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財団法人　日中医学協会

理事長　　中島章殿

Ⅰ．研究者氏名　劉 冬梅

研究機関 国立小児医療センター 病態生理研究指導者 宮坂勝之 職名 部長

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Ⅱ．過去の研究歴

1995.10 － 現在、国立小児医療センター・病態生理研究室で小児急症患者の生命予後に関する病態の治療を研究しております。研究内容：(1) 高頻度振動型人工換気法（HFO）の応用および気道、肺損傷 (2) 小児急症患者治療機器の開発。

Ⅲ．過去の研究実績

1. 口頭発表（in English）：The evaluation of infusion accuracy anel consistency of four disposable infusion pumps. 9th Asian Congress of Paediatrics, 23rd – 27th March 1997 Hongkong

2. 論文（in English）：Evaluation of extracorporeal membrane oxygenation system using a nonporous membrane oxygenator and a new method for heparin coating. Journal of Pediatric Surgery 32: 691 – 697, 1997.

Ⅳ．本年度の研究業績

(1) 学会、研究会等においての口頭発表（学会名・内容）

1. ディスポーサブル携帯型微量持続注入器の評価。
第19回日本麻酔・薬理学会総会．東京．6月12－13日．1997。

2. 四種類携帯型微量注入ポンプの精度と一定性の評価。
第6回日中臨床麻酔学討論会．北九州市．11月14日．1997.

(2) 学会誌等に発表した論文　　無 ・ (有)　（雑誌名・論文名）

1. Infusion speed accuracy and consistency of disposable infusion pumps.
J Pediatr Child Health 33: S95 1997.

2. Evaluation of continous intra-arterial blood gas monitoring under rapidly changing body temperature in pigs. Clin Pediatr Anesthesia 3: 153－158, 1997

Ⅴ．今後の研究計画及び希望

前から研究してきた研究テーマをつづけたいと思います。
(1) 高頻度振動型人工換気法の応用お及気道と肺損傷。
(2) 膜型人工肺（ECMO）による呼吸循環補助の研究。

Ⅵ. 研　究　報　告（日本語、又は英語で書いて下さい。 4,000字以上で記載して下さい。別紙可）

別紙で

劉会務

Ⅶ. 指導教官の意見

劉先生は、1995年10月に来日以来、当研究室で、「新しいヘパリン化処理法を応用した新生児用ECMOシステムの開発」をはじめとして、「高頻度振動換気法と気道損傷」、「腹圧の呼吸循環に及ぼす影響」など幅広い分野にわたり、活発に研究活動を続けている。

昨年度は、貴財団の補助を得て、「輸液ポンプの性能の検討」の研究にたずさわり、その成果を学会で報告し、高い評価を得ている。

吉坂勝之

Report

I graduated from Sun Yat-sen University of Medical Science at Guangzhou in 1988 and started my physician's career in Guangdzhou Children's hospital. During the past seven years, I have done clinical and research works in Pediatric Care medicine. In was promoted as an assistant in Pediatrics. Since the October of 1995, I have begun my study and research work in National Children's Medical Research Center, Tokyo. My research work is to develop the technology of artificial ventilation and artificial circulation. The purpose is to improve the survival rate and quality of life of critically ill children.

Here I should say thanks to the Japan-China Medical Association for their economic support for me. With these help, I have done my research work smoothly in the Department of Pathophysiology, National Children's Medical Research Center. Here I would like to introduce my research work which I have mainly done during the past one year.

