INTERFACE

SOCIETY FOR TECHNOLOGY IN ANESTHESIA

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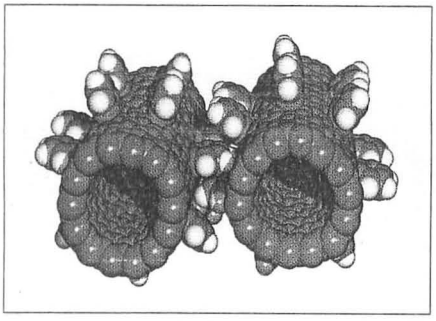
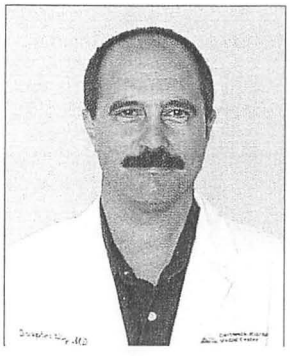
STA at the ASA in Dallas

STA Dinner Looks Ahead: Nanotechnology and the Future of Medicine



Molecular Gears

In our lifetimes most of us have witnessed astonishing progress in technology. We have progressed from the introduction of rotary dial telephones and television through the Nuclear Age, the Space Age, the Computer Age, and the Internet Age; all in the course of a few short decades.



Christopher Wiley, M.D.

Most of this steadily accelerating change has been driven by the explosion of information technology resulting from our ability to manipulate information at its most basic (binary) level using circuits of rapidly shrinking size and cost. The implications for society in general, and medicine in particular, have been profound.

What if there was a similar revolution in our ability to manipulate matter?

At our next annual ASA Dinner Meeting, Sunday, October 10 at 6:30 pm at the Adam's Mark Hotel, **Dr. Christopher Wiley**, Associate Professor of Anesthesiology at the Dartmouth-Hitchcock Medical Center and Senior Associate at the Foresight Institute (http:\\www.foresight.org), will answer that question. In "Nanotechnology and the Future of Medicine" he will introduce the rapidly growing field of molecular nanotechnology, which holds the potential to transform medicine as well as nearly all other aspects of our lives. Ξ

Breakfast Panel: Root Cause Analysis "Insight" or "Sound Bite"?

Increasingly, the public is aware that medical mistakes are a serious problem, and clinicians are being charged to identify "system" deficiencies. The anesthesia profession is to be credited with leading the safety movement in medicine.

This Fall, an ASA Breakfast Panel sponsored by STA will assemble a team of experts to discuss accident investigation methods. JACHO has implemented a Sentinel Event policy with the expectation that institutions will identify critical incidents and accidents, and then perform an analysis to look for root causes. This timely session is designed to help clinicians get beyond the rhetoric and learn practical techniques from a panel of experts.

It is logical that STA would provide a session to assist clinicians since members of the society have been influen-

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Breakfast Panel

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tial in using critical incident analysis methods as a way to improve patient safety.

Dr. Charlotte Bell, Chair of the STA Education Committee and Associate Professor of Anesthesiology at Yale, will kick the session off by introducing the panel.

Dr. George Blike, a human-error researcher from Dartmouth Medical School, will review the recent history of Sentinel Event/Accident Investigations in medicine. He will highlight the potential value in looking for "root causes" behind medical disasters using examples from other industries. He will also review a model characterizing features of anesthesia work.

Drs. David Feinstein and Dan Raemer, both from Boston and Harvard Center for Medical Simulation, will recreate a "sentinel event" using state-of-the-art telemedicine and simulation technology. They will use a panel from the audience to demonstrate the interactive nature of simulation.

Dr. Geetha Rao, from Exponent Failure Analysis Associates, is an expert in system failure analysis and provides experience with accident investigation strengths and weaknesses, both with examples outside and within medicine. She will perform a "root cause analysis" (RCA) of the event that has been demonstrated.

Finally, Dr. Bell will summarize the practical points of accident investigation and help the audience understand how to use RCA to improve medical systems.

This should be a well attended session on a popular day (Monday) at the ASA for the Breakfast Panel. This topic and the format will feature the strength of STA -- technology, human factors research, and simulation.

Hope to see you there!

