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Journal-related Activities at the 2003 American Society of Anesthesiologists Annual Meeting

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12th Annual Journal Symposium: Preconditioning Against Ischemia and Reperfusion Injury

Tuesday, October 14, 2003, 9:00 AM to 12:30 PM, in the Gateway Ballroom 102 in the Moscone Center, San Francisco, California

The 12th Annual ANESTHESIOLOGY Journal Symposium will offer an important look at a newly discovered phenomenon, preconditioning by volatile anesthetic agents against ischemia and reperfusion injury. Preconditioning was originally recognized to occur after brief periods of ischemia. Paradoxically, a brief period of myocardial ischemia preceding a prolonged ischemic insult does not increase tissue injury, but instead is protective, dramatically reducing the extent of myocardial infraction. Cardioprotection by a brief period of ischemia is referred to as ischemic preconditioning and has been found in every species in which it has been studied. Ischemic preconditioning offers an important endogenous protective mechanism against ischemia and reperfusion injury. Only recently has ischemic preconditioning been shown to be mimicked by pharmacologic agents. Preconditioning is fascinating because administration of a pharmacologic agent or exposure to brief ischemia triggers a *change in the tissue* that lasts for a significant period of time after the drug effects have dissipated. The tissue acts as if it has "remembered" the prior exposure to the initiating stimulus. Volatile anesthetics are capable of producing preconditioning against ischemic injury, and now that the protective properties of these drugs has been well described, new paths of research are pointing to a multitude of mechanisms whereby this occurs. These agents are not only protective in myocardium but also in renal and neural tissue (and possibly many more). Their ultimate impact on outcome following cardiac and noncardiac surgery is yet to be realized. The Symposium will take the audience on a brief "tour" of the basic cellular mechanisms whereby volatile anesthetics elicit tissue protection— especially of myocardium. This newly discovered area has important implications for anesthesiologists as certain opioids have also been shown to be tissue protective. Volatile anesthetics and opioids such as morphine interact and potentiate the cardioprotective properties of one another. Finally, and significantly, *impressive results of new clinical investigations* demonstrating the beneficial effects of volatile anesthetics on tissue injury in patients with coronary artery disease will be presented.

The Symposium will be moderated by Zeljko J. Bosnjak, Ph.D., and David C. Warltier, M.D., Ph.D., of the Medical College of Wisconsin, Milwaukee, Wisconsin. The speakers include:

- David C. Warltier, M.D., Ph.D, Professor of Anesthesiology, Pharmacology and Medicine, Medical College of Wisconsin
- Garrett J. Gross, Ph.D., Professor of Pharmacology & Toxicology, Medical College of Wisconsin
- Stefan De Hert, M.D., Professor of Anesthesiology, University Hospital, Antwerp, Belgium
- Michael Zaugg, M.D, Head, Cardiovascular Anesthesia Laboratory, Institute of Anesthesiology, University of Zurich, Switzerland

The speakers have all worked in the area of myocardial preconditioning for some time. Dr. Warltier will provide an overview of preconditioning by volatile anesthetics and will touch on potential mechanisms that have been established to date. Dr. Gross will devote his lecture to the protective properties of another group of drugs, the opioids that have profound effects on ischemia and reperfusion injury. Finally, Drs. De Hert and Zaugg will present clinical evidence for anesthetic preconditioning and possible signal transduction pathways in humans whereby this occurs.

A total of 21 posters will be presented and available for discussion. The text for each Abstract can be found on the ASA-Abstract Web site or in the CD-ROM that is included with this issue of the Journal.

Volatile Anesthetics Precondition Against Neutrophil-induced Contractile Dysfunction in Isolated Rat Hearts by Guochang Hu, M. Ramez Salem, George J. Crystal. University of Illinois College of Medicine, Chicago. *[1537]*

Effect of Desflurane-induced Preconditioning on Mitochondrial Transition Pore Opening by Vincent Piriou, Pascal Chiari, Odile Gateau Roesch, Jean Jacques

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Lehot, Michel Ovize. Centre Hospitalier Lyon Sud, France. *[1538]*

Role of Cyclooxygenase during Ischemic and Pharmacological Preconditioning in Dogs by Boris Mraovic, John G. Krolikowski, Paul S. Pagel, David C. Warltier, Judy R. Kersten. Medical College of Wisconsin, Milwaukee. *[1539]*