1. High Frequency Oscillation Ventilation (HFO)

High frequency oscillation ventilation (HFO) now has become popular in the critical care medicine area. HFO is mainly used in the management of acute respiratory failure with air leak, hypoplastic lung, and persistent pulmonary hypertension. In Japan, for the newborn patients with ARDS (acute respiratory distress syndrome), HFO were used surround 20-30%. HFO is considered a less invasive way of ventilation fragile lungs since it dose not

involve intermittent stretching of alveolar walls. Contrarily, in the low compliant, atelectatic lung, the conventional ventilation not only has to produces a pressure within the lung in excess of alveolar "opening pressure" in order to achieve oxygen exchange , but also has to use high level of positive end expiratory pressure (PEEP) to prevent the lung collapse during the expiratory phase of the respiratory cycle. It is this constant opening and closing of terminal airway units under high pressure that results in further injury to the already damaged lung. HFO offers an entirely different ventilation strategy for dealing with this form of lung disease. Increasing airway pressure by adjusting fresh gas flow can raise mean airway pressure (MAP) above alveolar opening pressure and maintain lung volume at this level, where the small airway pressure swing around the mean will be less injurious to the lung by avoiding the continual cycle of inflation and collapse terminal lung units. In 1993, Ogawa and Miyasaka et al conducted a multicenter randomized trial in nine neonatal centers in Japan. The result demonstrated HFO was effective and safe in the treatment of respiratory failure for preterm infants. There are now several publications demonstrating that HFO decreased barotrauma in very low weight infants, decreased incidence of BPD in infant respiratory distress syndrome and a reduction in the requirement for ECMO therapy in term infants with ARF (acute respiratory failure) and an OI>40. In addition, the ease of control of CO2 make HFO an attractive option in PPHN where the induction of a

respiratory alkalosis can reverse right to left ductal shunting without the necessity to hyperventilation with high peak inspiratory pressures which lead to pulmonary barotrauma. Following the recognition for its benefits. HFO has been extended to be used in infants, children and adults.

Last year, a new ventilator of HFO has been developed for using to the children and adults in Japan. I have been evaluated this ventilator in the animal experiments and confirm that this new ventilator can be used not only for children but also for adults. But there are some problems remained , for example, the protection from infection, deducing the noise, et al.

Many studies have been done about lung injury and lung protection strategy concerning HFO. But there is less studies about tracheobroncheal injury of HFO. Last year the experiment about airway injury has been done by us. In this experiment, we compared the airway histopathologic findings in kitten given Conventional Mechanical Ventilation (CMV) with those seen after HFOV. Seventeen normal kittens were paralyzed and mechanically ventilated for 24 hours. Seven were treated with CMV, and eleven with HFOV. A semiquantitative histopathologic scoring system was used to grade tissue changes in the cartilage cricoidea, mid trachea, trachea at the tip of endotracheal tube, carina, and right mainstem bronchi. The degree of damage was mild in both of groups, even the part at tip part of endotracheal tube and carina which were thought the main influenced part by fresh gas flow and vibration. There was no significant difference in the extent of injury

between the two groups. High-frequency oscillatory ventilation appears to result in no greater degree of airway damage than conventional positive pressure ventilation.

2. Disposable infusion pumps for home care and pain management.

The disposable infusion devices have the advantages of lightweight, great mobility, noneed of electricity, easy concealment and easy to be use by the patients. Now they have been widely used for infusion therapies and patient transportation. The potential problems now is that the flow rate may not consistent through the whole infusion, and the infusion accuracy may vary from device to device. The infusion speed may also be influenced by fluid viscosity, temperature, type of venous access, catheter patency, and patient body position.

Last year, we introduced a new disposable infusion device, Coopdecch Syrinjector (Daiken Medical, Japan), which is called a syringe type and using negative pressure for infusion. The infusion accuracy and consistency have been investigated by us. At the same time the influence of the room temperature, device's position also have been studied. The result suggested that the new disposable infusion device can provide more accurate and consistent infusion flow than other type disposable infusion devices, such as the balloon type. We also suggested this device can be used for intra-

arterial monitoring system.

3. Evaluation of an Extracorporeal Membrane Oxygenation System (ECMO) Using a Nonporous Membrane Oxygenator and a New Method for Heparin Coating.

Extracorporeal membrane oxygenation (ECMO) has been successfuly used to treat refractory neonatal respiratory failure. Its application in clinical uses tends to be wide, for example in premature newborn, in pediatric patients and adults who have the refractory heart and respiratory failure. At present bleeding complication is the principal cause of morbidity and mortality in infants treated with ECMO. This problem limits its usefulness in clinical application. To resolve the anticoagulation problem in ECMO system, heparin-coating or immobilization is the most explored and promising approach.