INTERFACE is the official newsletter of the Society for Technology in Anesthesia. The newsletter is published quarterly and mailed directly to the membership of the society. The editors invite suggestions, contributions and commentary about published items. Please send all correspondence to:

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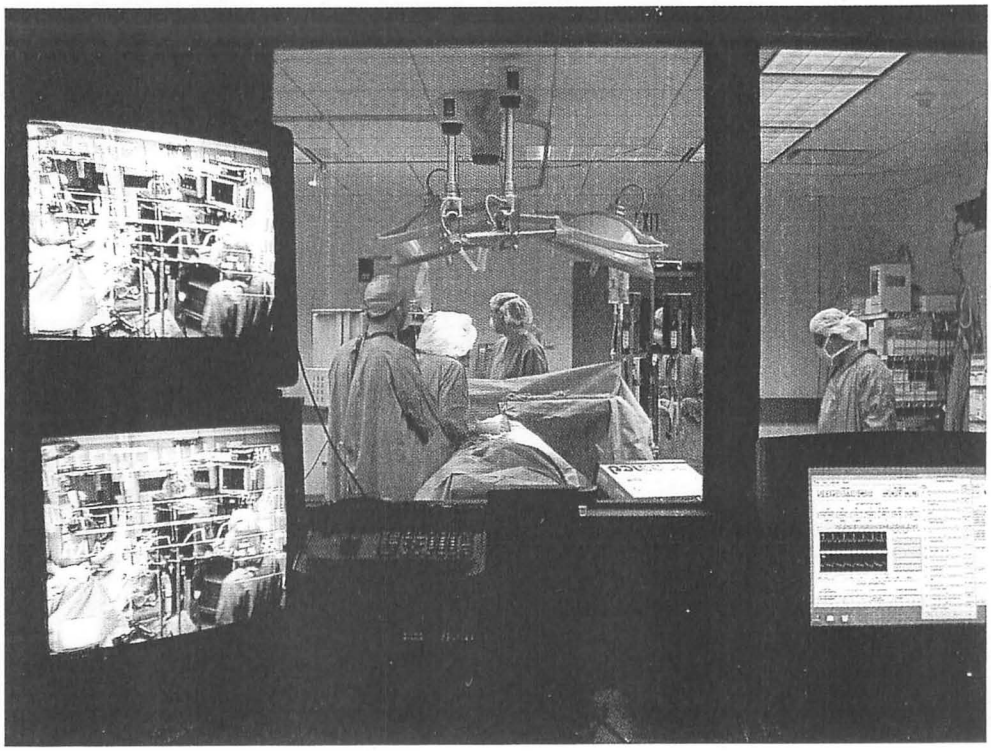

Boston and Harvard Center for Medical Simulation

Partial Liquid Ventilation In Acute Lung Injury and ARDS

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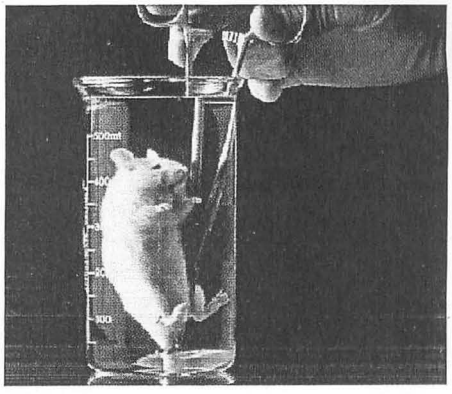
The prospect of liquid ventilation of injured lungs is a result of the development of non-toxic compounds possessing appropriate physical/chemical properties to support gas exchange coupled with the clinical search for improved therapies for acute lung injury and ARDS.

In over 30 years since the original description of the Acute Respiratory Distress Syndrome by Ashbaugh, Bigelow and Petty, little has changed in its treatment or mortality. A deepening understanding of the pathophysiology of this condition has led to supportive mechanical ventilation strategies to effect gas exchange with fewer complications. However, none of the many drug therapies tried (including surfactant, anti-oxidants, nitric oxide, steroids and anti-cytokine antibodies), or extra-pulmonary gas exchange techniques, has shown a decisive outcome benefit in large, controlled trials. Despite improved supportive care, published mortality for ARDS remains high, ranging from 40-60%.

Although resulting from a related but distinct pathologic process, Respiratory Distress Syndrome of Prematurity causes many of the same physiologic challenges seen in ARDS. Therefore, there is also interest in the use of partial liquid ventilation for this disease.

