四、讨论

应激性胃溃疡是一种较常见的危重病并发症，临床表现易合并出血，病情危重，死亡率高[3]，临床胃镜观察表明[4]，在重症监护患者中发生应激性胃溃疡占85%-100%，发生出血者占6%-20%，由它引起的消化道大出血和穿孔病死率很高。应激性胃溃疡的发生机制目前还不清楚，可能与神经内分泌及免疫系统异常表达有关。研究表明，应激时，神经内分泌系统发生改变，下丘脑-垂体-肾上腺皮质（HPA）轴和交感-肾上腺髓质（SAM）轴开始激活，糖皮质激素（GC）和儿茶酚胺大量释放。GC与其受体（GR）结合后[5]，可以抑制免疫细胞增殖，诱导免疫细胞凋亡，干扰细胞因子及抗体的分泌等。儿茶酚胺类物质也在一定程度上介导免疫调节。

体外实验表明[6-8]：应激产生的糖皮质激素和儿茶酚胺类物质能促进Th2细胞分泌，而抑制Th1细胞的分泌。正常机体内Th1/Th2细胞之间是处于一种平衡状态，应激时，这种平衡被打破，Th0细胞更倾向于Th2细胞分化转移，Th2细胞逐渐占优势，相应地，作为Th1/Th2细胞对应的特异性转录因子T-bet/Gata-3也逐渐失衡。这和本实验中T-bet/Gata-3应激后比值变小的结果是相符的。另外，本实验中还观察到应激3.5h后，Th17细胞和Treg细胞特异性的转录因子RORγt和Foxp3均出现下降。Freier等[9]发现，在急性精神应激后伴随着外周血中Treg细胞以及相关效应分子的降低，更有趣的是他们还观察到Treg细胞上的肾上腺素β1受体和糖皮质激素α受体过度表达，提示这些受体可能与应激抑制Treg细胞功能的作用机制有关。

凯时是一种以脂微球为载体的前列腺素E1新型制剂，具有高效低毒，靶向治疗的优点。它能靶向作用于炎症及血管损伤部位，并能有效地舒张全身动静脉血管。它可能通过调节腺苷酸环化酶和磷酸二脂酶活性促进细胞内环磷酸腺苷浓度增加，激活依赖环磷酸腺苷的一系列蛋白激酶使血管扩张，从而改变应激性胃溃疡病变部位的血流，起到缓冲 H+逆扩散，保护胃粘膜的作用。本实验也观察到凯时预处理组大鼠的溃疡较未用药组的减轻。另一方面，凯时还能升高血浆SOD活性，减低MDA含量，提示它具有抗氧化及清除自由基的作用。另外，本实验中还观察到大剂量凯时能降低应激大鼠Gata-3 mRNA表达而升高Foxp3 mRNA表达。这和文献[10、11]报道的前列腺素E1能促进Th2细胞因子分泌，促使Th1/Th2细胞平衡向Th2细胞方向转移的结论相悖，可能是由于文献报道的均为离体实验，且前列腺素E1与细胞共培养时间较长的缘故，而本研究中凯时组较应激组Gata-3 mRNA减低而Foxp3 mRNA升高，提示在急性应激早期，凯时可能具有改善应激导致的全身免疫抑制状态的作用，从而维持一种新的Th1/Th2细胞及Th17/Treg细胞动态平衡。

总之，应激性胃溃疡的发生发展可能与Th1/Th2细胞和Th17/Treg细胞失衡有关，具体机制有待进一步探讨。凯时具有抗氧化作用，且能减少应激性胃溃疡的发生，并在急性应激早期可能有保护机体免疫功能的作用。临床上与制酸药配伍可能更有利于应激性胃溃疡的预防与治疗。

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黄宏辉[1] 李天宝[2]
1.珠海市人民医院麻醉科
2.广东宝莱特医用科技股份有限公司

摘要

目的：研究数字血氧饱和度在危重患者监测的测量的准确度、重复性、稳定性、抗干扰能力。方法：选择28例低灌注、颤动的危重患者，应用数字式血氧饱和度监护仪，模拟式血氧饱和度监护仪，同时抽取动脉血作血气分析。结果：数字式血氧饱和度监护检测率89%，检测数据和血气分析数据高度一致P>0.05，模拟式血氧饱和度监护仪检测率4%，检测数据和血气分析数据无比较意义。结论：数字式血氧饱和度监护仪在危重患者的临床监测中有高准确度和良好的重复性、稳定性，抗干扰能力和良好的抗低灌注能力。

关键词：数字式血氧饱和度；危重患者；临床监护

责任作者及联系方式：黄宏辉，E-mail：hhhzhuhai@163.com

数字式血氧饱和度在危重患者监测的临床应用研究

Clinical Application of Digital Oxygen Saturation in Critical Patients' Detection Measurement

Hong-hui Huang[1], Tian-bao Li[2]

1.Department of Anesthesiology, People's Hospital of Zhuhai City
2.Guangdong Biolight Meditech Co., Ltd

Abstract

Objective: To study the accuracy, repeatability, stability and anti-jam capability of digital oxygen saturation monitor in critical patients' detection measurement.

Methods: First, to choose 28 hypo perfusion vibrant critical patients. Then to use digital oxygen saturation monitor and the analogue oxygen saturation monitor to respectively monitor the patients, at the same time to extract artery blood for blood gas analysis.

Results: The detection rate of digital oxygen saturation monitor is 89%, which is consistent with the data of blood gas analysis. (P>0. 05) The detection rate of analogue oxygen saturation monitor is 4%, which is meaningless to compare with the data of blood gas analysis.

Conclusion: The digital oxygen saturation monitor has the features of high precision, good repeatability stability, anti-jam capability and anti-hypoperfusion capacity in critical patients' detection measurement.

Key Words: Digital oxygen saturation; Critical patients; Clinical monitoring

Corresponding Author: Hong-hui Huang, E-mail: hhhzhuhai@163.com

无创伤脉搏血氧饱和度监测已广泛应用于临床危重症患者的监护和手术中麻醉的监护以及手术后患者的恢复情况、呼吸睡眠的研究、社区医疗监护等方面，它具有安全可靠、连续实时以及无创伤的特点[1]，现已在临床上发挥重要作用。但作为一种发展中的技术，其在测量的准确度、重复性、稳定性、抗干扰能力等方面还存在许多需要进一步探讨和完善的地方[2]。

目前的脉搏血氧饱和度检测系统多是通过模拟技术来完成的，如增益调节、双光束分离、交直流分离、滤波放大、脉搏波特征检出等一系列工作[3]。其在测量的准确度、重复性、稳定性、抗干扰能力等不佳。在低灌注、颤动的患者监测中出现很大误差甚至不能测量。数字血氧饱和度检测系统在低灌注、颤动的患者监测中表现出非常好的抗干扰性、准确性和重复性[4]。

一、临床资料与方法

本次临床应用研究在珠海市人民医院进行，采用广东宝莱特医用科技股份有限公司的配有数字式血氧饱和度的监护仪。自2008年2月至2010年2月，共监测呼吸机抢救呼吸衰竭病人28例，其中男16例，女12例，用数字式血氧饱和度监护的病种有：①重症胰腺炎、胸外伤、心胸大手术后，剖腹产术后大出血DIC引起急性呼吸窘迫综合征20例，胆道感染，肠梗引起中毒性休克8例。均应用数字式血氧饱和度监护，模拟式血氧饱和度监护同时抽取动脉血作血气分析，记录结果并作统计学分析。

二、结果

数字式血氧饱和度监护检测率100%，检测数据和血气分析数据高度一致P>0.05，模拟式血氧饱和度监护仪检测率10%，检测数据和血气分析数据无差异P>0.05见表一。

三、讨论

在麻醉、手术以及PACU和ICU大量临床应用资料表明，及时评价血氧饱和度和/或亚饱和度状态，了解机体氧合功能，尽早发现低氧血症，足以提高麻醉和重危病人的安全性；尽早探知SpO_2下降可有效预防或减少围术期和急症期的

表1
Table 1

观察病例	数字式血氧饱和度监测结果		模拟式血氧饱和度监测结果		血气分析数据	
	麻醉前10min	麻醉后30min	麻醉前10min	麻醉后30min	麻醉前10min	麻醉后30min
1	81	90	无结果	75	80.3	91
2	68	87	无结果	无结果	65	86
3	66	82	无结果	无结果	67	82.5
4	77	89	无结果	无结果	79.1	90
5	45	88	无结果	无结果	48	86.2
6	48	90	无结果	无结果	49	91
7	65	93	无结果	70	69	94
8	80	95	67	69	85	93.2
9	63	88	无结果	无结果	61.9	90
10	77	91	无结果	82	78	90.5
11	48	85	无结果	无结果	47.5	84
12	79	90	无结果	81	82.7	90.2
13	64	88	无结果	无结果	62	89
14	70	90	无结果	无结果	71	91.6
15	无结果	83	无结果	无结果	35	84.9
16	47	91	无结果	无结果	49.2	92.9
17	43	88	无结果	无结果	45	90.1
18	55	83	无结果	无结果	53.9	81.5
19	60	86	无结果	68	59	88
20	56	79	无结果	无结果	58.1	80
21	67	90	无结果	无结果	65	89.2
22	无结果	80	无结果	无结果	30	78.5
23	41	88	无结果	无结果	44.3	87
24	50	95	无结果	70	53.9	96.2
25	44	89	无结果	无结果	47	90
26	60	91	无结果	无结果	60.4	92
27	68	90	无结果	80	70.3	88
28	59	88	无结果	无结果	60	88.3
检测率	89%	100%	4%	29%	100%	100%

意外死亡。在手术室，脉搏血氧饱和度仪可以进行连续氧合评估，特别在对危重病人和不易通气的手术中，它能够快速提供信息[5]。SpO_2作为一种无创、反应快速、可靠的连续监测指标，已得到公认，用红外光谱光电法在无创测量血氧饱和度的应用方面已经获得较大的成功，脉搏血氧仪正处在大范围普及及应用阶段，但目前的脉搏血氧饱和度检测系统多是通过模拟技术来完成的如增益调节、双光束分离、交直流分离、滤波放大、脉搏波特征检出等一系列工作，低灌注、颤动的患者监测中出现很大误差甚至不能测量。

数字血氧饱和度技术的发展，将进一步突破技术上的局限性，使由于病人活动、低灌注、外界光线干扰等所造成的低信号/噪音比得以提高，加上针对数字信号的各种优化算法，使其在抗干扰上、特别是对于低灌注患者表现非常突出，在使用常规模拟血氧饱和度仪很难测量SpO_2时，数字血氧饱和度仪仍然能很好的测量出准确的结果，这点在临床上非常有用，也非常需要。

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中华医学会第十三届全国儿科呼吸学术会议

会议时间：2012-10-25至2012-10-29

会议地点：江西省南昌市

主办单位：中华医学会儿科学分会

中华医学会儿科学分会呼吸学组将于2012年10月下旬在江西省南昌市举办“中华医学会第十三届全国儿科呼吸学术会议”。会议将围绕儿童呼吸系统感染性疾病、间质性肺疾病、儿童哮喘及其他喘息性疾病、全身疾病在呼吸系统表现、呼吸系统疾病影像学、肺功能、支气管镜等进行交流和讨论。

会议形式包括大会讲座、专题讨论、专家面对面、代表发言、壁报以及青年医师英文病例报告。会议将邀请国内外专家，特别是港台专家参会并进行讲座。欢迎广大儿科医护人员积极参加，踊跃投稿，会议将对投稿论文进行评选，对优秀论文予以奖励，参会者将获国家Ⅰ类继续教育学分10分。

联系人：李佳

联系电话：010-85158128

E-mail：lijia@cma.org.cn

李文雯 万献尧
大连医科大学附属一院重症医学科 116011

摘要

感染性休克是当前严重威胁人类生命的疾病之一，积极的液体复苏作为一种重要的治疗手段越来越受到重视。但也会带来肺水肿等并发症，为减少患者的负担，我们可以一方面采取便捷可靠的指标作为评估和监测，另一方面根据不同时期以及不同患者的特点来采取相应的补液措施，以减少液体复苏带来的急性肺损伤。

关键词：感染性休克；肺水肿；液体复苏；指标

责任作者及联系方式：万献尧，E-mail：wanxianyao@gmail.com

感染性休克时液体复苏相关性肺损伤研究进展

Research Advances in Fluid Resuscitation Lung Injury with Septic Shock

Wen-wen Li, Xian-yao Wan

Department of ICU, the First Affiliated Hospital of Dalian Medical University, 116011

Abstract

Septic shock is one of life-threaten diseases. Aggressive fluid resuscitation which works as an important treatment has received more and more attention, but it also brings some complications such as pulmonary edema. In order to reduce the burden of patients, we can adopt the convenient and reliable index to assess and monitor on one hand and in the other we can take rehydration measures according to the features in different times and different patients to reduce the acute lung injury induced by fluid resuscitation.

Key Words: Septic shock; Pulmonary edema; Fluid resuscitation; Index

Corresponding Author: Xian-yao Wan, E-mail: wanxianyao@gmail.com

在过去的10年里，随着人口的老龄化，全身性感染的发病率正不断增长，全球每年约1800万人罹患严重感染，而感染性休克的病死率高达30%～60%[1]。感染性休克治疗中液体复苏一直被作为最基本、最重要的原则，早期液体复苏是治疗感染性休克的重要措施之一。但液体复苏在恢复有效循环血量的同时，也有可能会导致肺水肿加重及液体复苏相关性肺损伤。

一、液体复苏与感染性休克

感染性休克的发生与感染灶中的病原微生物及其释放的各种内毒素和外毒素刺激组织细胞产生释放大量的细胞因子和血管活性物质有关。这些细胞因子和血管活性物质可增加毛细血管壁通透性，使大量血浆外渗，导致血容量减少。同时亦可引起血管扩张，使血管床容量增加，导致有效循环血量的相对不足。

根据其血流动力学特点，可分为低动力型休克和高动力型休克。前者因其心输出量减少、外周阻力增高的特点又称为低排高阻型休克或冷休克；后者因其心输出量增加、外周阻力降低的特点又称为高排低阻型休克或暖休克。因此早期进行积极的容量复苏，则大部分感染性休克患者将进入高动力状态，促使低排高阻向高排低阻转换，大大减小了感染性休克的危害。

液体复苏的目标在于及时纠正组织灌注不足和组织缺氧，大量的临床实践证实其具有很好的效果[2-4]。早在2004年底，代表11个国际组织的各国危重症、呼吸疾病和感染性疾病专家组成委员会提出“全身性感染集束化治疗”，即以早期液体复苏为中心、配合其他有效监测和治疗手段的综合性治疗[5]，力求在休克早期纠正血流动力学异常，改善患者预后。在《2008年严重感染和感染性休克治疗指南》中已明确提出早期复苏目标：①中心静脉压（CVP）8～12mmHg；②平均动脉压（MAP）≥65mmHg；③尿量≥0.5ml/（kg·h）；④中心静脉（上腔静脉）血氧饱和度（$ScVO_2$）≥70%，混合静脉血氧饱和度（SvO_2）≥65%。

二、感染性休克与急性肺损伤

早期、足量的液体复苏可以维持适当的前负荷和器官灌注，是治疗感染性休克便捷有效的手段。但是充分扩容并不等同于超量补液，否则将容易诱发肺水肿，乃至急性肺损伤（ALI）的发生[6]。

首先，严重感染是引起ALI的首位高危因素，又是影响

ALI预后的首要原因。感染时由于炎症细胞的作用，使肺内炎症反应失控而导致肺泡毛细血管损伤，因此引起肺毛细血管通透性增高，血管内液体易进入组织间隙而导致肺水肿。

与此同时，发生感染性休克时组织处于缺血缺氧状态，氧自由基增加，最终导致血液动力学变化，循环障碍发生。感染性休克时由于肺的微循环灌注不足，肺表面活性物质减少，各肺泡不能维持相应的张力，发生肺萎陷，同时也可出现肺组织淤血、出血、间质水肿，继而发生严重实变。休克时冠脉灌注不足，心肌缺血缺氧，心肌纤维变性、坏死，心肌收缩受到抑制，导致心力衰竭，从而进一步加剧肺损伤。

当对感染性休克患者进行大量液体复苏时，将会导致过多的液体聚集在组织间隙，此时输入的液体必然多于排出，临床表现为液体正平衡。液体正平衡时间过长将引起组织器官水肿，氧弥散距离加大，微循环障碍，甚至出现多器官功能障碍综合征（MODS）[7]。

三、减少ALI的策略

液体复苏的目标在于及时纠正组织灌注不足和组织缺氧，但考虑到感染性休克患者易发生ALI的特点，因此为防止或减少其发生，应在保证有效循环血量的前提下尽可能保持适当负平衡。为此需要在有效的目标指导下，以方便可靠的指标做参考评估，根据感染性休克的特点采取有效的补液方式。

1. 以方便可靠的监测指标进行评估

为减少感染性休克的包括ALI在内的严重后果，需要在一些可检测可评估的监测指标指导下进行液体复苏，也就是所谓的早期目标指导性治疗（EGDT）。

严重感染与感染性休克时组织持续缺氧，传统临床监测指标往往不能对组织氧合的改变具有敏感的反应，因此监测和评估全身灌注指标以及局部组织灌注指标很有必要。

成人严重感染与感染性休克血流动力学监测与支持指南[8]提出：肺动脉漂浮导管是血流动力学监测的有效手段，通过漂浮导管获取的参数资料，可以更好地指导临床治疗。但其操作比较复杂，应用成本高。而$ScvO_2$与SvO_2有一定的相关性，$ScvO_2$在临床上可能更具可操作性，在一定程度上可以反映组织灌注状态[9-11]。但有学者提出，$ScvO_2$与SvO_2与心排出量或者组织氧合指数的相关性并不理想：以监测SvO_2来指导输血，尤其是陈旧袋装库存血，可能会导致不可预知的后果[12]。由此我们需要寻找更为有价值的监测指标。

严重感染与感染性休克时组织缺氧使乳酸生成增加，在常规血流动力学监测指标改变之前，组织低灌注与缺氧已经存在，乳酸水平已经升高。研究表明，血乳酸持续升高与APACHEⅡ密切相关，感染性休克患者如血乳酸>4mmol/L，病死率达80%，因此乳酸可作为评价疾病严重程度及预后的指标之一。有人通过研究证明，应用血乳酸清除率指导严重感染的液体复苏可以降低严重感染和感染性休克患者MODS的发生率及病死率[13]。连续监测血乳酸水平，尤其是乳酸清除率对于严重感染及感染性休克的液体复苏治疗非常重要。

由于技术和理论的进步，近年出现了一些新的无创或微创血流动力学监测方法，其中以脉波指示剂连续心排量监测技术（PiCCO）最具代表性。

PiCCO技术是经肺热稀释技术和脉搏波形轮廓分析技术的综合，用于血流动力学监测和容量监测管理，近年来逐渐广泛应用于危重症患者的血流动力学监测，并使大多数患者不再需要放置肺动脉导管。其容量性指标包括静态指标和动态指标[14]。PiCCO能提供每搏输出量、心室每搏做功指数、射血分数等指标监测心肌收缩力的变化情况[15]，能早期判断并指导对心功能的调整，有效促进血流动力学稳定、减轻肺水肿。同时，有研究表明，PiCCO能全面连续监测感染性休克血流动力学变化，并能反映血管外肺水，临床干扰因素少，能更精确判断感染性休克血流动力学异常并指导治疗，可能有利于改善感染性休克患者预后[16]。

2. 治疗策略的选择

对于液体复苏采用液体的选择也一直是近几年学者们争论的焦点。液体主要分为晶体液和胶体液，前者主要包括生理盐水、林格液和乳酸钠溶液等；后者主要包括白蛋白、血浆、明胶类、羟乙基淀粉类和右旋糖苷等。它们各有优点，晶体液费用低廉，使用方便，较少出现免疫变态反应，但容易引起肺水肿和全身组织水肿，同时还可引起疼痛和复视等不良反应。胶体液可以快速恢复血容量和氧供，改善微循环灌注，致肺水肿和全身水肿的发生率很低，但费用昂贵，易导致凝血功能障碍和变态反应发生及肾功能损害等。至于晶体液与胶体液究竟哪一种为更优选择，至今尚无定论。

以感染性休克为主的重症感染是导致ALI/急性呼吸窘迫综合征（ARDS的主要因素。临床研究显示，限制复苏液体用量有利于改善ALI/ARDS患者的氧合、减少住院时间[17]。说明休克复苏时液体用量减少有利于改善休克合并ALI/ARDS患者的氧合。

Murphy等[18]提出液体管理的两个策略，即保守性液体管理策略（CLFM）和开放性液体管理策略（LLFM）。CLFM指1周内至少连续2d使患者液体处于负平衡状态，即适当应用血管活性药物以限制液体入量，如果患者循环相对稳定，适当使用利尿剂，维持液体负平衡；而LLFM则指第1周内达不到连续2d液体负平衡，以较大量补液来维持血压，尽量减少血管活性药物的用量。对此，国内有学者通过研究表明[19]，达到6h EGDT+24h后CLFM者的ALI的发生明显降低，28d病死率亦有明显降低。对感染性休克患者6h内应进行充分的液体复苏，争取达到EGDT；24h后适当限制液体入量，从而改善感染性休克患者的预后。

有人根据氧自由基参与肺损伤的机制，建立了感染性休克大鼠模型，结果显示：2%氢气吸入联合早期液体复苏治疗感染性休克既维持了血流动力学稳定，减少了达到目标血压所需的补液量，又减轻了氧自由基损伤，从不同角度减轻了肺损伤的程度，改善了感染性休克时的内环境[20]。作为一种