Various types of heparin-coated surfaces have been developed to overcome the risk of major bleeding resulting from systemic heparinization during extracorporeal circulation. Two products with heparin-coated surfaces are now commercially available for cardiopulmonary bypass. Heparin is immobilized covalently in one (Carmeda Bioactive Surfaces; Medtronic, Anaheim, CA) and ionical in another (Duraflo II; Baxter, Irvine, CA). Covalent binding should be suited for those sircuit used for long periods because the covalently bound heparin is known to be more stable compared with ionically bound heparin. Heparin molecules, to allow their free

molecules. In Carmeda Bioactive Surfaces (CBAS), the bonds between heparin molecules and spacer molecules (polyethyleneimine; PEI) are covalent, but those between spacer molecules, and base material are ionic. We have recently developed a new method in which all the bonds involved are covalent with an aim of augmenting the stability of the immobilized heparin for long-term extracorporeal membrane oxygenation.

The major drawback of the current heparin-coated systems is inevitable plasma leakage caused by the use semipermeable membrane oxygenator. ECMO, in contrast to cardiopulmary bypass of relatively short duration, provides cardiopulmonary support over a long period. Freauent exchange of oxygenators caused by plasma leakage is a serious problem because it is accompanied by rapid hemodynamic changes, loss of circulating platelets, and greater reqirements for blood transfusion. Silicone-based membrane oxygenators are routinely used for long-term pulmonary support, but heparin coating these oxygenators has not yet been reported because of techical difficulties.

This study was performed to evaluate a new heparin-coated ECMO system that should reduce the amount of systemic jeparinization while preventing plasma leakage. A miniature ECMO system including a membrane oxygenator made of a double-layer poluolefin hollow fiber, which is know to be resistant to plasma leakage, was coated by heparin with a new covalent binding method. We evaluated the stability of the immobilized

heparin in vitro and the feasibility of this system in animals. Samples of hollow fibers and tubing were rinsed at 40 C for four days in normal saline, Ringer's lactate, and 1mol/L NaCl solution. Heparin activities on hollow fibers after rinsing were 99±2.3% (mean±SD), 96±3.9%, and 93±2.0% of the control in each solution, while those of the tubing were 87±4.1%, 86± 3.1%, and 76±8.6%, respectively. Veno-arterial ECMO using this heparin-coated system were performed no five beagles (8 to 12 Kg) for 10 hours. Neither major thrombus formation nor plasma leakage was detected during the procedure in spite of a low flow rate (300 ml/min) and reduced activated clotting time(mean. 128 seconds). Platelets decreased to 52% of the control ($p<.01$) at 1 hour, but no progressive decrease was seen thereafter. Antithrombin-III decreased ($p<.01$) and thrombin/antithrombin III complex increased ($p<.05$ at 4 hours and $p<.01$ at 6, 8, and 10 hours) during bypass, but the changes of fibrinogen and fibrinopeptide A were not significant. Fibrinogen/fibrin degeneration products, fibrinopeptide B β 15-42, and plasma-free hemoglobin levels did not rise significant. O2 transfer of the oxygenators at a flow fate of 300 ml/min were 12.3±0.4mL/min at 30 minutes, 14.3±1.2mL/min at 5 hours, and 14.7±4.7mL/min at 10 hours (no statistical difference). Histological examination of the brains and the kidneys showed no evidence of thrombolic sequela in any of the animals. These results suggest that this new system is a promising device for long-term ECMO in which the amount of systemic heparinization can be reduced

with the minimal possibility of plasma leakage.

Finally thanks the Japan-China Medical Association again. Also thanks my instructors, K Miyasaka, S Nakagawa, and all the staff of the Dep. of pathophysiology, National Children's Medical Research Center.

Thesis:

1. Infusion speed accuracy and consistency of disposable infusion pumps.

J Pediatr Chil Health 33:S95, 1997.