While unassisted liquid breathing by humans such as that depicted in the motion picture The Abyss (20th Century Fox, 1989), remains science fiction, the concept of total liquid ventilation is far from new. The adaptation to air breathing that precludes (in most species) survival under water, has intrigued scientists for years. The two essential requirements of any liquid breathing system are 1) solubility of the respiratory gases oxygen and carbon dioxide and 2) non-toxicity and non-reactivity of the liquid. Aqueous solutions at standard pressure contain an amount of oxygen comparable to that in air at 70,000 feet. However, Kylstra demonstrated in the early 1960's, that under hyperbaric conditions, mice could endure unassisted liquid ventilation in saline for up to 18 hours, with the limiting factor being carbon dioxide elimination rather than hypoxemia. As water dissolves only about one-half as much carbon dioxide as is contained in exhaled respiratory gas, the minute volume of liquid that must be circulated through the lungs to maintain normocapnia is nearly doubled. Furthermore, liquids are denser than air, causing the work of unassisted "breathing" of liquid to be many times that of gas-breathing. Even though various non-aqueous compounds provide much greater oxygen and carbon dioxide solubility and diffusivity than saline, it is unlikely that the human respiratory system could sustain unassisted, spontaneous ventilation with these liquids due to the markedly increased work of "breathing" them. Tidal breathing of the dense liquid, even if physiologically unnecessary for gas exchange, would probably have to be either suppressed or assisted in order to obviate the high energy cost of bulk liquid movement.

"While unassisted liquid breathing by humans, such as that depicted in the motion picture *The Abyss* (20th Century Fox, 1989), remains science fiction; the concept of total liquid ventilation is far from new."



Photograph courtesy of Alliance Pharmaceutical Corp., 1999

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Liquid Ventilation

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Clark and Golan reported acute and long-term survival of mice after submersion in perfluorocarbon liquid at normal atmospheric pressure. Perhaps most recognizable for their liquid-breathing mouse photograph, these authors also supported anesthetized cats and dogs with total liquid ventilation and, importantly, demonstrated their successful return to air breathing. However, concerns over work of breathing and the direct pulmonary toxicity of the compounds initially used (silicone oils and perflurobutyltetrahydrofurans) precluded further evolution toward human use until the development of newer perfluorocarbons (FC-77 and AF0141) in the 1980's.

Due to the requirement for a complex extra-corporeal gas exchange/ delivery system for *total* liquid ventilation in humans, most new clinical efforts have focused upon a *partial* liquid ventilation technique which Fuhrman et al described as "perfluorocarbon-associated gas exchange (PAGE)" using the the perfluorocarbon FC77 (3M, St. Paul, MN) in normal piglets with volume-controlled ventilation. Based upon the assumptions that transition to and from liquid ventilation was easily accomplished and that the gas/ liquid interface could be located *within* the respiratory system, partial liquid ventilation is accomplished by instillation of a volume of liquid equal to or less than functional residual capacity (FRC) into the respiratory system during conventional mechanical gas ventilation. Sufficient gas movement in the distal airways provides a "bubble-oxygenator" effect by which the alveolar-capillary membrane is functionally "extended proximally" in the airways to the new liquid-gas interface created by the perflubron. In contrast to the concept of tidal liquid breathing, in PLV, little bulk flow of liquid takes place during the ventilator cycle. When a dose equivalent to FRC was used (30 ml/kg in pigs), Fuhrman's group found that the lungs were airless during the last 1.5-2 seconds of a 3 second ventilator cycle. Indeed, depending upon drug dose and tidal volume, some lung will be airless during most if not all of the ventilatory cycle! Thus the perfluorocarbon liquid serves as both an interface for exchange as well a reservoir for respiratory gases, during conventional mechanical ventilation. Recently, Rich et al demonstrated 24 hour survival of awake, uninjured, spontaneously breathing rabbits undergoing partial liquid ventilation with ~10ml/kg of perflubron administered through a percutaneous intratracheal cannula. The clinical application of this demonstration is unclear however, as no data was reported regarding gas exchange or work of breathing.

The perfluorocarbon compound that has progressed through development to human clinical trials is AF0141, now Perflubron (LiquiVent™, Alliance Pharmaceutical Corp., San Diego, CA), a sterile preparation of perfluorooctyl bromide, $CF_3(CF_2)_6CF_2Br$ (MW=499). It is radio-opaque, insoluble in water and nearly twice as dense, with a specific gravity of 1.92 (at 25°C) and a low surface tension of 18 dynes cm^{-1}; all properties which may enhance it's potential to support injured lungs. Perflubron will dissolve approximately 50 ml of oxygen and 200 ml of carbon dioxide per 100 ml of liquid. (at 1 atm and 37°C). The drug is biochemically inert, minimally absorbed and eliminated predominantly through expired gases.