新的绿色抗氧化剂，氢气可能为感染性休克的治疗开辟新的前景。

但在以各种指南和研究结果做指导的同时，亦不能忽略患者的异质性以及应用指征的特殊性。因此全面收集证据，尽可能建立符合本地条件的高依从性的集束化治疗策略和有效的监测督导机制乃是必要之举[21]。

四、小结与展望

综上所述，液体复苏在感染性休克的治疗中起着至关重要的作用，可及时纠正循环血量不足，避免产生更加严重的后果。但与此同时，液体复苏易诱发肺水肿并发症的发生。因此，为尽可能减少ALI，可以在方便可靠的检测指标的指导下，及时观测血流动力学变化，根据不同情况采取不同的补液措施，力求达到最佳效果。相信在以后的临床及科研工作中，会提出更好的措施以解决两者之间的矛盾。

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第十三次全国呼吸病学学术会议

会议时间：2012-09-13至2012-09-16

会议地点：四川省成都市成都世纪城新国际会展中心

主办单位：中华医学会、中华医学会呼吸病学分会

由中华医学会、中华医学会呼吸病学分会主办的中华医学会呼吸病学年会-2012 （第十三次全国呼吸病学学术会议）将于2012年9月13～16日在四川成都召开。大会组委会诚挚地邀请全国各地的同道踊跃参加此次盛会。

一年一度的全国呼吸病学学术会议是国内呼吸病学界水平和规格最高的学术会议，也是展示我国呼吸病学最新研究成果、推动学科全面发展的一个重要平台，更是有重要影响力，呼吸同道广泛参与的业界盛会。

本次会议将围绕呼吸系统疾病的诊断、治疗、发病机制、流行病学及基础方面的学科进展，包括呼吸系统感染、肿瘤、慢性阻塞性肺疾病、支气管哮喘 、呼吸危重症与临床呼吸生理、睡眠呼吸障碍、肺间质疾病（包括结节病）、肺栓塞与肺血管病以及呼吸治疗，介入呼吸病学、烟草病学等各个方面的临床与基础医学的新进展进行广泛而深入的交流。会议将邀请国内外著名专家作专题报告和讲座，容量大，内容丰富、具有前沿性、导向性、实用性，形式生动，并开展论文交流、壁报展示、分组讨论等形式多样、内容丰富的学术活动。参会者将获得国家I类医学继续教育学分。

联系人：王娟

联系电话：010-8515 8249

E-mail：csrd2008@126.com

唐元章 综述 倪家骧 审校
首都医科大学宣武医院疼痛科

摘要

腰椎间盘源性疼痛是临床上的常见病、多发病。椎间盘病变是椎间盘源性疼痛的主要原因；交感神经在椎间盘的神经支配及腰椎间盘源性疼痛发病机制中的作用越来越引起重视。本文就交感神经在椎间盘的分布及椎间盘椎间盘源性交感神经相关症状机制研究进展方面进行综述。

关键词：腰椎间盘；交感神经；盘源性疼痛

责任作者及联系方式：倪家骧，Email：jiajiaxiang@163.net

交感神经在腰椎间盘源性疼痛中作用的研究进展

Research Advances of Sympathetic Nerve in Lumbar Disc Pain

Yuan-zhang Tang, Jia-xiang Ni

Department of Pain, Xuanwu Hospital of Capital Medical University

Abstract

Lumbar disc pain is the common and chronic diseases in clinics. Degenerative disc disease is the main cause of lumbar disc pain. The role of sympathetic nerve in the intervertebral disc innervation and Lumbar intervertebral disc pain pathogenesis is attracting more and more attention. In this article, research advances of sympathetic nerve in lumbar disc pain are reviewed.

Key Words: Degenerative disc disease; Sympathetic nerve; Discogenic Pin

Corresponding Author: Jia-xiang Ni, Email: jiajiaxiang@163.net

一、引言

椎间盘源性疼痛时指由于一个或者多个椎间盘内部结构和代谢功能出现异常，进一步影响到椎间盘周围组织的继发病变，刺激椎间盘内部或邻近疼痛感受器所引起的疼痛。椎间盘病变导致的疼痛疾病，病因复杂，发病率高，是困扰病人和医生的一大顽疾。既往研究多集中于椎间盘对脊神经的压迫或刺激而导致的临床症状，但近年来，交感神经在椎间盘源性疼痛中的作用逐渐引起重视，随着交感神经在椎间盘分布的阐明，认为椎间盘大部分都是由交感神经支配，而且研究证实交感神经可传递疼痛[1]，椎间盘病变的刺激因素通过交感干传导至上位腰脊神经节而产生范围模糊腰背痛，其特点类似于“内脏痛”；特别是随着“盘源性腰痛”，“盘源性腹痛”等概念的提出，椎间盘病变刺激或压迫交感神经而导致的临床相关症状逐渐明朗。

二、交感神经在椎间盘的分布

交感神经在椎间盘及周围的分布，构成了椎间盘病变侵犯交感神经引起临床症状的基础。随着椎间盘神经支配的逐渐揭示及交感神经传导疼痛理论的提出，椎管内交感神经支配成为研究报道的热点。

1. 椎间盘后方

先前的研究认为支配腰椎间盘后方的是窦椎神经，并提出窦椎神经是由脊神经返支和灰交通支组成的混合神经。Palmgren等[2]发现在正常人腰椎间盘纤维环浅层有交感神经的标志物神经肽Y的c端连接肽阳性神经纤维和感觉神经的标志物SP阳性神经纤维分布，提示人椎间盘有纤维环浅层交感神经和脊神经双重支配。Nakamura等[3]通过选择性地切除大鼠L2-L6的交感干和交感节，用乙酰胆碱酯酶组织化学方法研究腰椎间盘后方的神经分布，发现腰交感神经全切除的大鼠，腰椎间盘后方的神经分布几乎完全消失；双侧单节段或单侧多节段交感神经切除的大鼠，腰椎间盘后方的神经分布稍有减少。结果表明腰椎间盘后方的神经纤维是交感神经并呈多节段和双侧分布的。石作为等[4]通过在大鼠L5/6椎间盘右后壁注入辣根过氧化物酶（HRP）逆行追踪法观察腰交感干切除后L1、L2脊神经节内标记HRP阳性细胞数量，发现腰交感干切除组相比于保留腰交感干组，脊神经节内HRP阳性细胞数明显减少，提示HRP通过腰交感干逆行转运至上位脊神经节。最近，Takahashi[5]等在大鼠L5/6椎间盘不同部位进行DiL标记，观察神经支配，发现椎管内（椎间盘后方及后纵韧带、硬脊膜等）主要接受来自腰交感干的交感神经支配。Raoul等[6]在尸体解剖窦椎神经发现其起源于椎间盘、硬脊膜、后纵韧带及前纵韧带，经交感

干，大部分终止于L2脊神经节，少数分散终止于L3-L5脊神经节。Groen等[7]则研究证实腰椎间盘后方的神经支配来自于窦椎神经，窦椎神经仅由交感神经发出组成的。而我国陈金栋等[8]在尸体解剖研究也发现椎体和椎间盘盘后部及后纵韧带均有交感干发出的窦椎神经支配，支持Raoul的研究报道。因此，从目前报道来看，腰椎间盘后缘及其附近组织由窦椎神经支配，腰椎间盘后缘疼痛信息可经交感神经和脊神经两条通路传导，而交感神经系统主要参与腰椎的非节段性疼痛信息传递。

2. 椎间盘前方

腰椎椎体前外侧有椎旁神经节，并借节间支互相连接形成交感干。 由交感干神经节发出的交感节后纤维。随着椎间盘神经解剖的逐渐深入研究，椎间盘前方、前纵韧带、椎体前方的神经支配已经逐渐明确。Morinaga等[9]在大鼠L5/6椎间盘前侧应用逆行标记法研究其神经支配，并用组织学观察了所有腰脊神经节，结果发现只有在L1和L2脊神经节发现了逆行标记的HRP，提示L5/6椎间盘前侧疼痛信息传至L1、L2脊神经节，而不是传至同阶段的脊神经节。Ohrori等[10]研究大鼠椎体前侧神经支配，证实椎体前缘由交感神经支配，并经交感干传至多节段脊神经节。Raoul等[6]在尸体解剖证实椎间盘前缘、前纵韧带被交感干分支及交通支分支支配。而陈金栋等[8]在尸体解剖也证实椎体和椎间盘前侧为交感干分支和内脏神经支配，而椎体外侧、后外侧有交感干分支、交通支及脊神经分支共同支配，而最近Takahashi等[5]在试验中发现，L5/6间盘前方、侧方虽然是由L2脊神经节支配，但主要不是通过腰交感干，而是L2脊神经前支通过腰大肌肌支发出分支支配。

通过既往研究已经证实，人体椎间盘后侧由窦椎神经、前侧由交感干分支支配。有争议的是窦椎神经组成，部分学者认为其完全属于交感神经成分，而另有部分学者认为为交感神经和脊神经返支共同组成；而对于前方支配，腰交感干分支的支配理论也受到Takahashi等的挑战。虽然尚存在争议，但是交感神经在椎间盘及其附近结构前纵韧带、后纵韧带、硬脊膜等的分布是明确的；且研究结论一致证实，疼痛信号传递至L1、L2脊神经节。该传导通路也同时解释了椎间盘损伤导致的定位模糊的腰背痛。

三、椎间盘病变导致的疼痛性疾病

1. 腰椎间盘后方交感神经激惹（盘源性腰痛）

传统观点多认为椎间盘源性腰腿痛是由于刺激脊神经引起的，但是临床中常常发现，患者主诉有范围模糊的腰背部疼痛，累及腹股沟、髂骨翼、臀部等部位，不伴有明显的下肢放射性疼痛；在影像资料中常发现脊神经根和硬膜囊无明显受压，可见有下腰段椎间盘黑盘征，MRIT2加权像椎间盘后方高信号影的特点；应用传统的同节段脊神经受累的观点常解释不通，下位腰椎病变如何能影响到上位的腰脊神经根呢？随着腰椎间盘后方及相邻组织的神经支配逐渐揭示，目前多认为盘源性腰痛是由于椎间盘后方的窦椎神经受刺激经腰交感干而传递至非同节段上位腰脊神经节而产生的疼痛，其产生机制类似于“内脏痛”的特点[3]。由于椎间盘退变以后，髓核沿纤维环裂隙漏出，而作用于支配其相邻组织的神经而产生的无菌性炎症。而局部炎症反应，产生大量炎性介质刺激刺激相应神经，被认为是神经痛的主要原因[11]。基于对于椎间盘后方神经支配的解剖学研究，盘源性腰痛的机制逐渐阐明，椎间盘退变是盘源性腰痛的始发因素，椎间盘周边交感神经向上位腰脊神经节的传导则是腰背部疼痛的主要传导途径。在临床行L2脊神经节阻滞对于缓解盘源性腰背痛取得了较好的疗效[12]，动物实验运用射频方法毁损交感神经交通支对椎间盘源性疼痛也有明显的较少伤害性信息的传导[13]，也证实了盘源性腰痛经交感干向上位腰脊神经节传递的理论。

2. 腰椎间盘前方交感神经激惹（盘源性腹痛）

既往的研究多主要集中于椎间盘后缘椎管内结构受突出间盘压迫或致炎后引起的一系列症状，椎间盘向前或侧方突出一般认为不会引起疼痛，而被临床忽视，而致误诊的发生。

但随着椎间盘神经解剖的深入，椎间盘前方、前纵韧带、椎体前方仅由交感神经支配，而且腰椎前方有紧邻的肠系膜上丛、上腹下丛等内脏神经丛分布。那么既然椎间盘后方突出压迫或致炎相应神经可产生疼痛性疾病，当椎间盘前突或致炎分布于其前方的交感神经分支、交感干、内脏神经丛等是否也会产生临床症状呢？有研究报道[14]腰椎间盘前突或和侧前突可挤压推移腰大肌或前纵韧带加上其化学或免疫的作用可导致腰背痛或腰腿痛。杨辉等[15]报道一例伴腹痛腹胀的腰椎间盘突出症，腹痛腹胀症状与腰痛同时发作，MRI示L2/3椎间盘向左后及向前突出，经牵引等治疗，腹痛腹胀可缓解，后路椎板减压、髓核摘除术术后腹痛腹胀症状完全缓解。曹家树等[16]对腰椎间盘突出症引起下腹痛4例患者进行分析，认为腹交感干神经以及交感神经节,通过腹腔自主神经兴奋,引起反射性腹痛是可能原因之一。Ohtori等[10]证实椎体前缘由交感神经支配，疼痛信号经交感干传至多节段脊神经节。并用此解释腰椎骨质疏松患者后腰部范围模糊疼痛分布。虽然对于腰椎间盘前突、髓核破裂前漏目前尚没有大样本实验研究报道导致相关的临床症状，但是从解剖学机制上，腰椎椎体前外侧有椎旁神经节，并借节间支互相连接形成交感干。由交感干神经节发出的交感节后纤维，除经灰交通支随5对腰神经分布于下肢的血管、汗腺和竖毛肌外，还有穿过腰神经节，由节前纤维组成的腰内脏神经，终止于腹主动脉丛和肠系膜下丛内的椎前神经节，再由此发出的交感节后纤维直接或随血管分布至结肠左曲以下的消化管、盆腔的脏器和下肢血管。另外，腹腔丛位于T12-L1椎体前方，肠系膜下丛位于L3椎体水平腹主动脉前方，上腹下丛位于L5椎体前腹膜后间隙，支配下腹部及盆腔内的消化管、脏器等。当椎间盘前突压迫或髓核外漏引起局部无菌性炎症时，可激惹临近的交感干、内脏神经丛等而导致腹痛、便秘、下肢营养不良等相关交感神经炎性症状，我们称之为“盘源性腹

痛”。但是这只是理论上的猜想，尚需要大量的临床及基础实验证实。

四、总结

对椎间盘及周围组织解剖学研究的深入研究，有助于对于椎间盘源性疼痛的致病机制的深入研究。既往研究多集中于椎间盘对脊神经的压迫或致炎作用，而对临床上所见的盘源性疼痛无法从机制上进行解释，明确交感神经在椎间盘分布及其在椎间盘源性疼痛中所起的作用，将有助于临床上椎间盘源性疾病的诊断及治疗，特别是椎间盘前方交感神经受激惹所产生的交感神经相关良性腹痛、便秘等将有新的认识，对于该类病人进行正确的诊断和治疗。明确交感神经在椎间盘源性疼痛中所起的作用，还将有助于针对交感神经的有效的治疗方法的开展，并进一步推进椎间盘源性疼痛分子水平的研究，阐明其致痛机制提供基础。

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“麻醉安全、性命相托”基层公益行——毕节站

2012年7月22日，在卫生部、统战部的组织协调下，由中华医学会麻醉学分会主办，阿斯利康（中国）支持的“麻醉安全，性命相托”基层公益行在毕节市拉开序幕。毕节是胡锦涛同志亲自倡导，国务院批准建立的“开发扶贫、生态建设”试验区；也是中央统战部和各民主党派中央、全国工商联、无党派人士共建“同心工程”的品牌区。在这片革命老区的红色热土上，此次“麻醉安全、性命相托”基层公益行具有更大的时代和战略意义。

在卫生部霍小军副局长和麻醉学分会主任委员于布为教授的亲自带队下，来自全国各地三甲教学医院的专家教授们一行十数人，不远千里，顶风冒雨，来到这片改革试验区。

此次基层公益行是第十届中华麻醉学会 “群安计划”的主要实践形式和内容，也是符合并主动落实卫生部“保基本、强基层、建机制”的新医改原则，发挥大型公立医院的公益性，辐射、引领、提升基层医院麻醉学科水平，满足广大人民群众对临床增强医疗安全保障需求的重要举措。更是快速提高边远贫困地区的基层麻醉科临床实践，学科管理，发展建设能力，消除现阶段发展的不平衡性，从而更好的保障医疗安全，发挥主导舒适化医疗建设、提高医院工作效率，协调促进相关学科发展，促进中国麻醉学科水平的整体提升，进入国际先进水平，实现与我国经济建设和社会发展相称的学科实力的重要工作。从2012年3月19日项目正式启动，截止到6月16日，所设立的23个培训基地中，已经培训了1165名基层医院的麻醉科主任和骨干医生。

此次毕节行的各位麻醉专家分别来自全国各地的三级甲等教学医院，他们通过授课讲座、现场演示和直面交流等多重方式，与当地麻醉医师们就麻醉学科建设、人才梯队培养，临床质量控制，以及麻醉学新理论、新技术、新药物等进行多方面的交流指导。

在此之前，“麻醉安全、性命相托”的基层公益行活动已经在海南省陵水县顺利开展。而这样的“下基层”活动还将长期坚持下去。中华医学会麻醉学分会将组织不同批次的专家团，深入内蒙古、新疆、黑龙江、云南等多个地区的基层医院，计划每年培训1000名以上的基层麻醉医生，争取在5−7年的时间内，完成全国6000多家基层医院麻醉医生的培训工作。

我们相信在卫生部，中华医学会的领导支持下，在全国23家培训基地的认真努力下，在中国麻醉学专家学者的共同培育下，通过未来数年的不懈努力，将使我国基层医院麻醉学科的整体水平和建设能力有一个显著提升，从而促进整体医学学科的发展建设，更好的保障人民群众卫生健康事业的发展。为基层医疗机构“造血”，为生命健康保驾护航！

王家双
广州市红十字会医院疼痛科，广州，510220

摘要

虽然目前临床麻醉技术在不断提高，但是仍然有部分患者由于麻醉过程中的不当操作或接受常用浓度的局部麻醉药后会发生神经系统直接或间接的损伤，虽然非常严重的神经系统损害的发生率很低，但绝大部分病例成为医疗纠纷和经济赔偿的案例。由于目前临床仍然无法预测麻醉后神经损伤的可能性，一旦事件发生，治疗原则是早期、及时、有效实施治疗。除了常用的药物治疗外，早期交感神经或神经根阻滞， PCEA技术，脉冲射频和三氧介入治疗等都是比较有效的治疗方法，可以明显降低损伤后的危害程度和范围。

关键词：麻醉后神经损伤，脉冲射频治疗，三氧介入治疗，交感神经治疗

责任作者及联系方式：王家双，E-mail:wangjs994@yahoo.com.cn

临床麻醉后神经损伤的现代诊疗

The Progresses of Diagnosis and Treatment for Periphery Nerve Injury after L-E Anesthesia

Jia-shuang Wang

Department of Pain Medicine, Guangzhou Red Cross Hospital of Jinan University, Guangzhou, 510220

Abstract

There are still some patients with periphery nerve injury after L-E anesthesia can be seen in clinical with advancing for anesthesia recent years. Lots of the cases can be recovery after anesthesia and permanent injury in parts of them may be also seen in clinic and economic lost can not be avoided as well.

Nerve injury after L-E anesthesia still can not be prevent or forecast, early and in time, effectively treatment can decrease harmful effects to the patient with nerve injury after L-E anesthesia. The treatment of early sympathetic block, pulse-radiofrequency or ozone intervention is also effective for the patient.