2. Evaluation of continuous intra-arterial blood gas monitoring under rapidly changing body temperature in pigs.

Clinical Pediatric Anesthesia 3(1):153-158, 1997

3. Evaluation of an Extracorporeal Membrane Oxygenation System Using a Nonporous Membrane Oxygenator and a New Method for Heparin Coating

Journal of Pediatric Surgery 32(5):691-697, 1997

Presentation:

1. Evaluation of four disposable infusion pumps

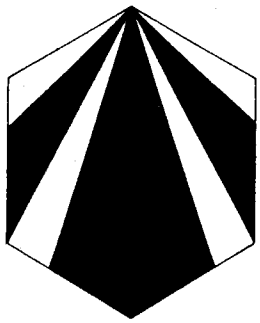
9th Asian Pediatric Congress. 23rd-27th March 1997, Hong Kong

2. Using of disposable infusion pumps for home care

24th Congress of Intensive Care Medicine of Japan, 15-16th May, 1997, Morioka, Iwate, Japan

第19回日本麻酔・薬理学会総会

講演抄録集



平成9年6月12日(木)・13日(金)

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プログラム

C－17　鼓室形成術直後に肺水腫を発生した１例

帝京大学市原病院集中医療センター　後藤　幸子、他6名

C－18　脳内結核腫で救急受診した若年者の術後管理の１例

帝京大学市原病院集中治療センター　白土　瑞技、他6名

薬物の効果と持続注入ポンプ　14:30～15:30　座長　古家（ふるいや）　仁(奈良医科大学)

C－19　ウリナスタチンが人工心肺中の interleukin-8 (IL-8)
および P-selectin に及ぼす影響

慶應義塾大学麻酔学教室　大内　貴志、他4名

C－20　ＡＲＤＳに対するウリナスタチンの経気道的投与
－急性期および慢性期での治療効果の比較検討－

埼玉医科大学総合医療センター麻酔科　川崎　潤、他6名

C－21　低用量アミノフィリン投与は全身麻酔後の低酸素血症に対して有効

近畿大学麻酔科学教室　田仲　毅至、他6名

C－22　ディスポーザブル携帯型持続微量ポンプの評価
－在宅疼痛管理応用の観点から－

国立小児医療研究センター病態生理研究室　劉　冬梅、他5名

C－23　微量輸液回路を用いたプロポフォールの簡便な投与方法

社会保険横浜中央病院麻酔科　増田都志彦、他5名

C－24　速度可変式簡易持続注入ポンプを用いた完全静脈麻酔においての
術中・術後疼痛管理

日本大学麻酔科学教室　長島　真治、他4名

疼痛管理　15:30～16:30　座長　宮崎　東洋(順天堂大学)

C－25　帯状疱疹後神経痛に対する末梢循環改善薬の効果
－PGE_1テストによる効果予測の有用性－

奈良県立医科大学麻酔学教室　山上　裕章、他4名

C－26　発症後長期間を経た帯状疱疹後神経痛症例に対する
硬膜外腔へのケタミン注入の効果

近畿大学麻酔科学教室　蔵　昌宏、他7名

C－27　帯状疱疹後神経痛の難治例に対する10%リドカインクリームの有用性

順天堂大学麻酔科学教室　井関　雅子、他6名

C－28　帯状疱疹後神経痛（ＰＨＮ）の鍼治療

北里研究所東洋医学総合研究所鍼灸診療部　石野　尚吾、他1名

C－29　持続皮下モルヒネ注入法による下腹部手術術後鎮痛法

杏林大学麻酔学教室　巌　康秀、他5名

C－２１　　低用量アミノフィリン投与は全身麻酔後の低酸素血症に有効

近畿大学医学部麻酔科学教室
○田仲毅至　蔵昌宏　有光正史　河田圭司　泉貴文　奥田隆彦　古賀義久

全身麻酔後の低酸素血症の原因には，前投薬・麻酔薬・術後疼痛また呼吸機能など多くの因子が挙げられる．今回，術後の回復室において低酸素血症(PaO_2＜80mmHg，FiO_2:0.4)に対して低用量アミノフィン(2mg/kg)を投与して，その影響について検討したので報告する．