Consistent with these properties are the findings that perfluorocarbon instilled in normal lungs results in a dose-dependent rightward shift of the pressure-volume curve, but with preserved hysteresis and unchanged

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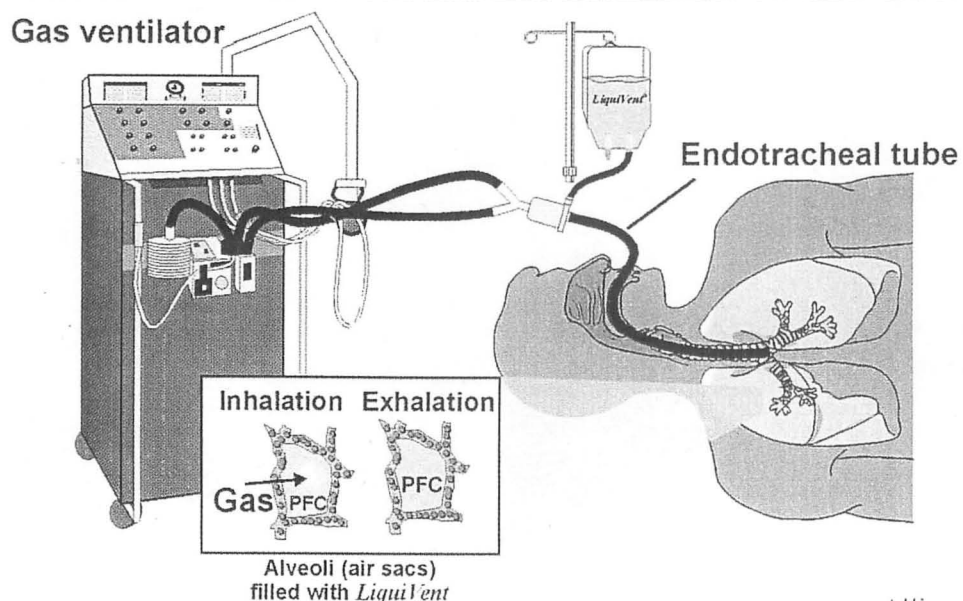
LiquiVent® Partial Liquid Ventilation



Liquid Ventilation

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peak and plateau airway pressures. A lower PaO_2 than with 1.0 FiO_2 gas ventilation is observed, but A-a O_2 Difference is comparable when the alveolar gas equation is corrected for the partial pressure of perflubron. (10.5 mmHg at 37°C) Although there is a measurably increased resistance to expiratory flow, carbon dioxide elimination and mechanical ventilation remain efficient with conventional equipment and return to gas ventilation is easily accomplished. There are no clinically significant, systemic effects of the drug and it appears to have no serious or long-lasting adverse effects upon the lung parenchyma.

The pathophysiologic characteristics of inflammatory ALI/ARDS include interstitial edema, alveolar infiltrate and diminished production of surfactant; conditions which lead clinically to diminished pulmonary compliance and ventilation/perfusion mismatching even to the extremes of true shunt and increases dead space to tidal volume ratio. Also important is that the distribution of disease within the lung is inhomogeneous, with predominance in dependent lung regions, causing non-uniformity of ventilation. Therefore efforts to recruit diseased units must be balanced against the deleterious effects upon healthy lung units and hemodynamics. In essence, a level of ventilator support is sought which permits adequate gas exchange while avoiding high inspiratory pressures and volumes (baro- or volutrauma), and high FiO_2. This is the basis of the so-called "lung-protective" strategies for ventilatory management in ARDS.

Several features of partial liquid ventilation may facilitate such protective strategies in ALI/ARDS.

1)Improved Gas Exchange by Diffusion: Low surface tension and high spreading capability may allow gravity-dependent access of liquid to non-ventilated alveoli. If the liquid then served as a reservoir and conduit for respiratory gases, shunt fraction could be reduced as *airless* lung participates in gas exchange, in effect off-setting the non-uniformity of gas exchange so typical of ARDS.

2)*Lung Recruitment ("Dependent PEEP")*: Being nearly twice as dense as water, perflubron fills more dependent lung zones first, therefore, in contrast to positive-end-expiratory pressure (PEEP), more diseased units (due to their dependent distribution) are preferentially exposed to the liquid. These recruited lung units are effectively stented open by the dense and incompressible liquid perflubron. This effect should allow better gas exchange during application of lung-protective (lower volume and pressure) mechanical ventilation strategies.