Key Words: Nerve injury after L-E anesthesia; Sympathetic block; Pulse-radiofrequency; Ozone intervention

Corresponding Author: Jia-shuang Wang, E-mail: wangjs994@yahoo.com.cn

临床麻醉后神经损伤发生比例虽然不高，但是大部分病情发生比较突然，许多患者的损伤状态无法在麻醉前预测。绝大部分病例成为医疗纠纷和经济赔偿的案例。美国ASA会议（2003-2011）资料及许多研究资料报道指出，临床麻醉技术本身和目前所常用浓度的局部麻醉药对于神经系统会产生直接或间接的损伤作用，虽然非常严重的神经系统损害的发生率很低，但是临床上出现的部分麻醉后神经系统并发症足以有理由引起我们的高度重视。

进入21世纪后，医学研究逐渐有关周围神经系统损伤的研究，2007年7月卫生部发出227号文件宣布正式建立临床疼痛科以后，许多临床医师开始对于外周神经系统、中枢神经系统和植物神经系统在受到损伤后发生的应激反应、结构和功能的异常改变有了最初步的认识和概念，但是对这些极其复杂一系列相互联系、影响以及所产生的继发性变化过程和结果仍然了解不多，在临床治疗方面更是缺乏经验，需要进一步学习新知识。

一、局部麻醉药与周围神经系统

1. 局部麻醉药与神经系统[1-5]

自从1884年澳大利亚的Karl-Kaller医生使用可卡因作为外科手术局部麻醉用药以来，人们逐渐开发出多种局麻药物，并在临床上成功使用一个多世纪，人们仍然在研究其作用机制和对神经系统可能的影响，由于局部麻醉药除了可以阻断Na^+通道，抑制Na^+内流和阻断神经冲动传导外，还能够阻断K^+或Ca^{++}通道，阻断NMDA受体等的多方面作用，同时也对神经系统存在潜在毒性作用[1-3]。

（1）对Na^+通道的作用

Na^+通道是一种膜蛋白，由一个大的α亚单位和1-2个β亚单位组成，α亚单位是局部麻醉药结合和离子传导部位，具有4种同源异构体：D1-D4，每种含有6个α螺旋跨膜片段。局部麻醉药主要结合在D1-S6，D3-S6和D4-S6部位。正常情况下，Na^+通道至少有3种自然状态：静止、开放和失活状态。Na^+通道的短暂开放使Na^+从细胞外进入细胞内，细胞膜发生去极化产生动作电位，膜电位可以影响Na+通道状态和局部麻醉药亲和力。局部麻醉药可以和许多不同位点结合而产生腰麻或硬膜外麻醉效果。

（2）对K^+或Ca^{++}通道和受体作用

局部麻醉药除了可以阻断Na+通道外，还具有阻断或抑制K^+或Ca^{++}通道和NMDA受体、神经肽受体等作用，这些作用对于解释局部麻醉药的作用强度或效能、毒性或副作用的差别等具有非常重要的临床意义和继续研究价值。

其他作用：局部麻醉药也可以阻断伤害性感受器、影响轴浆运输、直接作用于神经元细胞等。局部麻醉药还与H^+有比较复杂的协同作用和其他相互作用。另外研究表明，局部麻醉药产生的麻醉强度和持续时间与神经纤维中局部麻醉药的含量有关，麻醉药的神经阻滞强度随着分子量和脂溶性的增加而增强，这是因为分子量大或脂溶性强的局部麻醉药更容易在细胞膜上弥散，Na^+通道亲和力也增大。

局部麻醉药在临床常用的浓度下可能造成神经系统的损伤，这种损伤程度与药物浓度成为正比，即浓度越高，损害越重。损伤范围涉及感觉和/或运动神经系统，程度可以从短暂神经功能障碍（Transient neurologic symptoms，TNS）到延迟恢复，甚至不可逆性损伤。目前的临床调查发现可能造成神经系统的损伤药物涉及利多卡因、布比卡因、左旋布比卡因和罗哌卡因等[2、6]。

2. 麻醉过程与神经系统损伤的相关因素[6-10]

除了上述所提出的成损伤因素外，另外还有相关因素，如麻醉操作不当、神经系统缺血、放置导管过程中神经系统受到损伤或刺激、感染以及不同种类局部麻醉药处方等。此外，由于手术中的直接损伤、异常或特殊体位损伤、血压袖带或外科包扎过紧、病人已经存在的神经系统疾病或损伤而在手术前没有发现等因素也常常归咎于区域麻醉过程[6-7]。

（1）麻醉操作

除了局部麻醉药可能对神经系统产生直接的损伤外，麻醉穿刺过程操作不当是早期周围神经系统受到刺激或损伤的主要因素，主要发生于解剖不明、操作不熟练或粗暴操作，多发于基层医院。目前临床上使用神经刺激仪或B超引导实施神经阻滞镇痛或麻醉也会发生神经系统受到损伤的情况逐渐有资料报道[8-10]，应该逐步引起我们的关注。

（2）病人本身的因素

在临床麻醉过程中，部分病人麻醉前已经存在的疾病可能对神经系统本身产生影响或损害，如高血压、糖尿病、重要脏器功能减退或不全、骨质疏松、神经系统的损伤等会不同程度使局部或全身神经系统结构或功能发生一定程度的异常改变，使得它们在麻醉过程中对局麻药或其他损伤因素的敏感性增高。所以认真仔细的麻醉前访视、病情评估对于这类病人尤其重要。

（3）麻醉、手术过程中的特殊体位

有时麻醉、手术过程中的特殊体位，如膀胱截石位、上肢或下肢过伸位和其他特殊手术的强制体位或较长手术时间的一般体位等容易发生神经系统并发症。即使一般手术体位中如果衬垫放置不当也会发生神经损伤。但是总体来说，大多数的这类损伤是可以避免的，只要加强手术中的管理就会明显降低发生率。有关体位性神经系统损伤病人，投诉对象总是麻醉科和手术室。但是也有研究资料表明，部分病人本身体质差异与神经损伤有关，良好的手术中管理也不可能避免全部的神经损伤发生。

（4）麻醉和手术过程中导致神经系统缺血的因素

研究资料提出：在一些特殊的情况下或敏感的群体，局部麻醉药中加入的肾上腺素等血管收缩药会成为神经系统缺血的主要原因，肾上腺素通过收缩局部血管来延长局部麻醉药吸收，同时明显减少了作用区域内神经系统的血液供应，如果病人已经存在潜在的神经系统疾病或功能不全则很容易发生或加剧神经系统缺血。手术中长时间的低血压也容易加剧神经系统缺血现象。另外，过紧或不适当的血压袖带和外科包扎也容易发生或加剧神经系统缺血。

（5）麻醉中发生的神经系统损伤的出现时间

有趣的是，根据资料统计大多数临床麻醉过程中发生的神经系统损伤并非在麻醉后立即出现，常常在手术48小时后，甚至更长时间才会出现，目前人们还无法解释这种现象。究竟是此类损伤所产生的病理生理变化在48小时后才出现临床症状还是同时有其他导致神经系统进一步损害的因素共同作用的结果均有待于深入的研究观察证明。

二、麻醉后神经系统损伤的临床表现[11-14]

1. 临床表现

常常以下肢症状为主，主要表现为区域疼痛、麻木、感觉异常（烧灼感、针刺感或浅感觉减退）、运动障碍（足下垂、行走困难）和肌肉萎缩，绝大部分患者常常遗留明显的功能障碍。

2. 电生理检查

肌电图可见神经波幅和传导速度降低、潜伏期延长和异常自发电位，结果显示神经源性损伤或失神经支配现象[11、14]。

3. 红外热图检查

损伤早期局部显示高温现象，中、后期绝大部分损伤区域显示低温现象，经过及时、有效治疗低温现象可能改善[13]。

三、神经损伤疼痛临床治疗[7、14-16]

1. 治疗原则

麻醉后神经损伤疼痛的治疗具有很大的挑战性，需要临床采取及时、有效的方法才能够取得肯定的疗效，最大程度降低对患者的损害作用。现代治疗方法可以集中在下列几方面：

（1）神经功能调节治疗；

（2）消除神经源性炎症治疗；

（3）促进神经损伤修复治疗；

（4）早期及时、有效的的治疗；

（5）疗效巩固、慢性疼痛康复治疗。

对于药物治疗提倡选择合适的种类和周期，对于现代介入治疗方法要符合下列要求：

①在保证医疗安全的前提下，尽量生理功能干扰少、避免医源性损害；

②优选合理方案和最佳组合，治疗方案医师要充分熟悉；

③有效控制疼痛、促进神经系统损伤修复；

④患者充分的知情、同意，接受并理解治疗方案，主动配合治疗。

2. 药物治疗

（1）非甾体类抗炎药（NSAIDs）：神经损伤疼痛早期，特别是病史在3个月以内的患者，可以配合使用非甾体类抗炎药。如乐松、席乐保等。

（2）促进神经损伤修复治疗药物

①糖皮质激素

糖皮质激素是一把双刃剑。虽然多年来在临床使用上存在不同的观点，但是不能否认糖皮质激素类一直是许多早期神经损伤和慢性疼痛治疗中的常用药物之一。提倡早期、短期和足量使用。

②维生素治疗

维生素是一类维持机体正常代谢和机能所必需的低分子有机化合物，大多数维生素是某些酶的辅酶的组成部分。临床上主要用于补充疗法，以预防和治疗维生素缺乏症，在临床疼痛治疗中可起辅助（或协同）其他主线药物作用。

③牛痘疫苗接种提取物

如神经妥乐平或恩再适是将牛痘免疫病毒疫苗接种到家兔的皮肤组织，从其炎性组织中提炼而成的一种非蛋白小分子生物活性物质。其药理作用包括神经修复和营养作用、镇痛作用、改善冷感及麻木等神经症状、调节免疫作用等。许多资料报道在神经损伤疼痛的临床实综合治疗中能够取得比较明显的临床效果。

（3）抗惊厥药

与抗抑郁药一样，抗惊厥和抗心律失常药物在神经源性疼痛中取着一定的作用。传统使用的包括苯妥英钠和卡马西平，其中卡马西平对三叉神经痛有非常好的效果，但是对其他类型的神经痛效果不一定理想。目前临床上已经使用的代表药物包括加巴喷丁和普瑞巴林。

（4）抗抑郁药

三环类抗抑郁药（TCAs）被认为是广谱治疗的神经痛药物，是目前临床上治疗神经痛的首选药物。其作用机制尚未完全明确，可能通过抑制突触部位的5-HT和NE的再摄取而增强中枢神经系统内的内源性疼痛抑制机制。近年来研究发现三环类抗抑郁药的作用机理除阻滞5-HT和NE再摄取以外，还能阻断电压依赖性钠通道及-肾上腺能受体。阿米替林是三环类抗抑郁药的最佳代表性药物，广泛用于慢性疼痛治疗包括糖尿病性神经痛和带状疱疹后神经痛的治疗，效果肯定。阿米替林平均剂量为25～150mg/d，口服起效迅速。

三环类抗抑郁药均有相同的副作用，其一是直立性低血压，可能与-肾上腺素能受体阻滞相关；其二是较强的镇静作用，为组织胺受体阻滞的结果；其他还包括尿潴留、记忆力减退及心脏传导异常。

3. 早期交感神经或神经根阻滞

周围神经损伤后，会发生一系列涉及交感神经系统的异常变化，其中疼痛和感觉异常是最突出的特征，在损伤发生后，特别是在损伤的早期合理选用相应的交感神经或交感神经节阻滞，不仅可以及时缓解疼痛，还能明显减低由于神经损伤所产生的神经系统应激反应，对于神经损伤本身的治疗和预后都具有特别的临床意义。但是交感神经或交感神经节阻滞的具体操作技术要求高，而颈交感神经节（星状神经节）、胸交感神经节或腰交感神经节的具体定位和穿刺方法及注意事项也有差异。提倡规范化操作，避免发生并发症[14]。

4. 椎管内注药

对于神经损伤性疼痛椎管内注药也是可选用的方法，尤其是急性损伤期的病人早期使用有益于疼痛的缓解和病情的发展或预后，注药模式可根据具体病情采用单次硬膜外腔治疗、经硬膜外腔病人自控镇痛法（PCEA），临床上往往都能够取得较好的治疗效果，对于特殊病人还可以使用椎管内埋藏（硬膜外腔或珠网膜下腔）的药物输注系统治疗。

5. 脉冲射频和三氧介入治疗

近年来，在神经损伤疼痛的治疗中，脉冲射频和三氧治疗也逐渐显示出优势[14-15]。脉冲射频的最大优点在于脉冲电刺激神经系统，所以具有调整神经（Neuro-modulation）系统作用，主要通过调节神经功能达到治疗疼痛而不损伤神经组织，可以有效的促进神经损伤的修复和疼痛的缓解。而三氧治疗通过消除局部致痛物质、解除神经根粘连以及改善神经组织周围氧供和代谢，从而达到直接缓解疼痛的目标和促进神经损伤的修复过程。更具有临床意义的是在规范使用的原则下，不论脉冲射频和三氧治疗都具有很高的安全系数和可重复性，是神经损伤性疼痛疾病治疗新的希望[15-16]。

6. 心理治疗

及时的心理治疗能增进和改善患者的心理、行为和机体的生理机能，起到辅助治疗的作用，临床常用：①支持性暗示治疗；②解释性暗示治疗。支持性暗示可以重新树立患者对日常生活的信心和勇气，解释性暗示则帮助患者正确面对现实，重新认识自己的疾病并且能够主动配合医生的治疗。

7. 局部麻醉药静脉注射

利多卡因静脉点滴可有效缓解许多神经源性疼痛。它属于酰胺类局麻药，静脉给药后起效快，能够抑制周围神经的过度兴奋作用，提高痛阈，对中枢神经系统也有明显的兴奋和抑制双相作用，常规剂量为1.5-2mg/Kg,缓慢滴注。如果滴注过快，血药浓度过高，可引起房室传导阻滞以及抑制心肌收缩力和心输出量下降。

8. 电生理治疗

通过特殊频率的电流刺激能够直接缓解疼痛、促进神经损伤的修复，如HAN’S、TENS和微电流电极治疗均属于此治疗范围，可以用来配合治疗神经损伤疼痛的治疗。使用简单、方便、安全。

9. 脊髓电刺激技术和蛛网膜下腔埋藏泵技术

脊髓电刺激技术和蛛网膜下腔埋藏泵技术属于疼痛治疗的高端技术，由于价格比较高，临床上应当掌握适应症和禁忌症。根据目前报道的资料，这两种技术分别对于不同类型的神经损伤疼痛有治疗效果，前者对于缺血性疼痛疾病和麻醉后神经损伤疼痛有治疗优势，后者对于部分神经痛和晚期肿瘤疼痛有治疗优势。

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曹国庆

首都医科大学宣武医院疼痛科

摘要

臭氧(O_3)是一种强氧化剂，易分解，易溶于水，臭氧可安全有效的用于多种临床疾病的治疗。医用臭氧主要治疗方法有自体血疗法、臭氧直肠灌注疗法、臭氧气浴、臭氧局部注射等，本文综述其在皮肤类疾病中的应用。

关键词：医用臭氧；皮肤类疾病

责任作者及联系方式：曹国庆，E-mail:xwttcgq@yahoo.cn

医用臭氧在皮肤类疾病中的应用

Application of Medical Ozone in Skin Diseases

Guo-qing Cao

Department of Pain, Xuanwu Hospital of Capital Medical University

Abstract

Ozone (O_3) is a strong oxidizing agent, and it is easy to decompose and freely soluble in water. Ozone can be used in the treatment of many clinical diseases. The main treatment methods of medical ozone auto-blood therapy, ozone archosyrinx therapy, ozone gas bath and ozone local injection. In this article, the application of medical ozone in skin diseases is reviewed.

Key Words: Medical ozone; Skin diseases

Corresponding Author: Guo-qing Cao, E-mail: xwttcgq@yahoo.cn

臭氧(O_3)由三个氧原子组成，是一种强氧化剂，常温下半衰期约20分钟，易分解，易溶于水。早在第一次世界大战期间德国就将臭氧用于治疗厌氧菌感染所致的气性坏疽，1935年奥地利的派尔教授在德国外科协会年会首次进行了关于臭氧应用于外科治疗的演讲，使得臭氧真正用于临床，虽然臭氧治疗各种疾病的机制目前尚不十分明确，但大量报道表明臭氧可安全有效的用于多种临床疾病的治疗[1]。医用臭氧主要治疗方法有自体血疗法、臭氧直肠灌注疗法、臭氧气浴、臭氧局部注射等，本文对其在皮肤类疾病中的应用进行综述如下。

一、糖尿病性溃疡

臭氧治疗糖尿病性溃疡可采用臭氧袋法、臭氧水法、自体血液回输疗法、直肠灌注等。顾琛等[2]将糖尿病足感染的100例分组治疗， 治疗组在对照组治疗的基础上加臭氧气浴治疗，根据创面大小经导管注入浓度40mg/ml的臭氧20～50ml保持20min后吸净臭氧气体结束治疗， 每天1次，10次为1个疗程，根据情况重复2～4个疗程。结果显示臭氧气浴对治疗难治性糖尿病足安全、效果显著，保肢率高。

黎凤娟等[3]将60例2型糖尿病伴严重下肢血管病变合并糖尿病足的患者分为A、B、C三组。A组采用传统疗法，即药物+局部换药；B组传统法+下肢血管介入疗法；C组传统法+下肢血管介入+臭氧足部疗法。结果显示：C组临床症状、愈合情况及截肢率明显好于A、B组。说明下肢血管介入治疗术后辅助臭氧足疗，对糖尿病足治疗效果满意，可以促进患者康复及降低患者的病残率。杨雪英[4]将62例糖尿病足溃疡患者随机分为2组，对照组按常规治疗，实验组在常规治疗同时加用臭氧大自血与臭氧气浴联合治疗，结果发现实验组有效率为87.50%，对照组有效率为仅53.33%。表明臭氧大自血与臭氧气浴联合治疗糖尿病足溃疡疗效显著，值得推广。

二、烧伤

由于烧伤后感染、局部创面不愈合、伤处血液循环不良、低蛋白血症和营养不良以及药物等作用是影响烧烫伤创面愈合的主要因素，其中感染和血液循环不良也延迟伤口愈合，甚至长期不愈合的最常见原因，因此有大量文献报道了利用臭氧来治疗人体的烧伤。

谢卫国等[5]通过观察臭氧水对常见烧伤创面分离菌的体外杀菌作用及应用于烧伤创面的清创消毒效果。对臭氧水对创面的清创作用进行了探讨。结果显示：臭氧水对所有受试菌有迅速而完全的体外杀灭作用。应用于烧伤创面清创消毒，其细菌清除率为94.5%，临床总有效率97.1%。王艳霞等[6,7]对单位2007年1月～2008年9月住院的60例患者按臭氧消毒时间随机分为2min消毒组、4min消毒组、6min消毒组、8min消毒组，每组15例，每组在臭氧消毒前后均取创面分泌物做细菌培养及鉴定，并观察细菌量的变化。研究探索臭氧消毒对烧伤残余创面细菌的杀灭作用。结果显示：60例患者残余创面分泌物细菌培养中，以金黄色葡萄球菌为主，各组消毒后细菌数量明显减少，前后比较有显著差异。不同时间比较表明，消毒时间为4min、6min和8min均优于2min消毒组，细菌数量明显减少。表明臭氧治疗烧伤残余创面效果显著。

三、感染性伤口

万筱玲[8]将51例慢性伤口患者随机分为观察组和对照组，对照组采用常规方法换药护理伤口，观察组在对照组基础上采用臭氧外部充气疗法。观察两组伤口的愈合效果和愈合时

间。结果观察组在治疗效果和愈合时间上明显优于对照组,差异有统计学意义，表明臭氧外部充气疗法护理慢性伤口,可使患者伤口肉芽组织生长迅速,创面自行修复,伤口愈合时间缩短。郭火容[9]报道臭氧成功治疗感染性伤口两例。沈玉龙[10]对23例诊断为难治性溃疡患者治均采用臭氧联合美宝湿润烧伤膏治疗,观察治疗前后溃疡创面大小、深度、肉芽组织生长情况及溃疡愈合时间，发现疗效确切,总有效率达95.6%，表明臭氧联合美宝湿润烧伤膏治疗难治性溃疡经济方便,疗效可靠,值得进一步探讨。

四、褥疮

宋淑兰等[11]报道将48例褥疮患者分为两组，观察组用浓度为0.1%的新洁尔灭清洗创面后,暴露创面,用臭氧发生器对创面释放低浓度臭氧,每日治疗2次,每次60min。根据创面情况治疗3～10d,待创面炎症消失,完全干燥结痂后,停止治疗。观察组于治疗前、后3d分别取创面分泌物作细菌培养,以比较治疗前、后细菌生长情况,对照组用常规治疗方法,亦于治疗前、后3d取创面分泌物培养,并与观察组比较细菌的生长情况。结果发现观察组细菌菌落数及愈合情况明显优于对照组。故表明臭氧可安全有效的用于褥疮的治疗。夏威等[12]将55例糖尿病中度褥疮患者随机分为两组，对照组采用常规治疗；治疗组加行臭氧治疗（臭氧80mg/L通入装有双蒸馏水的密封瓶中,鼓泡通气10分钟,制得臭氧水20mg/L左右,局部冲洗创面,每次均现制即用， 尔后换用生理盐水冲洗， 保持创面湿润,再将一次性套袋完全罩于创面密封,将袋内气体抽净,充入袋中臭氧,保留30分钟,将充气袋中臭氧抽空后结束治疗,在感染严重期臭氧水维持浓度范围(20～40mg/L),若分泌物消失,肉芽组织出现， 臭氧水维持浓度范围(2～5mg/L)。观察两组创面愈合情况。结果显示臭氧治疗组与对照组相比,褥疮治疗临床疗效明显高于对照组， 治愈者愈合时间显著短低于对照组。表明局部臭氧应用治疗糖尿病重度褥疮,简单、经济、安全、有效，值得临床进一步推广应用。

五、其它

凌芝雄等[13]报道手足癣63例、甲癣149例、阴道念珠菌病75例均随机分为对照组(30、23、33例)和治疗组(33、26、42例)。手足癣和甲癣对照组用癣粉溶液浸泡患处30 min,治疗组则在浸泡全程加用臭氧治疗仪向水中输入臭氧；阴道念珠菌病对照组用0.1%新洁尔灭洗外阴阴道,治疗组用臭氧水拭洗外阴阴道。两组均口服氟康唑片150mg/d,连续3d。疗程结束后比较两组的疗效。结果手足癣治疗组治愈率明显高于对照组；甲癣对治疗组治愈率明显高于对照组；外阴念珠菌病治疗组治愈率高于对照组。各疾病两组间比较,差异均有统计学意义(P<0.05或0.01)。表明臭氧治疗手足癣、甲癣和阴道念珠菌病的疗效好,无副作用,值得推广。郭伟男等[14]通过臭氧治疗真菌性皮肤病病例对照研究，也表明臭氧治疗手足癣和阴道念珠菌病的疗效好,无副作用,值得推广。

六、展望

臭氧治疗越来越受到各国医学工作者的青睐，原因在于其简单、安全、创伤小、费用低。我们相信，在不久的将来，臭氧治疗能像其他治疗方法一样，造福于更多患者。

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2012年中华医学会全国麻醉学术年会

会议时间：2012-08-30至2011-09-02
会议地点：重庆市渝中区
主办单位：中华医学会麻醉学分会

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。

联系人：白雪
联系电话：010-85158614
E-mail：csa2012@live.cn

One Case of Ventricular Fibrillation in Bladder Cancer Surgery

Kun Li

Department of Anesthesiology, People's Hospital, Xinyu City, Jiangxi Province 338000

Key Words: Ventricular Fibrillation; Bladder Cancer
Corresponding Author: Kun Li, E-mail: likun2860@163.com