【対象と方法】全身麻酔後の回復室でフェイスマスクによる酸素投与(FiO_2: 0.4)にもかかわらず，動脈血ガス分析で低酸素血症(PaO_2＜80mmHg)を呈した58症例を対象とした．対象群ではFiO_2を0.5以上に上昇させて，15分後の動脈血ガス分圧・血圧・脈拍数について酸素投与前と比較検討した．一方，アミノフィリン群ではFiO_2を0.4のまま維持して，アミノフィリン2mg/Kgを5分間で静脈内投与し，投与終了10分後に同様の項目について測定して投与前値と比較した．統計学的検討としてpaired　*t*-testを用いて$p<0.05$を有意差ありとした．

【結果】対象患者の平均年齢，身長，体重および回復室入室後の動脈血ガス分圧では，両群間に有意差を認めなかった．PaO_2は対象群では平均67±6mmHg(mean±SD)から95±7mmHgに，アミノフィリン群では70±4mmHgから128±13mmHgとそれぞれ有意な上昇が認められた．FiO_2を考慮したとき，PaO_2はアミノフィリン群の方が対照群に比して有意に上昇した．$PaCO_2$・平均動脈圧・脈拍数は両群間に有意差を認めなかった．また，対象患者のうち術前術後の胸部レントゲン写真上明らかな異常所見を認めた症例はなかった．

【結語】術後の低酸素血症に対して2mg/kgのアミノフィリン投与は循環動態に影響を与えないで低酸素状態を改善するために有用である．

C－２２　　ディスポーザブル携帯型持続微量ポンプの評価
―在宅疼痛管理応用の観点から―

国立小児医療研究センター　病態生理研究室、国立小児病院　麻酔集中治療科*
○劉　冬梅、鈴木康之*、宮坂勝之、張　欽明、杉山正彦、中川　聡

ディスポーザブル携帯型持続微量ポンプ（DP）は、電気を必要とせず、また、軽量であるという利点から、入院中のみならず在宅での疼痛管理への応用が期待される。我々は、現在使用可能な４種類の DP の輸液速度の精度と一定性に加え、環境温や DP の位置が輸液速度に及ぼす影響を検討した。　【方法】対象の DP は、バルーン型であるバクスターインフューザー（バクスター、B）、DIB カテーテル（三矢メディカル、D）、シュアフューザーA（ニプロ、S）と、シリンダー内の陰圧を駆動源としたシリンジ型であるクーデックシリンジェクター（大研医器、C）の計４種類である。DP の輸液速度を、D では 1.7 ml/hr、S では 2.1 ml/hr、B と C では 2.0 ml/hr に設定し、その実際の輸液速度を小児用点滴輸液セットと光電センサーを用い測定した。実測した輸液の精度と分散を４種間で比較した。さらに、３種類の環境温設定（4、25、37 ℃）において、また DP の位置を３段階に変化させ（仮想した心臓と同じ高さと、それよりも 50 cm ずつ高い場合と低い場合）、同様の検討を行った。　【結果】環境温が 25 ℃で、心臓と同じ高さに DP を置いたときの輸液速度（輸液開始２時間から 22 時間まで）を表に示す。また、輸液速度は、環境温および DP の位置により影響を受けた。

【結論】DP の輸液速度の精度と一定性はポンプ間で異なり、なかではシリンジ型（C）が最も安定していた。また、輸液速度は環境温や DP の位置により影響を受けるため、在宅も含む臨床使用においては、それらを考慮する必要がある。

ポンプ（設定輸液速度；ml/hr）	B（2.0）	D（1.7）	S（2.1）	C（2.0）
平均輸液速度（ml/hr）	2.10	1.69	2.06	2.11
輸液速度の分散係数（%）	5.0	15.5	6.7	2.9