3)*Improved Compliance*: The high surface tension gas-liquid interface at the alveolar membrane is replaced by the low tension liquid-liquid one in perflubron-filled units. The surface tension at a gas-perflubron interface is far lower than that found in diseased lung with decreased surfactant. Thus gas bubbles may form more easily in the liquid than at the natural alveolar-capillary membrane, increasing compliance. There is laboratory evidence that perflubron actually increases pulmonary surfactant by stimulating phospholipid synthesis.

4)*Redistribution of Pulmonary Blood Flow*: Another effect of the high liquid density relative to body fluids is that some pulmonary blood flow is displaced from more dependent regions to higher ones, which have higher ventilation/perfusion ratios and may be less-diseased. Although this would predictably increase pulmonary vascular resistance in liquid filled regions, human clinical studies that have examined this effect have shown no significant deleterious effects of partial liquid ventilation with perflubron on filling pressures, cardiac performance or oxygen delivery.

5)*Alveolar Tamponade*: It has been suggested that alveolar exudate formation could be retarded in units filled by the dense, water-immiscible perflubron liquid.

6)*Pulmonary Lavage:* Where exudative material does occur, it will always be lighter than the perflubron. Such debris could float (especially from dependent regions) to more proximal airway locations from which it could be more easily removed. Alternatively, it is also possible that this lavage effect might predispose to focal airway obstructions, where large volumes of exudative material are raised and become inspissated.

7)*Inflammatory Suppression*: Finally perflubron may have some local, direct anti-inflammatory effect upon the injured lung. In various in vitro models, perflubron has been shown to: attenuate lipopolysaccharide-stimuated cytokine release by macrophages, minimally decrease neutrophil chemotaxis, and decrease super-oxide anion release. Reduction of IL-1 and IL-6 (possibly removing a stimulus for IL-10), white blood cell count, and protein capillary leak has been reported by Croce et al in trauma patients treated with PLV using perflubron. Some histopathologic studies of injured/treated lungs show less extensive inflammation.

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Liquid Ventilation

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Numerous studies of perflubron PLV in animal models of ARDS, (including surfactant washout and oleic acid injury models) demonstrated improved oxygenation and pulmonary compliance. Dosing studies suggested that although the beneficial effects upon gas exchange were dose-dependent, there appeared to be a peak effect that may occur below functional residual capacity (FRC). Conversely, when filling is not maintained by supplemental dosing (to replace evaporative and suctioning losses), the beneficial effects wane. Therefore the optimal dose appears to be some fraction of FRC which has yet to be precisely determined.

In the first Phase I clinical trials of PLV in humans by Hirschl (adults) and Greenspan (premature infants), patients already on extra-corporeal life support were treated with perflubron. Gas exchange (as evidenced by decreased physiologic shunt) and pulmonary compliance improved, while the drug appeared to be well tolerated. A subsequent Phase I-II study in adults has confirmed the effects on gas exchange, but showed no change in compliance. Therefore, in consideration of the need to protect the lungs from ventilator-induced injury while maximizing the therapeutic effect of the liquid, recent investigations have focused on using approximately one to two thirds of adult FRC. A multi-center, randomized Phase III trial is presently underway, designed to compare low- (10ml/kg) and high- (20ml/kg) dose perflubron PLV with a control group of adult ALI/ARDS patients, all managed with protocol-specified, standardized mechanical ventilation and weaning protocols. The primary outcome variable will be the number of ventilator-free days at 28 days after treatment.

Perflubron is believed to be safe for tracheal instillation based upon copious animal and human data. Elimination occurs quite rapidly through evaporation when dosing is halted, however small are amounts of the radio-opaque substance are visible on chest X-ray for several weeks after administration and computed tomography studies have found perflubron in extra-pulmonary locations including the mediastinum and lymph nodes. Important risks of treatment include: filling desaturation, bradycardia (especially during filling), and pneumo/"fluorothorax." In treated pediatric and adult patients followed for one-year or more, there appear to be no long-term deleterious effects of perflubron therapy. There does not appear to be histopathologic evidence of any unique pulmonary injury when treated, ARDS-diseased lungs are compared with untreated ones. Admittedly, the number of humans treated with perflubron is limited (<500) and as with any new drug, low-occurrence or long-term adverse effects may not become apparent until much larger numbers of patients treated and subsequently followed.