A 60-year-old 60kg male patient was admitted due to intermittent painless hematuria for 1 year and diagnosed as bladder cancer, so radical resection of bladder cancer was performed with tracheal intubation under general anesthesia. The patient had previously been healthy, with no history of hypertension, diabetes or coronary heart disease; preoperative blood, liver and kidney function electrolytes, ECG, chest radiograph and blood coagulation were all normal. 30min before the surgery, the patient received intramuscular injection of atropine 0.5mg and phenobarbital sodium 0.1g. Newly in the operating room, the patient's BP was 130/80mmHg, HR was 95 beats/min, and SpO_2 was 98%. Then right subclavian deep vein puncture was performed, and a 7F double-lumen central venous catheter was put in. At 9:15, anesthesia induction was started, combined with intravenous injection of midazolam 3mg, remifentanil 60ug, propofol 60mg, vecuronium 6mg and penehyclidine 0.5mg successively. Mechanical ventilation was performed after intubation, with tidal volume of 550ml at a frequency of 12 times/min. Anesthesia maintenance: continuous pump infusion of remifentanil and propofol, and intermittent injection of vecuronium to maintain muscle relaxation. The surgery started at 9:30 am and by 12:00, the patient's bleeding reached 1200ml. The patient was given infusion of lactated Ringer's solution 1000ml, hydroxyethyl starch 1000ml, succinylated gelatin 1000ml and erythrocyte suspension 4U. Blood pressure was maintained at 135 ~ 105 mmHg/80 ~ 60 mmHg, HR at 70 ~85/min and SPO_2 at 100%. By 13:15, the total bleeding reached 3000ml, so the patient continued to receive infusion of lactated Ringer's solution 1500ml, hydroxyethyl starch 500ml and erythrocyte suspension 4U. At 13:18, blood gas analysis was conducted, and the results showed pH 7.22, PCO_2 58mmHg, PO_2 556mmHg, BE-4.8mmol/L, HCO-3 23.1mmol/L, Na+ 140mmol/L, K+ 6.6mmol/L, Cl- 114mmol/L, HB 9.0g/dl, SO_2 100% and Hct 27%. The ventilator parameters were adjusted, and the patient received intravenous infusion of $NaHCO_3$ 100ml, as well as aggressive blood transfusion and fluid expansion treatment. At 14:09, blood gas: pH 7.28, PCO_2 48 mmHg, BE-4.6mmol/L, K+ 6.7mmol/L, HB 7.7g/dl and Hct 23%. It was found in blood re-check that two bags of the blood were only one day from the expiry date, so the blood transfusion was immediately stopped. The patient was then treated with 10% calcium gluconate 10ml and furosemide 20mg intravenously, as well as intravenous infusion of insulin 8U and $NaHCO_3$ 100ml, and transfusion of lactated Ringer's solution. At 15:05, ECG showed ventricular tachycardia, so the patient was immediately given lidocaine 100mg intravenously, but the effect was poor. Then ventricular tachycardia

soon changed to ventricular fibrillation, followed by cardiac arrest. So chest cardiac massage was performed immediately, combined with intravenous injection of epinephrine 1mg simultaneously, still ineffective. Intravenous injection of adrenaline (2mg) was given again, and electrical defibrillation was performed at the same time, two-way wave, 150J. Just like this, chest cardiac massage, intravenous epinephrine and defibrillation therapy were performed repeatedly. At 15:58, the patient restored sinus rhythm with BP of 110/78 mmHg and HR of 160 beats/min. During the whole process, totally 11mg of epinephrine was given intravenously and defibrillation was performed five times. Then the patient started to receive dopamine and adrenaline micro pump infusion. At 16:00, blood gas: PH 7.08 PCO_2 87 mmHg, BE -5.5mmol/L, K+ 3.8mmol/L, HB 9.1g/dl and Hct27%. In addition to aggressive blood transfusion and infusion therapy, ice packs were applied for head cooling, and the surgery was continued. At 17:50, the surgery ended, and the patient's BP was 100/60mmhg, HR 134 times/min and SPO_2 100%. After the operation, the patient was sent to ICU for further life-sustaining. The patient lost about 6500ml of blood in total during the surgery, and received infusion of erythrocyte suspension 12U, plasma 1000ml, rehydration 7700ml (lactated Ringer's solution 5000ml, hydroxyethyl starch 2000ml, succinyl gelatin 1000ml and $NaHCO_3$ 200ml). The patient awoke on the first day after surgery, got off the machines and tubes on the third day, and was cured and discharged on the 15th day, without sequelae in the subsequent one year of follow-up.

Discussion: Ventricular fibrillation is a severe arrhythmia leading to sudden cardiac death. Common causes for ventricular fibrillation include two categories: cardiogenic and non-cardiogenic. The common cause for cardiogenic ventricular fibrillation is coronary heart disease, especially acute myocardial ischemia; causes for non-cardiogenic ventricular fibrillation include anesthesia and surgery accidents, severe electrolyte and acid-base balance, electrocution, drowning, drug poisoning or allergy, etc. Hyperkalemia can lead to cardiac conduction block and various rapid ventricular arrhythmias, or even ventricular fibrillation in severe cases. There are many causes for hyperkalemia, among which too much transfusion of bank blood is an important factor. The clinical manifestations and treatment of this patient showed that ventricular fibrillation was caused by severe hyperkalemia due to transfusion of blood on the verge of expiry. Although aggressive treatment means were taken after hyperkalemia was found, such as injection of 10% calcium gluconate against the toxic effects of K+ on the myocardium, drip infusion of $NaHCO_3$ and insulin to promote K+ into cells, and intravenous infusion of furosemide to promote K+ excretion, ventricular fibrillation still occurred. Fortunately, the patient was successfully saved after aggressive treatment. Experience as follows:

(1) 2010 AHA Guidelines for CPR pointed out that the rescue for cardiac arrest is continuous external cardiac massage, electrical defibrillation and epinephrine treatment. The key to the successful treatment of this case is the perseverance and the spirit of never giving up. Especially for cases with hyperkalemia-induced ventricular fibrillation and cardiac arrest, during the rescue process of continuous chest compressions, as the concentration of potassium drops, its inhibition of the heart is also reduced, and thus the success rate of defibrillation is greatly improved.

(2) Blood transfusion is still a means of clinical therapy, but in the transfusion process, it is necessary to strictly check the validity of bank blood to prevent the transfusion of expired blood. Try to avoid the transfusion of blood that has been kept for too long so as to prevent hyperkalemia caused by too much damage of red blood cells. Meanwhile, control the infusion rate and the input in a unit period of time.

(3) Strengthen monitoring during surgery, such as observing ECG changes and blood gas analysis for timely detection and aggressive treatment of hyperkalemia.

(4) In bladder cancer surgeries, how to accurately observe the patient's urine output, understand the function of kidneys and indirectly learn about K+ excretion is a measure to be taken. Bilateral ureteral drainage can be adopted to observe the patient's urine output.

The "Trench Phenomena" of Platelet Parameters in Patients with Heparin-induced Thrombocytopenia after Cardiopulmonary Bypass: Report of 2 Cases

Yan Cui[1], *Ya Gao*[1], *Hai-tao Zhang*[2]

1. Department of Cardiac Surgery, Fu Wai Hospital, Beijing, China, 100037
2. Department of ICU, Fu Wai Hospital, Beijing, China, 100037

Abstract

Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication threatening multi-organ of the patient due to heparin therapy that usually begins 5 or more days after administration of heparin. Immediate diagnosis and the administration of alternative non-heparin anticoagulation are important for preventing thromboembolic complications. But the diagnosis of HIT can be ambiguous in certain patient populations, particularly in post-cardiac surgery patients experiencing cardio-pulmonary bypass treated with unfractionated heparin, who would develop a high incidence of anti-PF4/heparin antibodies (50%) but a much lower frequency (1–2%) of clinical HIT [2-4]. Here, we took a retrospective review of 419 cases undergone cardiac surgery with cardio-pulmonary bypass from 2010-10 to 2011-02 in which 2 cases diagnosed as HIT with the platelet 4 parameters' "trench" phenomena in our post cardiac operative intensive care unit. In the 2 cases, when the platelet reaches a specific low point, the platelet 4 parameters: large platelet ratio, mean platelet volume, platelet volume distribution width and plateletcrit would lower to zero and recover many times in the period of low level of platelet count, of which the platelet changing curves present a trench phenomenon. On the other hand, after the administration of substitute of non-heparin anti-coagulant, this 'trench phenomena' disappears with the increasing of platelet count. At the same, in the patients without HIT as we investigated from the data of 417 cases post cardiac-operation after cardiopulmonary bypass, there is no 'trench phenomena'. This platelet 4 parameters' "trench phenomena" may be a strong predictor of the HIT in the patient post-cardiac operation after cardiopulmonary bypass. But the clear mechanism behind the 'trench phenomena' still need further investigation and its clinical application also need much larger trial to prove.

Key Words: Heparin-induced thrombocytopenia; Trench phenomenon; Cardiopulmonary bypass

Corresponding Author: Hai-tao Zhang, E-mail: boy398672@yahoo.cn

Heparin-induced thrombocytopenia (HIT) is a life-threatening immune-mediated complication of heparin therapy that usually begins 5 or more days after starting heparin. This prothrombotic disorder is caused by immunoglobulin G (IgG) antibodies that recognize platelet factor 4 (PF4)/heparin complexes, resulting in platelet activation and thrombin generation[1]. Prompt diagnosis and the introduction of alternative non-heparin anticoagulation are important for preventing thromboembolic complications. However, the diagnosis of HIT can be problematic in certain patient populations, particularly in those with a high incidence of other explanations for thrombocytopenia. This is especially true in post-cardiac surgery patients treated with unfractionated heparin, which develop a high incidence of anti-PF4/heparin antibodies (50%) but a much lower frequency (1–2%) of clinical HIT[2–4]. Owing to the potential severity of HIT-related thrombotic complications, early diagnosis is essential so that heparin must be replaced rapidly with an alternative anticoagulant (sodium danaparoid, hirudin or argatroban); even in the absence of symptomatic thrombotic events. But an incorrect diagnosis of HIT can lead to heightened bleeding risk if heparin is replaced by therapeutic doses of non-heparin anticoagulants referred. So an early and exact diagnosis of HIT is much more important particularly in the post cardiac-operation patient with a high incidence of anti-PF4/heparin antibodies due to the cardiopulmonary bypass process.

Within the past 10–20 years, recognition of HIT has evolved from gross under-diagnosis to wild over-diagnosis. The widespread detection ofanti-PF4/heparin antibodies by commercially-available PF4-dependent immunoassays have promoted an over-diagnosis phenomenon. In our post cardiac-operative intensive care unit, we took a retrospectively review of the platelet 4 parameters within 2 HIT patients and 417 non-HIT patients. From the result, we found a typical changing trend of the platelet 4 parameters (large platelet ratio, mean platelet volume, platelet volume distribution width and plateletcrit) diagnosed as HIT different from non-HIT patients in the post cardiac-operative patients experiencing cardio-pulmonary bypass.

In patients undergoing cardiopulmonary bypass (CPB) surgery, platelet counts typically fall abruptly in association with cardiac surgery, and usually reach the postoperative nadir (typically 40–60% of the preoperative baseline platelet count) by the second or third postoperative day (POD)[5], with a subsequent increase in the platelet count to elevated levels during the second postoperative week (postoperative thrombocytosis). It is widely accepted that a relative platelet count fall of greater than 30%, 40%, or 50% (depending on the study[6–7]) that begins on or after POD 5 is a typical presentation of HIT[8]. In case 1 (Figure1), the platelet count falls immediately after surgery, starts to normalize within in the day 5 after surgery, typically reaching values above 100×10^9/L, and then decreases again. This typical profile of thrombocytopenia has been termed as pattern 1 by Pouplard and colleagues[7]. The platelet 4 parameters would lower to zero abruptly and recover for many times, when the platelet down to a low level for the first time, and then keep a relative steady high level when the platelet count reached a higher and stable level. Then when the platelet count down to another low level the second time, the platelet 4 parameters lower to zero abruptly and recover for many times the second time. And with the using of non-heparin anti-coagulant, the platelet count and platelet 4 parameters recover to a normal level. The arrow represent the starting time of using non-heparin anti-coagulant (Argartroban).

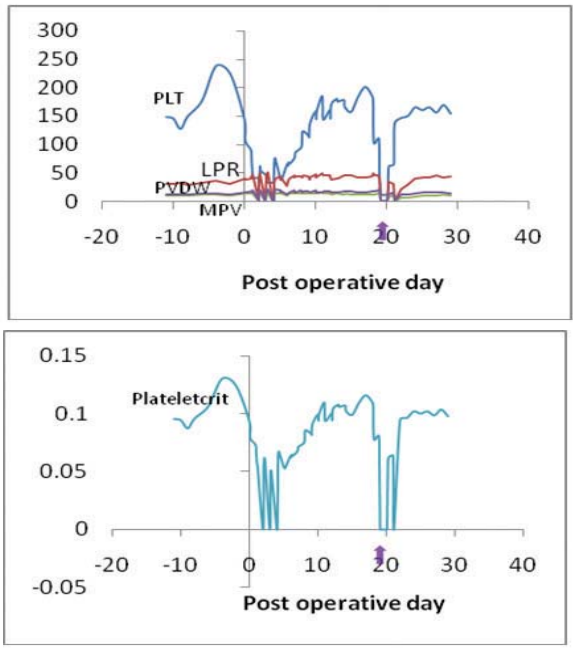
In the second case (Figure2), platelet counts did not recover as expected by day 5, but persisted at reduced levels (typically below 100×10^9/L) for more than 1 week. This is another possible (although apparently less common) platelet count presentation of HIT, described as pattern 2 by the same investigators[7] which is characterized by the feature of thrombocytopenia that becomes evident during, or that persists into, the second postoperative week. The platelet 4 parameters would also lower to zero abruptly and recover for many times when the platelet down to a low level at the beginning of post-operative day, and then even keep to zero for 2 days until the diagnosis of HIT and the using of non-heparin anti-coagulant argartroban. With the use of non-heparin anti-coagulant argartroban, the platelet count and platelet 4 parameters recover to a normal level. The arrow represent the starting time of using non-heparin anti-coagulant (Argartroban).

What the 2 cases share in common are the 4 platelet parameters' "trench phenomena", that is one of the platelet 4 parameters would lower to zero and recover many times, when the platelet count down to a low level, and then keep a relative steady high level when the platelet count reached a higher and stable level. At the same time, the trend of platelecrit curve is same with the platelet trend. But the other 3 platelet 4 parameters: LPR (large platelet ratio), PVDW (platelet volume distribution width) and

Table 1: The clinical data of the 2 cases adjudicated as having clinical heparin-induced thrombocytopenia (HIT) after cardiac surgery

Patient No.	1	2
Sex	Male	Female
Age(years)	75	65
The times platelet 4 parameters down to zero	9	3+three days' zero
Platelet count pattern	1	2
Type of operation	CABG	CABG
4T's score	5	6
Thrombotic event	Stroke and limbs thrombosis	Stroke and limbs thrombosis

Figure 1 The changing trend post and pre-operative day of platelet count and platelet 4 parameters: MPV (Mean platelet volume), LPR (Large platelet ratio), PVDW (Platelet volume distribution width), Plateletcrit in case 1. The blue curve shows the platelet count change of case 1 defined as pattern 1 by Pouplard and colleagues. The arrow represent the starting time of using non-heparin anti-coagulant (Argartroban). We set day 0 as the operation day.

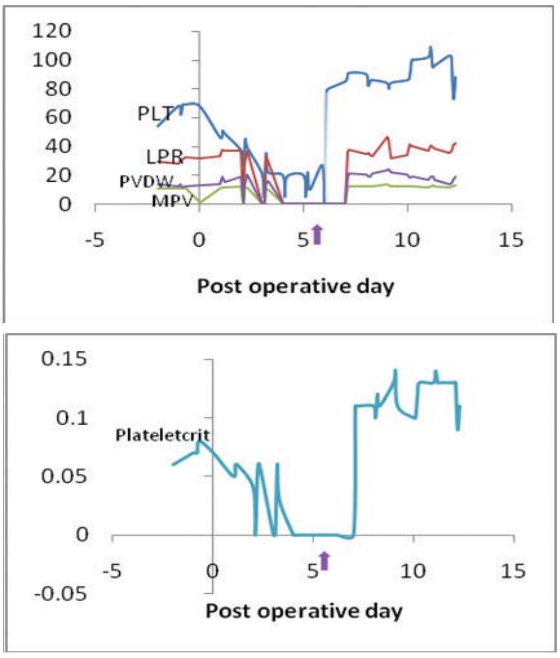


MPV (mean platelet volume) share the same trend of the changing curves.

Discussion

Circulating platelets are very different in size, metabolism, and functional activity. The largest are more reactive and produce a greater quantity of thrombogenic factors[8]. Automated counters provide platelet counts and generate the MPV and a measure of their size variability (PVDW). The MPV is useful also for monitoring recovery in thrombocytopenias because of an early increase with respect to the platelet concentration[9].Immune heparin-induced thrombocytopenia(HIT) is associated with antibodies directed against a complex of platelet factor 4 (PF4) and heparin. The reason that only a subset of patients with anti-PF4/heparin antibodies develops HIT still leaves us a paradox. Patients undergoing CPB have high circulating levels of both PF4 (560-750ng/mL) and heparin (3-4 Units/mL). When PF4 and UFH associate over a narrow range of molar ratios approximating 1:1, they formultra-large macromolecular complexes (ULCs,670 kDa). Assembly of macromolecular complexes is influenced profoundly by small changes in the stoichiometric ratio of PF4/heparin (PF4/heparin ratio or PHR)[10]. ULCs are more potent on a molar basis than smaller complexes in mediating the binding of HIT antibodies and causing heparin-dependent platelet activation in vitro. In this 2 cases, the 'trench phenomena' of LPR, PVDW and MPV downing to zero in the low level of platelet count may be due to that the larger ULCs bind to larger platelet preferentially because the larger platelet would have the suitable binding sites for the large ULCs. As for the smaller platelet, there would be little position for the binding process. After the complexes were finished and the large and active plateletsdie with new platelet were coming up, the platelet 4 parameters would increase again. But the reason why it increases so quickly is hard to explain. Is it the platelet system accustoming to the changing environment: vanishing quickly, then producing quickly? After all, this finding of the platelet 4 parameters' "trench phenomena" in the patients post cardiac-operation after cardio-pulmonary gives us a hint in discovering a clearer molecular mechanism of heparin-induced thrombocytopenia. Even, this phenomenon would be a strong predictor in diagnosing the heparin-induced thrombocytopenia especially among the patients post cardiac-surgery after cardio-pulmonary bypass. But all the clear mechanism and its clinical usage of the "trench phenomena" still need specific experiments and clinical trial to prove.

Figure 2 The changing trend post and pre-operative day of platelet count and platelet 4 parameters: MPV (Mean platelet volume), LPR (Large platelet ratio), PVDW (Platelet volume distribution width), Plateletcrit in case 2. The blue curve shows the platelet count change of case 2 defined as pattern 2 by Pouplard and colleagues. The arrow represent the starting time of using non-heparin anti-coagulant (Argartroban).We set day 0 as the operation day.



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张剑

云南省宣威市中医院麻醉科，宣威655400

摘要

声带息肉是耳鼻喉科的常见病，近年来发病率明显增加，多需手术治疗。支撑喉镜下行声带息肉摘除术手术时间较短，患者痛苦较少，越来越多的被临床采用，但因其对咽喉部刺激较强，要求声门显露满意，对麻醉有较高的要求。必须有较深的麻醉效果，否则会引起迷走神经反射、呛咳、支气管痉挛。单纯的表面麻醉难以配合。我院2007年以来采用全麻下支撑喉镜声带息肉摘除术，麻醉效果满意。

责任作者及联系方式：唐天云，Email：tangty1@hotmail.com

关键字：麻醉处理；声带息肉摘除术；支撑喉镜

支撑喉镜下声带息肉摘除术55例麻醉处理

The Anesthesia Management for Vocal Cord Polypectomy under Suspension Laryngoscope on 55 Cases

Jian Zhang

Department of Anesthesiology, Xuanwu Traditional Chinese Medicine Hospital, Yun'nan Province, 655400

Abstract

Vocal polyp is the common disease in otolaryngology. In recent years, the incidence of vocal polyp increases obviously and it is generally cured by surgery. The surgery time of vocal cord polypectomy under suspension laryngoscope is very short and it could lessen the pain. The surgery is widely adopted by the clinical treatment, but it has strong stimulation on the throat with satisfactory glottis visualization and high anesthetic effects. Significant anesthetic effect is a must, if not it will cause vagus nerve reflex, choking and bronchospasm. Simple surface anesthesia can hardly cope with the surgery. Out hospital adopted general anesthesia surgery of vocal cord polypectomy under suspension laryngoscope and the anesthetic effects was satisfactory.

Key Words: Anesthesia management; Vocal cord polypectomy; Suspension laryngoscope

Corresponding Author: Tian-yun Tang, Email: tangty1@hotmail.com

一、资料与方法

1. 一般资料

支撑喉镜下声带息肉病例55例，男33例，女22例，年龄28-76岁，体重45-78kg，ASAⅠ-Ⅱ级，病程1个月-5年不等，声音嘶哑为主要症状。单侧声带息肉40例，双侧声带息肉15例，55例术后病理检验报告均为声带息肉。

2. 麻醉方法

采用全身麻醉，小直径气管导管插管。患者入手术室后监测ECG、BP、HR、RR、SpO_2、$Petco_2$，建立外周静脉通道。术前15min给阿托品0.5ng静脉注射，声门喷洒2%利多卡因注射液3ml行表面麻醉。麻醉诱导依次静注芬太尼0.2mg，丙泊酚2-3mg/kg，维库溴铵0.1mg/kg，地塞米松10mg，面罩给氧去氮，过度通气，3min后以喉镜挑起会厌明视下气管插管，男性选用气管导管内径6.5-7.0号，女性选用气管导管内径6.0-6.5号，固定气管导管后接麻醉机行机控呼吸，呼吸频率为12-14次/分，潮气量为8-10ml/kg，气道内压力12-15CmH_2O，$Petco_2$为26-30mmHg，吸呼比（I:E）=1:2，SpO_2维持在99-100%。术中以丙泊酚5-8mg/kg/h和瑞芬太尼0.2-0.3ug/kg/min维导麻醉深度。声带息肉摘除后停止使用麻醉药，常规拮抗肌松剂。

二、结果

所有手术插管顺利，听诊双肺呼吸音清晰，建立了有效的气道。支撑喉镜下声门显露满意，声带保持静止。术中患者未出现应激反应，心率及血压维持在正常范围。患者于手术结束后3-5min内恢复自主呼吸，咽喉反射恢复良好，苏醒快，意识清醒，拔管后通气功能正常，无喉痉挛发生。术后随访55例声带息肉患者的声嘶症状完全消失，所有病例无并发症出现，效果良好。

三、讨论

声带息肉均在支撑喉镜下进行，放置支撑喉镜是刺激性很强的操作。往往引起血压急剧上升，手术时间短。既要求麻醉深度适宜，视野清晰，口腔必须保持开放状态，无咽喉不良反应，要求患者术后清醒快，保持良好通气，丙泊酚是新型的速效、短效、强效，适用范围广的静脉麻醉药。除孕、产妇及1月以下婴幼儿外均可使用。起效时间为30-40秒，用药2分钟后达到峰值，其清除率极高，为1.5-2.2L/min。对中枢的主要作用是镇静、遗忘，但能达到短时间镇痛。它也具有一定程度的呼吸抑制，尤其是与阿片类镇痛药复合使用时，其抑制交感神经反射的效应可抑制气管插管及上支撑喉镜的心血管应激反应。丙泊酚诱导迅速，术中麻醉深度易控制，血压波动较小，术后苏醒快。无肌肉不自主运动，咳嗽、呃逆等副作用[1]，无精神症状。瑞芬太尼是新型的短效阿片类镇痛药。静脉注射后起效迅速，药效消失快。经过组织和血浆中的非特异性酯酶迅速水解代谢，其底物效价仅为原来的0.1-0.3%，代谢产物无生物活性，重复及持续输注在体内无畜积现象。其作用时间短，时效半衰期为3-10min。清除率为40ml/kg/min，且不受体重、性别或年龄的影响。瑞芬太尼是强效的呼吸抑制剂，主要表现为呼吸驱动力的减弱，呼吸时间延长，呼吸频率减慢，其呼吸抑制程度输注与输注剂量有关，但停止输注后3-5min恢复自主呼吸。瑞芬太尼有很强的镇痛作用，可减弱及消除气管插管引起的躯体及自主神经反射，使患者能耐受气管插管，稳定血压的同时也减慢麻醉过浅的心动过速。

采用丙泊酚和瑞芬太尼持续静脉泵入行全麻下支撑喉镜声带息肉摘除术，不良反应少，能保持血流动力学的平衡，维持良好的麻醉效果。既保障良好的通气，能够完全抑制气管不良反射，满足手术要求，又可使患者迅速苏醒，保护反射迅速恢复，缩短术后拔管时间。

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“岁月鉴经典，凝聚创辉煌”

——2012北京医学会麻醉学分会学术年会会议纪要


北京医学会麻醉学分会第十一届委员会和部分老委员合影


北京医学会麻醉学分会第十一届委员会正副主任委员合影

作为北京医学会成立90周年系列活动之一，一年一度的“2012北京医学会麻醉学分会学术年会”于2012年7月13日至14日在北京国际会议中心举行，北京地区将近1600余麻醉医生参与本次大会。会议的特点体现在：

1. 面向国际，继续推进北京麻醉学会的国际化步伐

与韩国首尔麻醉学会举行第三届北京-首尔麻醉研讨会。本次研讨会由首尔麻醉学会现任学会会长柳建熙教授率团参加，前任会长具吉会教授以及韩国麻醉学会会长朴忠民教授也莅临本次会议。来自首尔市大学医院麻醉科的教授们给予了涵盖产科、超声引导下疼痛治疗等方面的精彩讲座。特邀的韩国教授采用韩语演讲，会场内配发韩语、汉语幻灯演示以及韩语同声翻译，以使讲者充分表达演讲的内容。担任韩语同声翻译人员均来自北京各大医院的麻醉科医生，充分展示了北京的人才储备实力。

2. 学术板块内容多元化，充分展示北京麻醉学会的学术实力

北京医学会麻醉学分会的学术年会从2006年起，将分会场从1个增加至5个，学术板块从4个增加至20个，学术板块按照学术内容分为多个亚专业，其中设立1个中青年论坛板块，以充分展示北京中青年麻醉医师的风采；另外设立3个病例讨论专场，以加强北京地区复杂病例的临床思维和诊治能力。

各版块的学术内容讲题由北京麻醉学会各位在各亚专业领域的著名麻醉专家组织，其内容几乎涵盖当年最新的麻醉进展，讲者从老专家到中青年麻醉医生，充分展示了北京雄厚的学术实力。

3. 连续多年设立Workshop单元，推动临床麻醉技能培训

北京每年的学术年会期间均设立Workshop单元，今年的单元内容为困难气道培训，培训教师由具有丰富困难气道处理经验的麻醉专家担任，有将近100余名麻醉医生接受了系列困难气道的理论以及临床技能以训练。

4. 会场展区设立麻醉图书售卖区，展示北京麻醉专家的治学风采

为了更好展示北京麻醉专家的治学精神以及大家风采，每年北京麻醉学会均邀请各大出版社参与北京麻醉年会期间的麻醉图书售卖，这些图书中有相当部分图书为北京麻醉专家近几年出版的专著、译作和教材，充分展示北京麻醉界的学术实力，并且激发年轻麻醉医生奋发向上的精神。

5. 北京医学会麻醉学分会实现顺利换届

2012年为北京医学会麻醉学分会换届年，经过前期所有委员的充分沟通、协商及准备，按照北京医学会的换届管理组织规定，7月13日下午在北京五洲皇冠假日酒店第八会议室，由北京医学会金大鹏会长主持举行了“北京医学会麻醉学分会第十一届委员会的换届选举会”及第一次工作会议。

为了进一步推动大北京地区麻醉事业的发展，本届专业委员会将委员名额从上届29名增加至39名，增加的名额大部分分配给郊区县医院、厂矿医院、中医系统代表以及军队三甲医院，以充分容纳更多优秀麻醉专家进入麻醉学会，推动北京麻醉事业的平衡发展。

经过民主选举，本次会议选举产生了以北京协和医院黄宇光教授为主任委员、以解放军总医院米卫东教授、北京同仁医院李天佐教授、北京大学第三医院郭向阳教授、北京宣武医院王天龙教授、北京友谊医院田鸣教授为副主任委员等39位麻醉专家的新一届委员会，前任主任委员岳云教授为名誉主委，在第一次工作会议上，金大鹏会长对本届委员会未来工作给予了很大的期望，希望本届学会能在前面学会工作的基础上，搭建更大的学术平台，充分调动北京市的专家资源，提出更高的工作目标，力争引领全国。

在年会的闭幕晚宴上，岳云教授对北京医学会麻醉学分会第十届麻醉专业委员会的工作进行了回顾和总结，黄宇光教授发表就职感言，老主委李树人教授发表寄语，体现老一辈麻醉专家对北京麻醉事业的期望。北京麻醉学会历任部分主任委员李树人教授、王恩真教授、吴新民教授、叶铁虎教授、岳云教授与学会领导、全体委员、中青年委员以及部分老专家共同出席交接仪式。

北京医学会麻醉学分会在迎来北京医学会成立90华诞之际，将继续以“岁月鉴经典，凝聚创辉煌”的精神和意志，发挥北京麻醉学会团队的力量，推动北京麻醉学会的更大发展。


北京医学会麻醉学分会第十一届全委会第一次工作会场

《2012年中国医疗器械最具竞争力企业10强》竞争力报告

实力的显示：评选数据监测结果及分析

主　办：上海市生物医学工程学会　医疗信息研究院
主　编：范关荣　中华医学会理事
副主编：于布为　中华医学会麻醉学分会主任委员　　祁　吉　中华医学会放射学分会原主任委员　　康熙雄　中国医院协会临床实验室委员会主任委员
　　王新房　中华医学会超声学会名誉主任委员　　陈宪敏　上海医学会放射学分会原主任委员

2011-2012年度中国医疗器械企业竞争力评比体系构成的指标权重和其反映的意义及价值

指标	因素	子因素	指标名称	指标权重	指标性质及主要意义	可反映的其他含义和影响
医疗器械企业竞争力综合指标	直接计量指标（财务数据硬指数）权重为70%	规模子因素	销售收入	26%	规模	市场份额
			净资产	6%	资本实力	融资能力
			净利润	12%	盈利水平	规模
		效率子因素	总资产利润率	11%	资金利用效率	负债的影响，融资能力
			净资产收益率	11%	资本盈利和增值能力	负债的影响
			全员劳动贡献率	5%	员工劳动效率	销售收入及冗员
		增长子因素	近三年销售收入平均增长率	15%	业务增长	市场份额、成长性
			近三年净利润平均增长率	14%	持续盈利能力	成长性
				合计：100%		
	间接计量指标（软指数）权重为30%		技术创新	34%	长期发展潜力和潜在的技术竞争力	技术密集程度和技术优势
			客户满意度	18%	反映客户忠诚度和市场份额的变化	企业长期的盈利能力和员工满意度
			品牌知名度	12%	公司品牌形象	吸引人才竞争中的优势
			企业家及管理水平	11%	整合，分配企业资源的能力	驾驭外部环境和获取外部资源的能力
			企业文化	25%	企业凝聚力和员工对组织的认同感和忠诚度	企业持续发展的能力和组织动员能力
				合计100%		

《2011-2012年度中国医疗器械最具竞争力企业10强》评选活动工作总结

我们从2008年起进行中国医疗器械企业竞争力检测项目，目前已经对中国医疗器械企业的竞争力连续进行了四年的检测。通过对中国医疗器械企业竞争力的检测，发现中国医疗器械企业竞争力的现状和变化趋势，以及同医疗器械企业竞争力相关的重要现象和问题，从而能更好地帮助医疗器械企业提升竞争力。

本年度的中国医疗器械企业竞争力报告以2011年中国医疗器械企业竞争力检测结果为背景，专注于探讨中国医疗器械企业创新对企业竞争力的影响。中国医疗器械企业竞争力研究一直有两个方向，即医疗器械企业竞争力表现的测评与企业竞争力源泉的探求。当然这两方面也不是完全独立，在检测过程中可能会发现一些新问题，从而促进我们进一步研究医疗器械企业竞争力来源；对医疗器械企业竞争力来源进行研究的过程，也有助于我们对竞争力的概念及表现进行深入的理解，从而更好地进行医疗器械企业竞争力的检测和形成更科学的检测方法。

经过几年来的海外市场拓展及推广，“年度中国医疗器械竞争力报告”得到了海外人士的极大关注及认同；评选数据及结果纷纷被引用和参考。2012年中国医疗器械企业竞争力报告除每年的医疗器械企业竞争力检测结果分析和行业市场分析报告之外，今年的研究主题是中国医疗器械企业创新与企业竞争力的影响。

研究结果显示：我国医疗器械企业研发投入不足的主要原因之一是研发过程不确定性过高。我国目前医疗器械企业规模较小，难以通过多个项目的研发分散风险，孤注一掷的研究投资几近赌博，投错项目方向的事例和公司不在少数，与我们民族文化中力求规避风险传统不符，因而在目前阶段，国家强调企业为自主创新主体时，尚需加大基础研究的力度，鼓励产学研的结合；目前还需发挥医疗器械行业协会的作用，对单个企业无力承担的项目，组织有关单位进行联合攻关，研究风险共担，成果共享。更应该加大风险投资的力度，使企业的新产品研发更有活力。

此外，采取措施保护医疗器械企业的知识产权，维护企业创新收益是必需的，研究结果表明医疗器械企业研发不足的原因还在于研发收益的不确定性。研发收益的不确定性有其必然性的一面。但由于我国知识产权保护不力，也加大了医疗器械企业研发收益的不确定性。因而激励企业自主创新的主要外部条件之一，是必须有严格的知识产权保护制度。

最后更重要的是，加大人才培养力度，降低医疗器械企业高层次人才的成本。研究报告分析了我国医疗器械企业多采取低成本战略的重要原因之一是企业生产高质量产品的成本高于国外医疗器械企业。我国医疗器械企业生产高质量产品成本高的重要原因之一是企业使用高质量人才的成本过高。例如，我国目前医疗器械企业支付员工工资的一部分不能在税前扣除，而必须计入应税额中。企业不能在税前将付给高素质劳动者工资完全扣除，而必须在税后列支（实际操作是不能在税前抵扣，效果相当于在税后列支），这种做法加大了医疗器械企业使用高素质劳动力的成本，特别是对于大量使用高素质人才进行研发的医疗器械企业，加大了医疗器械企业研发的成本。这一问题不彻底解决，中国医疗器械企业的技术创新将受到极大地限制，更不利于中外医疗器械企业之间的公平竞争。

中国医疗器械企业竞争力的提升最重要的莫过于对主业的关注。与大家分享我们的调研结果，目的只有一个：看看市场已经发生了的事实，分析最具竞争力的医疗器械企业如通用、西门子等企业，怎么应对外界环境的变化，从理论的高度概括总结出我们的医疗器械行业应该如何去思考，如何在专注主业的基础上付诸实践。

最后，我谨代表《年度中国医疗器械市场最具竞争力企业10强》评审委员会和组委会全体工作人员感谢业界同仁过去四年给予此项评选活动的支持与关注。我们将在未来一年里一如既往地为行业传递最前沿和最宝贵的信息，为提升中国医疗器械行业竞争力贡献自己的力量！

中华医学会理事
医疗信息研究院院长
二零一二年七月

范关荣

The competitiveness report on "the Top 10 competitiveness enterprises in the medical devices industry of China during 2011-2012"

The strength show: the monitoring results and analysis of the evaluation data

The significance and value of the competitiveness evaluation system for the top 10 competitiveness enterprises in the medical devices industry of China during 2011-2012

Index	Factors	Sub-factors	Names of index	Weight of index	Qualities and essences of index	Other meanings and effects reflected
Comprehensive competitiveness index of medical devices enterprises	Standard value weighted of the direct data(fundamental index for the financial data) 70% weight	Scale sub-factors	Sales revenues	26%	Scale	Market share
			Net assets	6%	Capital strength	Financing capacity
			Net profit	12%	Profitability	Scale
		Efficiency sub-factors	Return on total assets	11%	Capital utilization efficiency	Liability influences, financing capacity
			Return on net assets	11%	Technical profit and added value ability	Liability influences
			Sales revenues contribution per employee	5%	Labor efficiency	Sales revenue and redundant personnel
		Increase sub-factors	The average growth rate of sales revenues for the last three years	15%	Business growth	Market share and growth
			The average growth rate of net profit for the last three years	14%	Sustained profitability	Growth
				Total:100%		
	Standard value weighted of indirect data(the survey data) 30% weight		Technology innovation	34%	The potential for long-term development and technical competitiveness	Technological intensity and superiority
			Customer satisfaction	18%	Reflect and customer loyalty and changes of market share	Long-term profitability and employees' satisfaction of the enterprise
			Brand awareness	12%	Brand image	Competitive advantages on attracting more talents
			Management level of enterprise	11%	Abilities on integrating and allocating enterprise resources	Abilities on managing the external environment and access external resources
			Corporation culture	25%	Cohesive force in enterprise and employees' identity and loyalty on the organization	Capacities on sustainable development and organization and mobilization
				Total:100%		

Since 2008, we have carried out the testing program of the competitiveness enterprises in the medical devices industry of China, which has been done for 4 years. By means of testing, we can discover the current situation and changing trend of the competitiveness enterprises in the medical devices industry of China and the important phenomenon and problems related to the competitiveness of medical devices industry, which could preferably help the medical devices enterprises to promote their competitiveness.

2012's report on the competitiveness enterprises in the medical devices industry of China, which is in the context of the testing results in 2011, is concentrated on the influence of innovation in China medical devices enterprises on their competitiveness. There are always two directions of the research on the competitiveness enterprises in the medical devices industry of China, namely, evaluations on the performance of the competitiveness in the medical devices enterprises and exploration on the source of enterprises competitiveness. Surely, the two directions are not entirely independent with each other. In the process of testing, we will probably find some new problems, thus contributing to our further study on the source of the competitiveness in the medical devices enterprises. The process of the study on the resource of enterprises competitiveness is also helpful to our deep understanding on the conception and expression of the competitiveness, which could better test the competitiveness of medical devices enterprises and form a more scientific testing method.

After years of overseas marketing and promotion, the competitiveness report on "Top 10 competitiveness enterprises in the medical devices industry of China" has gained great concerns and recognitions overseas. The evaluation data and results in the report have been cited and referred widely. 2012's report on the competitiveness enterprises in the medical devices industry of China includes not only every year's competitiveness testing results and market analysis report in the medical devices industry, and also the subject in this year that is the influence of innovation from the Chinese medical devices enterprises on the competitiveness.

The results show that one of the main reasons why China medical devices enterprises have inadequate investment in R&D is that the uncertainty in the procedure of R&D is too high. At present, the scale of China medical devices enterprises is too small to spread the risk with R&D in multiple projects. The desperate research investments nearly like a gamble, and many companies make a wrong direction of the project, which is inconsistent with the traditions that striving to avoid risks in our national culture. At the present time, when stressing enterprises as the main bodies of independent innovation, the government still needs to make more investment in fundamental research and encourage the combination of production, teaching and research. The government also needs to urge the Industry Institution of Medical Devices to play its role and organize related units to conduct the projects with joint efforts that the single enterprise cannot afford, which forms risk sharing and achievements sharing. The government should also intensify the strength of risk investment, and enable the R&D of new products in enterprises more dynamical.

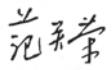
In addition, it is necessary to take measures to protect the intellectual property in the medical devices enterprises and preserve their innovation profits. The results show that the reasons that China medical devices enterprises have inadequate investment in R&D also lie in the uncertainty of the R&D profits. The uncertainty has its inevitability. But the lacking in protection of intellectual property also enlarges the uncertainty of the R&D profits in the medical devices enterprises. Therefore one of the main external conditions in encouraging enterprises to improve independent innovation is to have strict intellectual property protection system.

In the end, the most important is to strengthen the efforts in personnel training and lower the costs of high-qualified talents in medical devices enterprises. The report analyzes that one of the most important reasons why most of China medical devices enterprises adopt low-cost strategy is that the cost of producing high-quality products is higher than that in foreign medical devices enterprises. The reason that the high cost of China medical devices enterprises producing high-quality products is because of the high cost of employing high-qualified talents. For example, currently part of the salaries which China medical devices enterprises pay for staffs cannot be taken off before the tax, but have to be included in the tax. Enterprises cannot entirely take off the salaries paying for the high-qualified talents before the tax, but to be disbursed from the cost and dispenses after the tax (the practical operation cannot be deducted before the tax; the effects are equal to be disbursed from the cost and dispenses after the tax). This practice increases the cost of medical devices enterprises employing high-qualified talents, especially those who employ many high-qualified talents to do R&D and also increases the cost of the R&D in medical devices enterprises. If this problem cannot be resolved completely, the technological innovation of China medical devices enterprises will be restricted greatly, which is against the fair competition between Chinese and foreign medical devices enterprises.

The key to upgrading the competitiveness in China medical devices enterprises is mainly to focus on their main business. The only purpose of sharing our research results is to see the fact having taken place in the market, analyze the competitive medical devices enterprises, such as GE healthcare and Siemens Medical, how to deal with the changes in the external environment, and summarize theoretically that how the medical devices enterprises should think, and how they should practice on the basis of focusing on their main business.

In the end, on behalf of all staff of Accreditation Committee and Organizing Committee of "the Top 10 competitiveness enterprises in China medical devices industry", I extend my greetings to all the colleagues in this industry for your support and concern on the selection in the last 4 years. In the coming year, we will transmit the forefront and precious industry information as always, and contribute to improving the competitiveness of China medical devices industry!