Possible directions of clinical research with PLV in ALI/ARDS include: combination with other modalities such as high-frequency ventilation or ECLS, for which perflubron might have complementary effects; as well as pulmonary delivery of nitric oxide, surfactant or other drugs. Whether non-medicinal applications such as deep water diving, will ever be realized is unclear.

Partial liquid ventilation with perflubron has evolved from laboratory curiosity to the bedside of critically ill ARDS patients. In contrast to the narrow therapeutic targets of most other therapies proposed for ARDS, PLV appears to offer a unique and multi-faceted approach by directly and indirectly improving pulmonary gas exchange, permitting mechanical ventilation using lung-protection strategies, and possibly locally suppressing pulmonary inflammation and stimulating surfactant production. Although PLV with perflubron is perhaps the most promising treatment proposed for ARDS since its description, enthusiasm for its widespread clinical utility must be tempered while awaiting the results of randomized, controlled Phase III trials, currently in progress.

References:

Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. Lancet 60:233-239,1967

Kylstra JA: Experiments in water-breathing. Scientific American 219 (2):66-74, 1968

Clark LC Jr., Gollan F: Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. Science 152 (730):1755-1756, 1966

Furhman BP, Paczan PR, DeFrancisis: Perfluorocarbon-associated gas exchange. Crit Care Med 19:712-722, 1991

Rich PB, Reickert CA, Mahler SA, et al: Prolonged partial liquid ventilation in spontaneously breathing awake animals. Crit Care Med 27 (5):941-945,1999

Croce MA, Fabian TC, Patton JH, et al: Partial liquid ventilation decreases the inflammatory response in the alveolar environment of trauma patients. Journal of Trauma 45 (2):273-280,1998

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Meetings Minder

1999

The Society for Computers in Anesthesiology
Annual Meeting October, 1999
Dallas, Texas
http://gasnet.med.yale.edu/societies/scia
Contact: scia@AcmeAnesthesia.com

Seventh Foresight Conference on Molecular Nanotechnology , October 15-17, 1999
Santa Clara, CA.
http://www.foresight.org

American Medical Informatics Association
November 6-10, 1999 - Washington, DC
www.amia.org

ESCTAIC and SCATA combined fall meeting
November 11-13, 1999
Glasgow, Scotland
Contact : Pradeep Ramayyya(pramayya@scata.org.uk) or Gavin Kenny(Gavin_Kenny@compuserve.com)

Japanese Society for Technology in Anesthesia
Annual Meeting
November, 1999
Mito City
Email: m-kato@mail.cc.tohoku.ac.jp

Annual Scientific Meeting in Anesthesiology 1999
November 5-7, 1999
Hong Kong, China

NYSSA Postgraduate Assembly in Anesthesiology (PGA)
December 11-15, 1999
New York, NY
Http://www.nyssa-pga.org

2000

Society for Technology in Anesthesia
January 12-15, 2000
Orlando, FL
http://gasnet.med.yale.edu/societies/sta/

3rd Biennial Difficult Airway Management
January 22-27, 2000
Vail, CO
http://cme.med.uth.tmc.edu/

Medicine Meets Virtual Reality 2000
January 27 - 30, 2000
Newport Beach, CA
http://www.amainc.com/MMVR/MMVR.html

2nd Virtual Congress in Anesthesiology
February 3-4, 2000
On-line
Http://www.reanimation.com

International Ergonomics Association 15th Triennial Congress in San Diego
July 30-August 4, 2000

6th Congress of Anesthesiology and Intensive Medicine
September 28—October 1, 2000
Kallithea-Halkidiki, Northern Greece
http://users.otenet.gr/~fkanak/foten5.htm

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Hirschl RB, Pranikoff T, Wise C: Initial experience with partial liquid ventilation in adult patients with the acute respiratory distress syndrome. JAMA 275 (5):383-389,1996

Greenspan JS, Wolfson MR, Rubenstein SD, et al: Liquid ventilation of human preterm neonates. J Pediatr 117:106-111,1990

Hirschl RB, Conrad S, Kaiser R, et al: Partial liquid ventilation in adult patients with ARDS: a multicenter phase I-II trial. Adult PLV Study Group. Annals of Surgery 228(5):692-700,1998

Meaney JF, Kazerooni EA, Garver KA, et al: Acute respiratory distress syndrome: CT findings during partial liquid ventilation. Radiology 202(2):570-573,1997