Director of the Chinese Medical Association
Dean of Medical Information Research Institute
July, 2012 Guan-rong Fan



一、《2011－2012年度中国医疗器械麻醉与监护领域最具竞争力企业10强》榜单

2011-2012年度中国医疗器械麻醉与监护领域最具竞争力企业10强榜单

公司	排名	直接计量硬指标财务数据加权标准值（权重为70%）									间接计量软指标加权标准值（权重为30%）						竞争力综合指数 (A*70%+B*30%)	竞争力综合得分	数据来源
		销售收入 权重26%	净资产 权重6%	净利润 权重12%	总资产利润率 权重11%	净资产收益率 权重11%	全员劳动贡献率 权重5%	近三年销售收入平均增长率 权重15%	近三年净利润平均增长率 权重14%	直接计量硬指标财务数据加权标准值合计 (A)	技术创新 权重34%	客户满意度 权重18%	品牌知名度 权重12%	企业家及管理水平 权重11%	企业文化 权重25%	间接计量软指标加权标准值合计 (B)			
通用	1	1.1678	0.0763	0.4406	－0.1927	0.0013	0.0157	－0.0080	－0.0460	1.4550	0.7594	0.5052	0.6398	0.2671	0.5627	2.7342	1.8388	1000	上市公司年报
德尔格	2	1.0451	0.0049	0.0828	0.0707	0.0944	0.0143	－0.0040	0.1400	1.4482	0.6586	0.6005	0.6062	0.2686	0.5433	2.6772	1.8169	995	上市公司年报
飞利浦	3	0.9265	0.2073	－0.0244	0.0660	0.0178	0.0075	－0.0075	0.0762	1.2694	0.5382	0.5348	0.5536	0.2795	0.6236	2.5297	1.6475	983	上市公司年报
迈瑞	4	1.0349	0.0022	0.0094	0.1085	0.0527	－0.0004	0.0053	0.0012	1.2138	0.4577	0.6224	0.6319	0.2696	0.3272	2.3088	1.5423	981	上市公司年报
日本光电	5	－0.0758	－0.0055	－0.0231	0.0909	0.0519	0.0147	－0.0070	－0.0271	0.0190	0.4534	0.1540	0.1561	0.1658	0.5054	1.4347	0.4437	900	上市公司年报
力康	6	0.0014	－0.0212	－0.0423	0.0733	0.0105	－0.0037	－0.0026	－0.0252	－0.0098	0.2472	0.2465	0.2569	0.2677	0.3169	1.3352	0.3937	898	当地公布的税务资料、行业咨询研究资料、企业自报数据和医院及医疗机构采购招标结果
宝莱特	7	－0.0885	－0.0211	－0.0433	0.0612	－0.0120	－0.0033	0.0011	0.0475	－0.0584	0.9153	0.2052	0.1947	0.1556	0.2658	1.1366	0.3001	892	上市公司年报
上海医疗器械	8	－0.1103	－0.0208	－0.0454	0.0482	－0.0222	－0.0024	－0.0027	0.0048	－0.1508	0.2287	0.2088	0.2049	0.2210	0.1938	1.0572	0.2116	884	母公司上市年报
谊安	9	－0.0669	－0.0217	－0.0456	0.0235	－0.0360	－0.0037	－0.0033	0.0001	－0.1536	0.2494	0.1852	0.1955	0.1971	0.1995	1.0267	0.2005	883	当地公布的税务资料、行业咨询研究资料、企业自报数据和医院及医疗机构采购招标结果
理邦	10	－0.1167	－0.0184	－0.0431	－0.0227	－0.0688	－0.0039	0.0054	－0.0251	－0.2933	0.2182	0.2056	0.2187	0.1975	0.2424	1.0824	0.1194	861	上市公司年报

注1：关于销售收入指标数据，由于所参选企业的销售收入来自其众多产品的销售收入，我们因此所采集的数据是以医疗器械各子领域榜单相关的产品在中国市场的收入作为销售收入。例如：放射领域榜单的销售收入数据采集自各企业其放射产品在中国市场的销售收入。

注2：净利润所采用的数据是该参选企业各子领域相关产品的净利润，如果该公司的年报未体现相关数据，我们将采用该公司整体的利润率按产品贡献比例来推算。

注3：其余的六个评选指标（净资产，总资产利润率，净资产收益率，全员劳动贡献率，近三年销售收入平均增长率，近三年净利润平均增长率）的数据采用将以该参选企业对外公布整体业绩所提供的相关指标为参考标准，不再作细别区分。

注4：净资产收益率有不同的定义方式，为了避免因为上市公司与非上市公司企业所得税税率不同而造成的净利润不可比的问题，我们因此将公式中的分子定义为利润总额而非净利润，计算净资产收益率的公式为：净资产收益率=利润总额/净资产

注5：从监测数据中可以发现，如果企业竞争力主要来源于增长类指标（即近三年销售收入平均增长率&近三年净利润平均增长率），企业竞争力监测指数往往是不稳定的。造成这些企业竞争力不稳定的主要原因是：这些企业原来的销售收入的基数很小，近两年销售增加后会使企业近三年的销售收入平均增长率很高，从而远高于所在行业企业的平均水平。企业可能由于一个指标标准值的异常偏高而使该企业的竞争力基础数据的标准值整体很高。但在第二年或第三年，当该企业的销售收入增长率降到正常的平均水平，而其他指标却没有更高的增长时，该企业的竞争力监测指数就会显著下降。为了避免由于某一个财务指标的异常变动而影响企业竞争力评选结果的客观性，我们进行了一个可行的改进方法，对增长类指标（近三年销售收入平均增长率、近三年净利润平均增长率）的标准值设定上下限[1,-1]，并通过统一的一致性检验，从而可以避免由于某一个增长类指标标准值的异常而对硬指标基础数据标准值产生过大影响。

Ranking of Top 10 competitiveness enterprises in China medical devices industry during 2011-2012

1. Ranking of Top 10 competitiveness enterprises in the anesthesia and monitoring field of China medical devices industry during 2011-2012

Rankings of Top 10 competitiveness enterprises in the anesthesia and monitoring field of China medical devices industry during 2011-2012

Company	Ranking	Standard value weighted of the financial data(70% weight)									Standard value weighted of the survey data (30% weight)						Comprehensive index of competitiveness (A*70%+B*30%)	Comprehensive score of competitiveness	Source of financial data
		Sales revenues weight 26%	Net assets weight 6%	Net profit weight 12%	Return on total assets weight 11%	Return on net assets weight 11%	Sales revenues contribution per employee weight 5%	The average growth rate of sales revenues for the last three years weight 15%	The average growth rate of net profit for the last three years weight 14%	Total standard value weighted of the financial data (A)	Technology innovation weight 34%	Customer satisfaction weight 18%	Brand awareness weight 12%	Management level of enterprise weight 11%	Corporation culture weight 25%	Total standard value weighted of the survey data (B)			
GE Healthcare	1	1.1678	0.0763	0.4406	－0.1927	0.0013	0.0157	－0.0080	－0.0460	1.4550	0.7594	0.5052	0.6398	0.2671	0.5627	2.7342	1.8388	1000	Annual report of listed company
Draeger Medical	2	1.0451	0.0049	0.0828	0.0707	0.0944	0.0143	－0.0040	0.1400	1.4482	0.6586	0.6005	0.6062	0.2686	0.5433	2.6772	1.8169	995	Annual report of listed company
Philips Healthcare	3	0.9265	0.2073	－0.0244	0.0660	0.0178	0.0075	－0.0075	0.0762	1.2694	0.5382	0.5348	0.5536	0.2795	0.6236	2.5297	1.6475	983	Annual report of listed company
Mindray	4	1.0349	0.0022	0.0094	0.1085	0.0527	－0.0004	0.0053	0.0012	1.2138	0.4577	0.6224	0.6319	0.2696	0.3272	2.3088	1.5423	981	Annual report of listed company
Nihon Kohden	5	－0.0758	－0.0055	－0.0231	0.0909	0.0519	0.0147	－0.0070	－0.0271	0.0190	0.4534	0.1540	0.1561	0.1658	0.5054	1.4347	0.4437	900	Annual report of listed company
Heal Force	6	0.0014	－0.0212	－0.0423	0.0733	0.0105	－0.0037	－0.0026	－0.0252	－0.0098	0.2472	0.2465	0.2569	0.2677	0.3169	1.3352	0.3937	898	Taxation、research & survey information；self-reported figures and hospital's tender results
Biolight	7	－0.0885	－0.0211	－0.0433	0.0612	－0.0120	－0.0033	0.0011	0.0475	－0.0584	0.9153	0.2052	0.1947	0.1556	0.2658	1.1366	0.3001	892	Annual report of listed company
Shanghai Medical Instruments	8	－0.1103	－0.0208	－0.0454	0.0482	－0.0222	－0.0024	－0.0027	0.0048	－0.1508	0.2287	0.2088	0.2049	0.2210	0.1938	1.0572	0.2116	884	Annual report of listed parent company
Aeonmed	9	－0.0669	－0.0217	－0.0456	0.0235	－0.0360	－0.0037	－0.0033	0.0001	－0.1536	0.2494	0.1852	0.1955	0.1971	0.1995	1.0267	0.2005	883	Taxation、research & survey information；self-reported figures and hospital's tender results
Edan	10	－0.1167	－0.0184	－0.0431	－0.0227	－0.0688	－0.0039	0.0054	－0.0251	－0.2933	0.2182	0.2056	0.2187	0.1975	0.2424	1.0824	0.1194	861	Annual report of listed company

Note 1: (About revenues) Because some enterprises have lots of products in different fields, the revenues here refer to one enterprise's sales revenues in China market in special sub-field of medical devices industry. For example: the revenues in the list of the radiology field are the sales revenues of enterprises' radiation products in China market.

Note 2: (About net profit) The indicator refers to the net profit of one enterprise's related products in a special sub-field. If the annual report didn't show the related data, we will calculate it from the total profit rate and products contribution proportion of the enterprise.

Note 3: The other six indicators (net assets, return on total assets, return on net assets, revenues per employee, the average growth rate of revenues for the last three years, and the average growth rate of net profit for the last three years) refer to the related indicators data of overall performance published by the enterprise.

Note 4: The return on net assets has different definitions. In order to avoid the problem of the incomparable value of net income caused by the different income tax rate between listed companies and non-listed companies, we will definite the numerator as the total profit rather than the net profit, the formula for calculating The return on net assets is: The return on net assets = Total profit / Net assets

Note 5: The monitoring data shows that if the competitiveness of enterprises comes mainly from the growth indicators (that is, the average growth rate of revenues for the last three years & the average growth rate of net profit for the last three years), the index of enterprises competitiveness is often unstable. The main reason for this instability is that some enterprises with small original revenues base have rapidly increasing in sales revenues during the past 2 years, which makes the average growth rate of the past 3 years much higher than the industry average level. An extremely high index may cause the enterprises' overall competitiveness standard value of fundamental data improved significantly. But in the future 2 or 3 years, with the growth rate of sales revenues remaining average and other index without rapid increase, the monitoring data will fall. To avoid unfair competition due to this problem, we make some viable improvement by setting the indicator of growth index (the average growth rate of revenues and net profits for the last 3 years)into the limitation of [1,-1]. With the consistency of statistical test, the overdone impact on overall standard value of fundamental data by the abnormal data of growth index can be eliminated.

二、《2011－2012年度中国医疗器械放射领域最具竞争力企业10强》榜单

2011-2012年度中国医疗器械放射领域最具竞争力企业10强榜单

公司	排名	直接计量硬指标财务数据加权标准值（权重为70%）									间接计量软指标加权标准值（权重为30%）						竞争力综合指数	竞争力综合得分	数据来源
		销售收入	净资产	净利润	总资产利润率	净资产收益率	全员劳动贡献率	近三年销售收入平均增长率	近三年净利润平均增长率	直接计量硬指标财务数据加权标准值合计	技术创新	客户满意度	品牌知名度	企业家及管理水平	企业文化	间接计量软指标加权标准值合计			
		权重26%	权重6%	权重12%	权重11%	权重11%	权重5%	权重15%	权重14%	(A)	权重34%	权重18%	权重12%	权重11%	权重25%	(B)	(A*70%+B*30%)		
西门子	1	1. 1048	0. 2716	0. 1756	-0. 0311	0. 0221	0. 0645	-0. 1500	0. 0890	1. 5465	0. 7544	0. 5861	0. 6040	0. 2529	0. 6012	2. 7986	1. 9221	1000	上市公司年报
通用	2	1. 1258	0. 0662	0. 5617	-0. 0652	0. 0236	0. 0593	-0. 1500	-0. 0957	1. 5257	0. 7379	0. 6020	0. 6208	0. 2455	0. 5948	2. 8010	1. 9083	998	上市公司年报
飞利浦	3	0. 7037	0. 1971	-0. 0211	0. 0935	0. 0401	0. 0252	-0. 1500	0. 1400	1. 0285	0. 6996	0. 5540	0. 5726	0. 2274	0. 5702	2. 6238	1. 5071	987	上市公司年报
锐珂	4	0. 0798	-0. 0111	-0. 0088	0. 1317	0. 2513	0. 0330	-0. 1500	-0. 1125	0. 2134	0. 6452	0. 5192	0. 5387	0. 1447	0. 5226	2. 3704	0. 8605	947	母公司上市年报
东芝	5	0. 1426	0. 0044	0. 0290	-0. 0319	0. 1411	0. 0371	-0. 1500	-0. 0733	0. 0990	0. 6412	0. 4699	0. 4392	0. 1188	0. 4905	2. 1596	0. 7172	935	上市公司年报
日立	6	-0. 0925	-0. 0033	-0. 0265	0. 0179	-0. 0094	-0. 0314	0. 0229	0. 0480	-0. 0743	0. 7332	0. 4313	0. 4051	0. 2705	0. 6183	2. 4584	0. 6855	931	上市公司年报
爱克发	7	-0. 0615	-0. 0056	-0. 0129	-0. 0803	-0. 0697	0. 0315	-0. 1500	0. 1400	-0. 2085	0. 5698	0. 3979	0. 3584	0. 3592	0. 3692	2. 0545	0. 4704	919	上市公司年报
万东	8	-0. 0150	-0. 0304	-0. 0306	-0. 0008	-0. 0142	-0. 0153	-0. 1500	-0. 1215	-0. 3778	0. 4866	0. 4358	0. 4759	0. 2301	0. 3268	1. 9552	0. 3221	910	上市公司年报
岛津	9	-0. 0781	-0. 0185	-0. 0233	-0. 0024	-0. 0065	-0. 0314	-0. 1500	-0. 0952	-0. 4054	0. 6057	0. 3735	0. 4739	0. 1392	0. 4111	2. 0034	0. 3172	908	上市公司年报
新华医疗器械	10	-0. 2672	-0. 0298	-0. 4824	0. 0432	0. 0416	-0. 0009	0. 1500	0. 1400	-0. 4055	0. 4849	0. 3328	0. 3821	0. 2285	0. 2184	1. 6467	0. 2101	899	上市公司年报

注1：关于销售收入指标数据，由于所参选企业的销售收入来自其众多产品的销售收入，我们因此所采集的数据是以医疗器械各子领域榜单相关的产品在中国市场的收入作为销售收入。例如：放射领域榜单的销售收入数据采集自各企业其放射产品在中国市场的销售收入。
注2：净利润所采用的数据是该参选企业各子领域相关产品的净利润，如果该公司的年报未体现相关数据，我们将采用该公司整体的利润率按产品贡献比例来推算。
注3：其余的六个评选指标（净资产，总资产利润率，净资产收益率，全员劳动贡献率，近三年销售收入平均增长率，近三年净利润平均增长率）的数据采用将以该参选企业对外公布整体业绩所提供的相关指标为参考标准，不再作细别区分。
注4：净资产收益率有不同的定义方式，为了避免因为上市公司与非上市公司企业所得税税率不同而造成的净利润不可比的问题，我们因此将公式中的分子定义为利润总额而非净利润，计算净资产收益率的公式为：净资产收益率=利润总额/净资产
注5：从监测数据中可以发现，如果企业竞争力主要来源于增长类指标（即近三年销售收入平均增长率&近三年净利润平均增长率），企业竞争力监测指数往往是不稳定的。造成这些企业竞争力不稳定的主要原因是：这些企业原来的销售收入的基数很小，近两年销售增加后会使企业近三年的销售收入平均增长率很高，从而远高于所在行业企业的平均水平。企业可能由于一个指标标准值的异常偏高而使该企业的竞争力基础数据的标准值整体很高。但在第二年或第三年，当该企业的销售收入增长率降到正常的平均水平，而其他指标却没有更高的增长时，该企业的竞争力监测指数就会显著下降。为了避免由于某一个财务指标的异常变动而影响企业竞争力评选结果的客观性，我们进行了一个可行的改进方法，对增长类指标（近三年销售收入平均增长率、近三年净利润平均增长率）的标准值设定上下限[1,-1]，并通过统一的一致性检验，从而可以避免由于某一个增长类指标标准值的异常而对硬指标基础数据标准值产生过大影响。

2. Ranking of Top 10 competitiveness enterprises in the radiology field of China medical devices industry during 2011-2012

Rankings of Top 10 competitiveness enterprises in the radiology field of China medical devices industry during 2011-2012

Company	Ranking	Standard value weighted of the financial data(70% weight)									Standard value weighted of the survey data (30% weight)						Comprehensive index of competitiveness	Comprehensive score of competitiveness	Source of financial data
		Sales revenues	Net assets	Net profit	Return on total assets	Return on net assets	Sales revenues contribution per employee	The average growth rate of sales revenues for the last three years	The average growth rate of net profit for the last three years	Total standard value weighted of the financial data	Technology innovation	Customer satisfaction	Brand awareness	Management level of enterprise	Corporation culture	Total standard value weighted of the survey data			
		weight 26%	weight 6%	weight 12%	weight 11%	weight 11%	weight 5%	weight 15%	weight 14%	(A)	weight 34%	weight 18%	weight 12%	weight 11%	weight 25%	(B)	(A*70%+B*30%)		
Siemens Healthcare	1	1. 1048	0. 2716	0. 1756	-0. 0311	0. 0221	0. 0645	-0. 1500	0. 0890	1. 5465	0. 7544	0. 5861	0. 6040	0. 2529	0. 6012	2. 7986	1. 9221	1000	Annual report of listed company
GE Healthcare	2	1. 1258	0. 0662	0. 5617	-0. 0652	0. 0236	0. 0593	-0. 1500	-0. 0957	1. 5257	0. 7379	0. 6020	0. 6208	0. 2455	0. 5948	2. 8010	1. 9083	998	Annual report of listed company
Philips Healthcare	3	0. 7037	0. 1971	-0. 0211	0. 0935	0. 0401	0. 0252	-0. 1500	0. 1400	1. 0285	0. 6996	0. 5540	0. 5726	0. 2274	0. 5702	2. 6238	1. 5071	987	Annual report of listed company
Carestream Healthcare	4	0. 0798	-0. 0111	-0. 0088	0. 1317	0. 2513	0. 0330	-0. 1500	-0. 1125	0. 2134	0. 6452	0. 5192	0. 5387	0. 1447	0. 5226	2. 3704	0. 8605	947	Annual report of listed parent company
Toshiba Medical	5	0. 1426	0. 0044	0. 0290	-0. 0319	0. 1411	0. 0371	-0. 1500	-0. 0733	0. 0990	0. 6412	0. 4699	0. 4392	0. 1188	0. 4905	2. 1596	0. 7172	935	Annual report of listed company
Hitachi Medical	6	-0. 0925	-0. 0033	-0. 0265	0. 0179	-0. 0094	-0. 0314	0. 0229	0. 0480	-0. 0743	0. 7332	0. 4313	0. 4051	0. 2705	0. 6183	2. 4584	0. 6855	931	Annual report of listed company
Agfa Healthcare	7	-0. 0615	-0. 0056	-0. 0129	-0. 0803	-0. 0697	0. 0315	-0. 1500	0. 1400	-0. 2085	0. 5698	0. 3979	0. 3584	0. 3592	0. 3692	2. 0545	0. 4704	919	Annual report of listed company
WanDong Medical	8	-0. 0150	-0. 0304	-0. 0306	-0. 0008	-0. 0142	-0. 0153	-0. 1500	-0. 1215	-0. 3778	0. 4866	0. 4358	0. 4759	0. 2301	0. 3268	1. 9552	0. 3221	910	Annual report of listed company
Shimadzu	9	-0. 0781	-0. 0185	-0. 0233	-0. 0024	-0. 0065	-0. 0314	-0. 1500	-0. 0952	-0. 4054	0. 6057	0. 3735	0. 4739	0. 1392	0. 4111	2. 0034	0. 3172	908	Annual report of listed company
SHINVA	10	-0. 2672	-0. 0298	-0. 4824	0. 0432	0. 0416	-0. 0009	0. 1500	0. 1400	-0. 4055	0. 4849	0. 3328	0. 3821	0. 2285	0. 2184	1. 6467	0. 2101	899	Annual report of listed company

Note 1: (About revenues) Because some enterprises have lots of products in different fields, the revenues here refer to one enterprise's sales revenues in China market in special sub-field of medical devices industry.
For example: the revenues in the list of the radiology field are the sales revenues of enterprises' radiation products in China market.
Note 2: (About net profit) The indicator refers to the net profit of one enterprise's related products in a special sub-field. If the annual report didn't show the related data, we will calculate it from the total profit rate and products contribution proportion of the enterprise.
Note 3: The other six indicators (net assets, return on total assets, return on net assets, revenues per employee, the average growth rate of revenues for the last three years, and the average growth rate of net profit for the last three years) refer to the related indicators data of overall performance published by the enterprise.
Note 4: The return on net assets has different definitions. In order to avoid the problem of the incomparable value of net income caused by the different income tax rate between listed companies and non-listed companies, we will definite the numerator as the total profit rather than the net profit, the formula for calculating The return on net assets is: The return on net assets = Total profit / Net assets
Note 5: The monitoring data shows that if the competitiveness of enterprises comes mainly from the growth indicators (that is, the average growth rate of revenues for the last three years & the average growth rate of net profit for the last three years), the index of enterprises competitiveness is often unstable. The main reason for this instability is that some enterprises with small original revenues base have rapidly increasing in sales revenues during the past 2 years, which makes the average growth rate of the past 3 years much higher than the industry average level. An extremely high index may cause the enterprises' overall competitiveness standard value of fundamental data improved significantly. But in the future 2 or 3 years, with the growth rate of sales revenues remaining average and other index without rapid increase, the monitoring data will fall. To avoid unfair competition due to this problem, we make some viable improvement by setting the indicator of growth index (the average growth rate of revenues and net profits for the last 3 years)into the limitation of [1,-1]. With the consistency of statistical test, the overdone impact on overall standard value of fundamental data by the abnormal data of growth index can be eliminated.

三、《2011－2012年度中国医疗器械超声领域最具竞争力企业10强》榜单

2011-2012年度中国医疗器械超声领域最具竞争力企业10强榜单

公司	排名	直接计量硬指标财务数据加权标准值（权重为70%）									间接计量软指标加权标准值（权重为30%）						竞争力综合指数	竞争力综合得分	数据来源
		销售收入	净资产	净利润	总资产利润率	净资产收益率	全员劳动贡献率	近三年销售收入平均增长率	近三年净利润平均增长率	直接计量硬指标财务数据加权标准值合计	技术创新	客户满意度	品牌知名度	企业家及管理水平	企业文化	间接计量软指标加权标准值合计			
		权重26%	权重6%	权重12%	权重11%	权重11%	权重5%	权重15%	权重14%	(A)	权重34%	权重18%	权重12%	权重11%	权重25%	(B)	(A*70%+B*30%)		
通用	1	0.8207	0.0729	0.5921	-0.1054	0.0125	0.1490	-0.0720	0.0061	1.4759	0.6919	0.6321	0.6375	0.2725	0.6224	2.8564	1.8901	1000	上市公司年报
飞利浦	2	0.9561	0.2039	-0.0220	0.0534	0.0290	0.0678	-0.0665	0.0624	1.2841	0.7011	0.5504	0.5511	0.2031	0.5101	2.5158	1.6536	986	上市公司年报
西门子	3	0.5199	0.2784	0.4164	-0.0713	0.0109	0.1615	-0.0687	0.0343	1.2814	0.5576	0.5541	0.5483	0.2281	0.5776	2.4657	1.6367	985	上市公司年报
迈瑞	4	0.2540	-0.0012	-0.0109	0.1158	0.0639	-0.0120	0.0616	0.0278	0.4990	0.3167	0.4711	0.4716	0.1688	0.2995	1.7277	0.8676	944	上市公司年报
百胜	5	0.2065	-0.0186	-0.0174	0.0743	0.0782	0.0727	-0.0287	0.0190	0.3860	0.3877	0.2913	0.2938	0.2369	0.4246	1.6343	0.7605	935	上市公司年报
日立阿洛卡	6	0.2972	0.0034	-0.0073	-0.0223	-0.0205	0.0824	-0.0096	0.0280	0.3513	0.3596	0.3396	0.3407	0.2042	0.3922	1.6363	0.7368	933	上市公司年报
东芝	7	0.1959	0.0111	-0.0133	-0.0721	0.1300	0.0962	-0.1044	0.0095	0.2529	0.3594	0.2601	0.2593	0.2101	0.5807	1.6696	0.6779	923	上市公司年报
三星麦迪逊	8	0.0819	-0.0234	-0.0237	-0.0293	-0.0115	0.0894	-0.0257	0.0168	0.0745	0.3645	0.3446	0.3458	0.2092	0.3974	1.6615	0.5506	907	母公司上市年报
蓝韵	9	0.0323	-0.0242	-0.0255	-0.0259	-0.0030	-0.0347	-0.0185	0.0156	-0.0839	0.2630	0.2441	0.2666	0.2951	0.2236	1.2924	0.3290	894	当地公布的税务资料、行业咨询研究资料、企业自报数据和医院及医疗机构采购招标结果
开立	10	-0.1374	-0.0451	-0.0364	0.1354	0.0880	-0.1542	0.0327	0.0286	-0.0884	0.4409	0.0952	0.0761	0.3304	0.3263	1.2689	0.3188	893	当地公布的税务资料、行业咨询研究资料、企业自报数据和医院及医疗机构采购招标结果

注1：关于销售收入指标数据，由于所参选企业的销售收入来自其众多产品的销售收入，我们因此所采集的数据是以医疗器械各子领域榜单相关的产品在中国市场的收入作为销售收入。例如：放射领域榜单的销售收入数据采集自各企业其放射产品在中国市场的销售收入。
注2：净利润所采用的数据是该参选企业各子领域相关产品的净利润，如果该公司的年报未体现相关数据，我们将采用该公司整体的利润率按产品贡献比例来推算。
注3：其余的六个评选指标（净资产，总资产利润率，净资产收益率，全员劳动贡献率，近三年销售收入平均增长率，近三年净利润平均增长率）的数据采用将以该参选企业对外公布整体业绩所提供的相关指标为参考标准，不再作细别区分。
注4：净资产收益率有不同的定义方式，为了避免因为上市公司与非上市公司企业所得税税率不同而造成的净利润不可比的问题，我们因此将公式中的分子定义为利润总额而非净利润，计算净资产收益率的公式为：净资产收益率=利润总额/净资产
注5：从监测数据中可以发现，如果企业竞争力主要来源于增长类指标（即近三年销售收入平均增长率&近三年净利润平均增长率），企业竞争力监测指数往往是不稳定的。造成这些企业竞争力不稳定的主要原因是：这些企业原来的销售收入的基数很小，近两年销售增加后会使企业近三年的销售收入平均增长率很高，从而远高于所在行业企业的平均水平。企业可能由于一个指标标准值的异常偏高而使该企业的竞争力基础数据的标准值整体很高。但在第二年或第三年，当该企业的销售收入增长率降到正常的平均水平，而其他指标却没有更高的增长时，该企业的竞争力监测指数就会显著下降。为了避免由于某一个财务指标的异常变动而影响企业竞争力评选结果的客观性，我们进行了一个可行的改进方法，对增长类指标（近三年销售收入平均增长率、近三年净利润平均增长率）的标准值设定上下限[1,-1]，并通过统一的一致性检验，从而可以避免由于某一个增长类指标标准值的异常而对硬指标基础数据标准值产生过大影响。
注6：日立超声领域的销售收入包括日立阿洛卡的超声的销售收入。

3. Ranking of Top 10 competitiveness enterprises in the ultrasound field of China medical devices industry during 2011-2012

Rankings of Top 10 competitiveness enterprises in the ultrasound field of China medical devices industry during 2011-2012

Company	Ranking	Standard value weighted of the financial data(70% weight)									Standard value weighted of the survey data (30% weight)						Comprehensive index of competitiveness	Comprehensive score of competitiveness	Source of financial data
		Sales revenues	Net assets	Net profit	Return on total assets	Return on net assets	Sales revenues contribution per employee	The average growth rate of sales revenues for the last three years	The average growth rate of net profit for the last three years	Total standard value weighted of the financial data	Technology innovation	Customer satisfaction	Brand awareness	Management level of enterprise	Corporation culture	Total standard value weighted of the survey data			
		weight 26%	weight 6%	weight 12%	weight 11%	weight 11%	weight 5%	weight 15%	weight 14%	(A)	weight 34%	weight 18%	weight 12%	weight 11%	weight 25%	(B)	(A*70%+B*30%)		
GE Healthcare	1	0.8207	0.0729	0.5921	-0.1054	0.0125	0.1490	-0.0720	0.0061	1.4759	0.6919	0.6321	0.6375	0.2725	0.6224	2.8564	1.8901	1000	Annual report of listed company
Philips Healthcare	2	0.9561	0.2039	-0.0220	0.0534	0.0290	0.0678	-0.0665	0.0624	1.2841	0.7011	0.5504	0.5511	0.2031	0.5101	2.5158	1.6536	986	Annual report of listed company
Siemens Healthcare	3	0.5199	0.2784	0.4164	-0.0713	0.0109	0.1615	-0.0687	0.0343	1.2814	0.5576	0.5541	0.5483	0.2281	0.5776	2.4657	1.6367	985	Annual report of listed company
Mindray	4	0.2540	-0.0012	-0.0109	0.1158	0.0639	-0.0120	0.0616	0.0278	0.4990	0.3167	0.4711	0.4716	0.1688	0.2995	1.7277	0.8676	944	Annual report of listed company
Esaote Medical	5	0.2065	-0.0186	-0.0174	0.0743	0.0782	0.0727	-0.0287	0.0190	0.3860	0.3877	0.2913	0.2938	0.2369	0.4246	1.6343	0.7605	935	Annual report of listed company
Hitachi Aloka Medical	6	0.2972	0.0034	-0.0073	-0.0223	-0.0205	0.0824	-0.0096	0.0280	0.3513	0.3596	0.3396	0.3407	0.2042	0.3922	1.6363	0.7368	933	Annual report of listed company
Toshiba Medical	7	0.1959	0.0111	-0.0133	-0.0721	0.1300	0.0962	-0.1044	0.0095	0.2529	0.3594	0.2601	0.2593	0.2101	0.5807	1.6696	0.6779	923	Annual report of listed company
Samsung Medison	8	0.0819	-0.0234	-0.0237	-0.0293	-0.0115	0.0894	-0.0257	0.0168	0.0745	0.3645	0.3446	0.3458	0.2092	0.3974	1.6615	0.5506	907	Annual report of listed parent company
Landwind Medical	9	0.0323	-0.0242	-0.0255	-0.0259	-0.0030	-0.0347	-0.0185	0.0156	-0.0839	0.2630	0.2441	0.2666	0.2951	0.2236	1.2924	0.3290	894	Taxation、research & survey information、self-reported figures and hospital's tender results
Sonoscape	10	-0.1374	-0.0451	-0.0364	0.1354	0.0880	-0.1542	0.0327	0.0286	-0.0884	0.4409	0.0952	0.0761	0.3304	0.3263	1.2689	0.3188	893	Taxation、research & survey information、self-reported figures and hospital's tender results

Note 1: (About revenues) Because some enterprises have lots of products in different fields, the revenues here refer to one enterprise's sales revenues in China market in special sub-field of medical devices industry.
For example: the revenues in the list of the radiology field are the sales revenues of enterprises' radiation products in China market.
Note 2: (About net profit) The indicator refers to the net profit of one enterprise's related products in a special sub-field. If the annual report didn't show the related data, we will calculate it from the total profit rate and products contribution proportion of the enterprise.
Note 3: The other six indicators (net assets, return on total assets, return on net assets, revenues per employee, the average growth rate of revenues for the last three years, and the average growth rate of net profit for the last three years) refer to the related indicators data of overall performance published by the enterprise.
Note 4: The return on net assets has different definitions. In order to avoid the problem of the incomparable value of net income caused by the different income tax rate between listed companies and non-listed companies, we will definite the numerator as the total profit rather than the net profit, the formula for calculating The return on net assets is: The return on net assets = Total profit / Net assets
Note 5: The monitoring data shows that if the competitiveness of enterprises comes mainly from the growth indicators (that is, the average growth rate of revenues for the last three years & the average growth rate of net profit for the last three years), the index of enterprises competitiveness is often unstable. The main reason for this instability is that some enterprises with small original revenues base have rapidly increasing in sales revenues during the past 2 years, which makes the average growth rate of the past 3 years much higher than the industry average level. An extremely high index may cause the enterprises' overall competitiveness standard value of fundamental data improved significantly. But in the future 2 or 3 years, with the growth rate of sales revenues remaining average and other index without rapid increase, the monitoring data will fall. To avoid unfair competition due to this problem, we make some viable improvement by setting the indicator of growth index (the average growth rate of revenues and net profits for the last 3 years)into the limitation of [1,-1]. With the consistency of statistical test, the overdone impact on overall standard value of fundamental data by the abnormal data of growth index can be eliminated.
Note 6: The sales revenues of Hitachi Medical include the sales revenues of Aloka in the ultrasound field.

四、《2011－2012年度中国医疗器械检验领域最具竞争力企业10强》榜单

2011-2012年度中国医疗器械检验领域最具竞争力企业10强榜单

公司	排名	直接计量硬指标财务数据加权标准值（权重为70%）									间接计量软指标加权标准值（权重为30%）						竞争力综合指数	竞争力综合得分	数据来源
		销售收入	净资产	净利润	总资产利润率	净资产收益率	全员劳动贡献率	近三年销售收入平均增长率	近三年净利润平均增长率	直接计量硬指标财务数据加权标准值合计	技术创新	客户满意度	品牌知名度	企业家及管理水平	企业文化	间接计量软指标加权标准值合计			
		权重26%	权重6%	权重12%	权重11%	权重11%	权重5%	权重15%	权重14%	(A)	权重34%	权重18%	权重12%	权重11%	权重25%	(B)	(A*70%+B*30%)		
罗氏	1	1. 2577	0. 1995	0. 2026	0. 0879	0. 3831	0. 0750	−0. 0852	−0. 0594	2. 0612	0. 7278	0. 4730	0. 5096	0. 2838	0. 5576	2. 5518	2. 2084	1000	上市公司年报
贝克曼库尔特	2	0. 8556	0. 1399	0. 1790	0. 0088	0. 0086	0. 0501	−0. 0181	−0. 0020	1. 2219	0. 6917	0. 3805	0. 3418	0. 1404	0. 7188	2. 2732	1. 5373	971	上市公司年报
雅培	3	0. 8588	0. 1459	0. 1734	0. 0065	0. 0355	0. 0482	−0. 0259	−0. 0641	1. 1783	0. 6133	0. 3736	0. 3732	0. 1998	0. 6427	2. 2026	1. 4856	968	上市公司年报
希森美康	4	0. 8176	−0. 0049	0. 0282	0. 0131	−0. 0037	0. 0253	−0. 0335	−0. 0080	0. 8341	0. 5291	0. 4610	0. 3314	0. 1699	0. 6114	2. 1028	1. 2147	954	上市公司年报
西门子	5	0. 2266	0. 1750	0. 0758	−0. 0232	−0. 0056	0. 0606	−0. 0518	0. 0778	0. 5352	0. 6605	0. 2942	0. 3248	0. 2184	0. 5993	2. 0972	1. 0038	950	上市公司年报
日立高新	6	0. 1862	0. 1364	−0. 0126	−0. 0013	−0. 0076	0. 1199	−0. 0427	0. 1400	0. 5183	0. 6097	0. 3870	0. 3686	0. 1901	0. 5239	2. 0793	0. 9866	939	上市公司年报
强生	7	0. 1948	0. 1627	0. 2073	0. 0281	0. 0487	0. 0729	−0. 0618	−0. 1345	0. 5182	0. 5103	0. 3092	0. 2958	0. 2651	0. 6418	2. 0222	0. 9694	938	上市公司年报
迈瑞	8	0. 1894	−0. 0046	0. 0115	0. 0431	0. 0206	−0. 0078	0. 0786	0. 0432	0. 3740	0. 3133	0. 3256	0. 3473	0. 1987	0. 3134	1. 4983	0. 7113	923	上市公司年报
科华生物	9	0. 1299	−0. 0257	−0. 0621	0. 1189	0. 0897	−0. 0069	0. 1159	0. 0107	0. 3704	0. 3097	0. 3294	0. 3201	0. 2050	0. 2852	1. 4494	0. 6941	922	上市公司年报
迪瑞	10	0. 0808	−0. 0482	−0. 0640	0. 0064	0. 1267	−0. 0242	0. 1500	0. 1400	0. 3675	0. 2883	0. 3094	0. 3011	0. 1886	0. 2538	1. 3412	0. 6596	910	参股公司年报

注1：关于销售收入指标数据，由于所参选企业的销售收入来自其众多产品的销售收入，我们因此所采集的数据是以医疗器械各子领域榜单相关的产品在中国市场的收入作为销售收入。例如：放射领域榜单的销售收入数据采集自各企业其放射产品在中国市场的销售收入。
注2：净利润所采用的数据是该参选企业各子领域相关产品的净利润，如果该公司的年报未体现相关数据，我们将采用该公司整体的利润率按产品贡献比例来推算。
注3：其余的六个评选指标（净资产，总资产利润率，净资产收益率，全员劳动贡献率，近三年销售收入平均增长率，近三年净利润平均增长率）的数据采用将以该参选企业对外公布整体业绩所提供的相关指标为参考标准，不再作细别区分。
注4：净资产收益率有不同的定义方式，为了避免因为上市公司与非上市公司企业所得税税率不同而造成的净利润不可比的问题，我们因此将公式中的分子定义为利润总额而非净利润，计算净资产收益率的公式为：净资产收益率=利润总额/净资产
注5：从监测数据中可以发现，如果企业竞争力主要来源于增长类指标（即近三年销售收入平均增长率&近三年净利润平均增长率），企业竞争力监测指数往往是不稳定的。造成这些企业竞争力不稳定的主要原因是：这些企业原来的销售收入的基数很小，近两年销售增加后会使企业近三年的销售收入平均增长率很高，从而远高于所在行业企业的平均水平，企业可能由于一个指标标准值的异常偏高而使该企业的竞争力基础数据的标准值整体很高。但在第二年或第三年，当该企业的销售收入增长率降到正常的平均水平，而其他指标却没有更高的增长时，该企业的竞争力监测指数就会显著下降。为了避免由于某一个财务指标的异常变动而影响企业竞争力评选结果的客观性，我们进行了一个可行的改进方法，对增长类指标（近三年销售收入平均增长率、近三年净利润平均增长率）的标准值设定上下限[1,-1]，并通过统一的一致性检验，从而可以避免由于某一个增长类指标标准值的异常而对硬指标基础数据标准值产生过大影响。

4. Ranking of Top 10 competitiveness enterprises in the laboratory medicine field of China medical devices industry during 2011-2012

Rankings of Top 10 competitiveness enterprises in the laboratory medicine field of China medical devices industry during 2011-2012

Company	Ranking	Standard value weighted of the financial data(70% weight)									Standard value weighted of the survey data (30% weight)						Comprehensive index of competitiveness	Comprehensive score of competitiveness	Source of financial data
		Sales revenues	Net assets	Net profit	Return on total assets	Return on net assets	Sales revenues contribution per employee	The average growth rate of sales revenues for the last three years	The average growth rate of net profit for the last three years	Total standard value weighted of the financial data	Technology innovation	Customer satisfaction	Brand awareness	Management level of enterprise	Corporation culture	Total standard value weighted of the survey data			
		weight 26%	weight 6%	weight 12%	weight 11%	weight 11%	weight 5%	weight 15%	weight 14%	(A)	weight 34%	weight 18%	weight 12%	weight 11%	weight 25%	(B)	(A*70%+B*30%)		
Roche Diagnostics	1	1. 2577	0. 1995	0. 2026	0. 0879	0. 3831	0. 0750	−0. 0852	−0. 0594	2. 0612	0. 7278	0. 4730	0. 5096	0. 2838	0. 5576	2. 5518	2. 2084	1000	Annual report of listed company
Beckman Coulter	2	0. 8556	0. 1399	0. 1790	0. 0088	0. 0086	0. 0501	−0. 0181	−0. 0020	1. 2219	0. 6917	0. 3805	0. 3418	0. 1404	0. 7188	2. 2732	1. 5373	971	Annual report of listed company
Abbott	3	0. 8588	0. 1459	0. 1734	0. 0065	0. 0355	0. 0482	−0. 0259	−0. 0641	1. 1783	0. 6133	0. 3736	0. 3732	0. 1998	0. 6427	2. 2026	1. 4856	968	Annual report of listed company
Sysmex	4	0. 8176	−0. 0049	0. 0282	0. 0131	−0. 0037	0. 0253	−0. 0335	−0. 0080	0. 8341	0. 5291	0. 4610	0. 3314	0. 1699	0. 6114	2. 1028	1. 2147	954	Annual report of listed company
Siemens Healthcare	5	0. 2266	0. 1750	0. 0758	−0. 0232	−0. 0056	0. 0606	−0. 0518	0. 0778	0. 5352	0. 6605	0. 2942	0. 3248	0. 2184	0. 5993	2. 0972	1. 0038	950	Annual report of listed company
Hitachi-hitec	6	0. 1862	0. 1364	−0. 0126	−0. 0013	−0. 0076	0. 1199	−0. 0427	0. 1400	0. 5183	0. 6097	0. 3870	0. 3686	0. 1901	0. 5239	2. 0793	0. 9866	939	Annual report of listed company
Johnson&Johnson	7	0. 1948	0. 1627	0. 2073	0. 0281	0. 0487	0. 0729	−0. 0618	−0. 1345	0. 5182	0. 5103	0. 3092	0. 2958	0. 2651	0. 6418	2. 0222	0. 9694	938	Annual report of listed company
Mindray	8	0. 1894	−0. 0046	0. 0115	0. 0431	0. 0206	−0. 0078	0. 0786	0. 0432	0. 3740	0. 3133	0. 3256	0. 3473	0. 1987	0. 3134	1. 4983	0. 7113	923	Annual report of listed company
Kehua Bio-Engineering	9	0. 1299	−0. 0257	−0. 0621	0. 1189	0. 0897	−0. 0069	0. 1159	0. 0107	0. 3704	0. 3097	0. 3294	0. 3201	0. 2050	0. 2852	1. 4494	0. 6941	922	Annual report of listed company
Dirui	10	0. 0808	−0. 0482	−0. 0640	0. 0064	0. 1267	−0. 0242	0. 1500	0. 1400	0. 3675	0. 2883	0. 3094	0. 3011	0. 1886	0. 2538	1. 3412	0. 6596	910	Annual report of listed sharing company

Note 1: (About revenues) Because some enterprises have lots of products in different fields, the revenues here refer to one enterprise's sales revenues in China market in special sub-field of medical devices industry.
For example: the revenues in the list of the radiology field are the sales revenues of enterprises' radiation products in China market.
Note 2: (About net profit) The indicator refers to the net profit of one enterprise's related products in a special sub-field. If the annual report didn't show the related data, we will calculate it from the total profit rate and products contribution proportion of the enterprise.
Note 3: The other six indicators (net assets, return on total assets, return on net assets, revenues per employee, the average growth rate of revenues for the last three years, and the average growth rate of net profit for the last three years) refer to the related indicators data of overall performance published by the enterprise.
Note 4: The return on net assets has different definitions. In order to avoid the problem of the incomparable value of net income caused by the different income tax rate between listed companies and non-listed companies, we will definite the numerator as the total profit rather than the net profit, the formula for calculating The return on net assets is: The return on net assets = Total profit / Net assets
Note 5: The monitoring data shows that if the competitiveness of enterprises comes mainly from the growth indicators (that is, the average growth rate of revenues for the last three years & the average growth rate of net profit for the last three years), the index of enterprises competitiveness is often unstable. The main reason for this instability is that some enterprises with small original revenues base have rapidly increasing in sales revenues during the past 2 years, which makes the average growth rate of the past 3 years much higher than the industry average level. An extremely high index may cause the enterprises' overall competitiveness standard value of fundamental data improved significantly. But in the future 2 or 3 years, with the growth rate of sales revenues remaining average and other index without rapid increase, the monitoring data will fall. To avoid unfair competition due to this problem, we make some viable improvement by setting the indicator of growth index (the average growth rate of revenues and net profits for the last 3 years)into the limitation of [1,-1]. With the consistency of statistical test, the overdone impact on overall standard value of fundamental data by the abnormal data of growth index can be eliminated.

五、《2011－2012年度中国医疗器械骨科领域最具竞争力企业10强》榜单

2011-2012年度中国医疗器械骨科领域最具竞争力企业10强榜单

公司	排名	直接计量硬指标财务数据加权标准值（权重为70%）									间接计量软指标加权标准值（权重为30%）						竞争力综合指数	竞争力综合得分	数据来源
		销售收入	净资产	净利润	总资产利润率	净资产收益率	全员劳动贡献率	近三年销售收入平均增长率	近三年净利润平均增长率	直接计量硬指标财务数据加权标准值合计	技术创新	客户满意度	品牌知名度	企业家及管理水平	企业文化	间接计量软指标加权标准值合计			
		权重26%	权重6%	权重12%	权重11%	权重11%	权重5%	权重15%	权重14%	(A)	权重34%	权重18%	权重12%	权重11%	权重25%	(B)	(A*70%+B*30%)		
强生	1	1.0882	0.2628	0.6374	0.0429	0.0660	0.0771	-0.1103	-0.0304	2.0337	0.5498	0.3502	0.3359	0.3197	0.6812	2.2368	2.0946	1000	上市公司年报
史塞克	2	0.6498	0.1354	0.0264	0.0813	0.0682	0.0441	0.0029	0.0022	1.0103	0.5437	0.3439	0.3336	0.2697	0.5637	2.0546	1.3236	981	上市公司年报
美敦力	3	0.3601	0.2449	-0.0004	0.0622	0.0790	0.0395	-0.0270	0.0254	0.7837	0.5182	0.3070	0.2683	0.1669	0.6450	1.9054	1.1202	973	上市公司年报
美国捷迈	4	0.4434	0.0890	0.0040	0.0517	0.0352	0.0686	-0.0783	-0.0152	0.5984	0.4790	0.2792	0.2650	0.2488	0.6101	1.8821	0.9835	965	上市公司年报
施乐辉	5	0.2602	0.0392	-0.1534	0.1417	0.1049	0.0454	-0.0551	0.0284	0.4113	0.4527	0.2426	0.2537	0.2378	0.6188	1.8056	0.8296	956	上市公司年报
德国贝朗	6	0.1184	0.0300	-0.2306	-0.0113	0.0254	-0.0089	-0.0086	0.0183	-0.0673	0.4748	0.2085	0.2391	0.1827	0.5636	1.6687	0.4535	934	上市公司年报
美国巴奥米特	7	0.2430	0.0379	-0.3058	-0.1220	-0.1259	0.0386	-0.0590	-0.1400	-0.4332	0.4419	0.2328	0.2285	0.2018	0.5921	1.6971	0.2059	917	上市公司年报
威高	8	-1.0046	-0.0011	-0.2645	0.5023	0.2397	-0.0231	0.1500	-0.0548	-0.4561	0.2325	0.2445	0.2663	0.2176	0.3323	1.2932	0.0687	895	上市公司年报
创生	9	-0.4080	-0.0254	-0.2608	0.1160	0.0328	-0.0243	0.1500	-0.0590	-0.4787	0.2196	0.2409	0.2325	0.2201	0.3855	1.2986	0.0545	886	上市公司年报
康辉	10	-0.6415	-0.0252	-0.2621	0.0556	-0.0019	-0.0169	0.1500	0.0515	-0.6905	0.2469	0.2682	0.2598	0.2473	0.3126	1.3348	-0.0829	878	上市公司年报

注1：关于销售收入指标数据，由于所参选企业的销售收入来自其众多产品的销售收入，我们因此所采集的数据是以医疗器械各子领域榜单相关的产品在中国市场的收入作为销售收入。例如：放射领域榜单的销售收入数据采集自各企业其放射产品在中国市场的销售收入。
注2：净利润所采用的数据是该参选企业各子领域相关产品的净利润，如果该公司的年报未体现相关数据，我们将采用该公司整体的利润率按产品贡献比例来推算。
注3：其余的六个评选指标（净资产，总资产利润率，净资产收益率，全员劳动贡献率，近三年销售收入平均增长率，近三年净利润平均增长率）的数据采用将以该参选企业对外公布整体业绩所提供的相关指标为参考标准，不再作细别区分。
注4：净资产收益率有不同的定义方式，为了避免因为上市公司与非上市公司企业所得税税率不同而造成的净利润不可比的问题，我们因此将公式中的分子定义为利润总额而非净利润，计算净资产收益率的公式为：净资产收益率=利润总额/净资产
注5：从监测数据中可以发现，如果企业竞争力主要来源于增长类指标（即近三年销售收入平均增长率&近三年净利润平均增长率），企业竞争力监测指数往往是不稳定的。造成这些企业竞争力不稳定的主要原因是：这些企业原来的销售收入的基数很小，近两年销售增加后会使企业近三年的销售收入平均增长率很高，从而远高于所在行业企业的平均水平，企业可能由于一个指标标准值的异常偏高而使该企业的竞争力基础数据的标准值整体很高。但在第二年或第三年，当该企业的销售收入增长率降到正常的平均水平，而其他指标却没有更高的增长时，该企业的竞争力监测指数就会显著下降。为了避免由于某一个财务指标的异常变动而影响企业竞争力评选结果的客观性，我们进行了一个可行的改进方法，对增长类指标（近三年销售收入平均增长率、近三年净利润平均增长率）的标准值设定上下限[1,-1]，并通过统一的一致性检验，从而可以避免由于某一个增长类指标标准值的异常而对硬指标基础数据标准值产生过大影响。
注6：由于辛迪思于2011年被强生收购，故强生骨科的财务数据将包括辛迪思相关的财务数据。

5. Ranking of Top 10 competitiveness enterprises in the orthopedics field of China medical devices industry during 2011-2012

Rankings of Top 10 competitiveness enterprises in the orthopedics field of China medical devices industry during 2011-2012

Company	Ranking	Standard value weighted of the financial data(70% weight)									Standard value weighted of the survey data (30% weight)						Comprehensive index of competitiveness	Comprehensive score of competitiveness	Source of financial data
		Sales revenues	Net assets	Net profit	Return on total assets	Return on net assets	Sales revenues contribution per employee	The average growth rate of sales revenues for the last three years	The average growth rate of net profit for the last three years	Total standard value weighted of the financial data	Technology innovation	Customer satisfaction	Brand awareness	Management level of enterprise	Corporation culture	Total standard value weighted of the survey data			
		weight 26%	weight 6%	weight 12%	weight 11%	weight 11%	weight 5%	weight 15%	weight 14%	(A)	weight 34%	weight 18%	weight 12%	weight 11%	weight 25%	(B)	(A*70%+B*30%)		
Johnson&Johnson	1	1.0882	0.2628	0.6374	0.0429	0.0660	0.0771	-0.1103	-0.0304	2.0337	0.5498	0.3502	0.3359	0.3197	0.6812	2.2368	2.0946	1000	Annual report of listed company
Stryker	2	0.6498	0.1354	0.0264	0.0813	0.0682	0.0441	0.0029	0.0022	1.0103	0.5437	0.3439	0.3336	0.2697	0.5637	2.0546	1.3236	981	Annual report of listed company
Medtronic	3	0.3601	0.2449	-0.0004	0.0622	0.0790	0.0395	-0.0270	0.0254	0.7837	0.5182	0.3070	0.2683	0.1669	0.6450	1.9054	1.1202	973	Annual report of listed company
Zimmer	4	0.4434	0.0890	0.0040	0.0517	0.0352	0.0686	-0.0783	-0.0152	0.5984	0.4790	0.2792	0.2650	0.2488	0.6101	1.8821	0.9835	965	Annual report of listed company
Smith&Nephew	5	0.2602	0.0392	-0.1534	0.1417	0.1049	0.0454	-0.0551	0.0284	0.4113	0.4527	0.2426	0.2537	0.2378	0.6188	1.8056	0.8296	956	Annual report of listed company
B. Braun	6	0.1184	0.0300	-0.2306	-0.0113	0.0254	-0.0089	-0.0086	0.0183	-0.0673	0.4748	0.2085	0.2391	0.1827	0.5636	1.6687	0.4535	934	Annual report of listed company
Biomet	7	0.2430	0.0379	-0.3058	-0.1220	-0.1259	0.0386	-0.0590	-0.1400	-0.4332	0.4419	0.2328	0.2285	0.2018	0.5921	1.6971	0.2059	917	Annual report of listed company
WEGO	8	-1.0046	-0.0011	-0.2645	0.5023	0.2397	-0.0231	0.1500	-0.0548	-0.4561	0.2325	0.2445	0.2663	0.2176	0.3323	1.2932	0.0687	895	Annual report of listed company
Trauson	9	-0.4080	-0.0254	-0.2608	0.1160	0.0328	-0.0243	0.1500	-0.0590	-0.4787	0.2196	0.2409	0.2325	0.2201	0.3855	1.2986	0.0545	886	Annual report of listed company
Kanghui	10	-0.6415	-0.0252	-0.2621	0.0556	-0.0019	-0.0169	0.1500	0.0515	-0.6905	0.2469	0.2682	0.2598	0.2473	0.3126	1.3348	-0.0829	878	Annual report of listed company

Note 1: (About revenues) Because some enterprises have lots of products in different fields, the revenues here refer to one enterprise's sales revenues in China market in special sub-field of medical devices industry.
For example: the revenues in the list of the radiology field are the sales revenues of enterprises' radiation products in China market.
Note 2: (About net profit) The indicator refers to the net profit of one enterprise's related products in a special sub-field. If the annual report didn't show the related data, we will calculate it from the total profit rate and products contribution proportion of the enterprise.
Note 3: The other six indicators (net assets, return on total assets, return on net assets, revenues per employee, the average growth rate of revenues for the last three years, and the average growth rate of net profit for the last three years) refer to the related indicators data of overall performance published by the enterprise.
Note 4: The return on net assets has different definitions. In order to avoid the problem of the incomparable value of net income caused by the different income tax rate between listed companies and non-listed companies, we will definite the numerator as the total profit rather than the net profit, the formula for calculating The return on net assets is: The return on net assets = Total profit / Net assets
Note 5: The monitoring data shows that if the competitiveness of enterprises comes mainly from the growth indicators (that is, the average growth rate of revenues for the last three years & the average growth rate of net profit for the last three years), the index of enterprises competitiveness is often unstable. The main reason for this instability is that some enterprises with small original revenues base have rapidly increasing in sales revenues during the past 2 years, which makes the average growth rate of the past 3 years much higher than the industry average level. An extremely high index may cause the enterprises' overall competitiveness standard value of fundamental data improved significantly. But in the future 2 or 3 years, with the growth rate of sales revenues remaining average and other index without rapid increase, the monitoring data will fall. To avoid unfair competition due to this problem, we make some viable improvement by setting the indicator of growth index (the average growth rate of revenues and net profits for the last 3 years)into the limitation of [1,-1]. With the consistency of statistical test, the overdone impact on overall standard value of fundamental data by the abnormal data of growth index can be eliminated.
Note 6: Synthes was acquired by Johnson & Johnson in 2011, so the financial data of Johnson & Johnson include the relevant financial data of Synthes in the orthopedics field.

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2012北京·第六届全国实用疼痛注射及神经阻滞技术新进展高级培训班的报到通知

中华医学会继续教育与宣武医院疼痛科于2007～2011年举办了五届疼痛注射和神经阻滞治疗高级培训班，得到了同行的大力支持，有来自全国千余位专家和代表到会，反响热烈，获得了同行们的好评。为进一步推广和普及疼痛治疗的门诊注射及神经阻滞技术，促进我国实用疼痛诊疗技术的发展。中华医学会继续教育部、首都医科大学宣武医院疼痛科定于2012年10月23-28日在北京举办“第六届全国实用疼痛注射及神经阻滞技术新进展高级培训班”。

本活动为国家级继续教育项目[项目编号：2012-04-11-211，10学分]。

疼痛的注射和神经阻滞技术是疼痛科、麻醉科、骨科、康复科、骨伤科、神经科、中医科等多个学科疼痛治疗的重要手段，其特点是方法简便实用，容易掌握，安全性高,对于各种常见的疼痛具有疗效确切，立竿见影的效果，有良好的经济和社会效益。该技术特别适用于各专业医生开展疼痛治疗，也适合基层医疗单位包括社区诊所的全科医生掌握应用。由于目前该项基本的实用治疗技术尚不普及，在许多基层医疗单位还是空白，经过培训的医师短缺、疼痛治疗操作不规范，影响了疼痛治疗。许多病人为了缓解疼痛，多年滥用止痛药物，导致消化道溃疡穿孔、肝肾功能衰竭等并发症，影响了工作、劳动和生活质量。

一、报到日期：2012年10月23日报到（全日）

讲课日期：2012年10月24日～27日

会议地点：瑞尔威饭店（丰台区莲花池东路116-2号，北京西客站东附楼）

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二、学习班邀请我国著名疼痛学专家严相默、倪家骧、马骏、岳剑宁、孙海燕、赖光辉、武百山、杨立强、何明伟等，结合自己长期的临床经验进行专题讲解，欢迎学员将平时工作中的难题带到现场提问，与专家直接交流。学习班既重视基本操作技能的培训，也注重该领域内技术新进展的介绍。内容包括：

1. 图解疼痛疾病基本体格检查；

2. 疼痛疾病的影像学识别诊断；

3. 疼痛注射及神经阻滞技术总论；

4. 门诊关节疼痛、肌筋膜炎、腱鞘炎等注射治疗技术；

5. 门诊颈交感神经阻滞治疗头痛、痛经、心绞痛、面神经炎、突发性耳聋；

6. 门诊神经阻滞治疗三叉神经痛、舌咽神经痛、带状疱疹等多种神经痛；

7. 超声引导下的门诊介入治疗；

8. 臭氧注射和射频疗法在门诊的应用；

9. 膝关节灌洗术治疗骨性关节炎；

10. 疼痛治疗并发症预防及纠纷防范。

本次学习班将为部分优秀学员提供首都医科大学宣武医院疼痛诊疗科门诊和病房现场观摩。为提高学习效果，对讲课内容采用大量图片和现场照片展示，对部分操作内容，用现场录像展示。

为了增强学习效果和活跃学术气氛，促进学术交流，本次学习班将专门设立小型专题讨论会，给学员提供与专家面对面交流的机会。

三、会务与住宿费用：会务费：1280元，住宿费150元左右／床／天，免餐费。会务费、住宿费及往返路费由学员单位报销。

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[请务必注明会议名称、会议地点、参会代表姓名、省（市）、工作单位及科室、电话及邮编]或：宣武医院疼痛科

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首都医科大学宣武医院疼痛科

会议讯息

2012 Information of Notification、Exhibition and Scientific Meeting 展

国内会议信息

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：重庆市渝中区
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

第十三次全国呼吸病学学术会议
时　　间：2012年9月13-16日
地　　点：四川省成都市
　　成都世纪城新国际会展中心
主办单位：中华医学会
　　中华医学会呼吸病学分会
联 系 人：王娟
电　　话：010-8515 8249
邮　　箱：csrd2008@126.com

首届五次亚洲齿科麻醉学术联盟年会（FADAS）暨2012年中华口腔医学会口腔麻醉学专业委员会学术年会
时　　间：2012年9月14-15日
地　　点：陕西省西安市
主办单位：亚洲齿科麻醉学术联盟
　　中华口腔医学会
　　口腔麻醉学专业委员会
联 系 人：每晓鹏
邮　　箱：meixp@fmmu.edu.cn

2012年湖北省医学会麻醉学分会学术年会
时　　间：2012年10月14-16日
地　　点：湖北恩施州
主办单位：省医学会麻醉学分会
联 系 人：武庆平
电　　话：027-85351643
邮　　箱：wqp1968@163.com

2012年（第二届）中日国际消化疾病论坛暨挑战直肠癌-战略与艺术综合研讨会
时　　间：2012年10月19-21日
地　　点：北京
主办单位：N/A
联 系 人：樊老师、赵老师
电　　话：010-5242 8196
传　　真：010-8485 5358
邮　　箱：cjds@htbr.cn

中国医师协会2012年眼科准分子激光角膜屈光手术学术研讨会
时　　间：2012年10月24-29日
地　　点：广西南宁
主办单位：中国医师协会事业发展部
联 系 人：孙静怡
电　　话：010－65286512
传　　真：010－65287282
邮　　箱：cmdazfz@163.com

中华医学会第十三届全国儿科呼吸学术会议
时　　间：2012年10月25-29日
地　　点：江西省南昌市
主办单位：中华医学会儿科学分会
联 系 人：李佳
电　　话：010-85158128
邮　　箱：lijia@cma.org.cn

第13届亚太临床微生物暨感染病会议（APCCMI）会议
时　　间：2012年10月25日-280日
地　　点：中国北京国家会议中心
主办单位：亚太临床微生物暨感染病协会
联 系 人：卞晓雪
电　　话：8610-67122288-274
邮　　箱：bianxiaoxue@mpco.cn

第十届中国介入放射学（CSIR）学术大会暨2012国际栓塞会议（GEST）
时　　间：2012年10月30日
地　　点：江苏南京
主办单位：中华医学会放射学分会介入学组
联 系 人：刘芳
电　　话：010-84288944
邮　　箱：liufang@cyberzone.cn

国际会议信息

第22届欧洲呼吸学大会
时　　间：2012年9月1-9月5日
地　　点：奥地利
主办单位：European Respiratory Society
联 系 人：Austropa Interconvention
电　　话：+43 1 58800-513/514
传　　真：+43 1 58800-520
邮　　箱：ers2012hotel@interconvention

2012年第24届国际高血压会议（ISH）
时　　间：2012年9月30-10月4日
地　　点：澳大利亚-悉尼
主办单位：国际高血压学会（ISH）
联 系 人：Arinex Ptv. Limited
电　　话：+61 3 9417 0888
邮　　箱：ish2012@arinex.com.au

2012年第31届世界内科医学会议
时　　间：2012年11月11-15日
地　　点：智利—圣地亚哥
主办单位：智利内科协会
联 系 人：Ms. Viviana Oliva
电　　话：+56 2 946 2644
邮　　箱：voliva@kenes.com

国内展会信息

第21届中国国际医用仪器设备展览会暨技术交流会
时　　间：2012年8月16日-18日
地　　点：北京国家会议中心
主办单位：中华人民共和国卫生部
电　　话：010-88393923
传　　真：010-88393924
邮　　箱：info@chinahospep.com

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
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

第68届中国医疗器械（秋季）博览会
时　　间：2012年10月18日-21日
地　　点：成都世纪城新国际会展中心
主办单位：国药励展展览有限责任公司
联 系 人：钟蕾
电　　话：010-84556609
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第二十五届国际医疗仪器设备展览会
时　　间：2013年3月28日-30日
地　　点：北京国家会议中心
主办单位：中国人民解放军总后勤部卫生部
联 系 人：韩晓
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邮　　箱：yalatu8888@126.com

国际展会信息

2012年第32届俄罗斯（莫斯科）口腔医学展览会
时　　间：2012年9月17-20日
地　　点：莫斯科 国际展览中心
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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
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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
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2012年西非尼日利亚国际医疗器械展览会
时　　间：2012年10月16-18日
地　　点：尼日利亚 格拉斯
主办单位：英国IIR展览
联 系 人：石磊
电　　话：021-55139199
传　　真：021-51686946
邮　　箱:sales-3@dongsinexpo.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

[illegible]

[1] [illegible] 0876 [illegible] 163, 65-

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

[3] [illegible] 0883-165, 2/5

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

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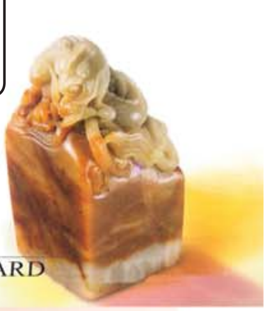

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