Xenon Induces Myocardial Protection by Preconditioning: Involvement of Protein Kinase C (PKC) by Octavian Toma, Nina C. Weber, Detlef Obal, Benedikt Preckel, Wolfgang Schlack. University Hospital, Duesseldorf, Germany. *[1540]*

Src-Tyrosine Kinases Mediate Isoflurane-induced Myocardial Protection In Vivo by Lynda M. Ludwig, Katsuya Tanaka, Paul S. Pagel, Judy R. Kersten, David C. Warltier. Medical College of Wisconsin, Milwaukee. *[1541]*

Xenon Prevents Hypoxic–Ischemic Induced Brain Damage in the Neonatal Rat by Daqing Ma, Mahmuda Hossain, Nicholas P. Franks, Mervyn Maze. Imperial College London, United Kingdom. *[1542]*

Differential Activation of Mitogen-activated Protein Kinases in Ischemic and Anesthetic Preconditioning by Michael Zaugg, Rafaela da Silva, Thomas Pasch, Marcus C. Schaub. University Hospital Zurich, Switzerland. *[1543]*

Unraveling the Gene Expression Patterns in Ischemic and Anesthetic Preconditioning by Gene Chip Analysis by Michael Zaugg, Rafaela da Silva, Pavel V. Sergeev, Thomas Pasch, Marcus C. Schaub. University Zurich, Switzerland. *[1544]*

Isoflurane Inhibits NFkB Activation in Response to Simulated Ischemia in Renal Tubular Cell Line, LLC-PK1 by Masanori Matsumoto, Michiko Yamaguchi, Hideo Hashiguchi, Hiroaki Morooka, Koji Sumikawa. Nagasaki University School of Medicine, Nagasaki, Japan. *[1545]*

Echocardiographic Evidence for Sevoflurane-mediated Preconditioning during Minimally Invasive Direct Coronary Artery Bypass Grafting (MIDCAB): Assessment of the Myocardial Performance Index by Jochen Renner, Berthold H. Bein, Dorothee Caliebe, Andrea Paris, Peter H. Tonner. University Hospital Schleswig-Holstein, Kiel, Germany. *[1546]*

The Relative Order of Reactive Oxygen Species and Protein Kinase C-δ in the Signal Transduction of Sevoflurane-induced Cardioprotection by Arthur R. Bouwman, Tomas Simunek, Christa Boer, Jaap J. de Lange, René J. P. Musters. VU University Medical Center, Amsterdam, Netherlands. *[1547]*

The Effect of Myocardial Function Protection of Sevoflurane Preconditioning in Senescent Rats by Roman Sniecinski and Hong Liu. University of California, Davis, California. *[1548]*

Integrated Pharmacological Preconditioning with Isoflurane, G Protein-coupled Receptor Agonists, and Nitric Oxide Donors: An Ideal Alternative to Ischemic Preconditioning by Hajime Otani, Hiroji Imamura, Mayu Takahashi, Shinichi Nakao, Koh Shingu. Kansai Medical University, Moriguchi, Osaka, Japan. *[1549]*

Effect of Protein Kinase C Inhibition by Staurosporin on Isoflurane Preconditioning in the Rat Heart In Vivo by Detlef Obal, Jost Muellenheim, Saskia Dettwiler, Wolfgang Schlack. University Hospital Duesseldorf, Germany. *[1550]*

The Mechanism of Sevoflurane-induced Cardioprotection Is Independent of the Applied Ischemic Stimulus in Rat Trabeculae by Christa Boer, Arthur R. Bouwman, Wouter de Ruijter, Jaap J. de Lange, René J. P. Musters. VU University Medical Center, Amsterdam, Netherlands. *[1551]*

The Role of ROS and Mitochondrial KATP Channels in the Effects of Isoflurane on the Sarcolemmal KATP Channels by Jianzhong An, Anna Stadnicka, Wai-Meng Kwok, Zeljko J. Bosnjak. Medical College of Wisconsin, Milwaukee. *[1552]*

Morphine Preconditions Purkinje Cells Against Cell Death under In Vitro Simulated Ischemia–Reperfusion Conditions by Young Jin Lim, Shuqiu Zheng, Zhiyi Zuo. University of Virginia, Charlottesville, VA & Seoul National University College of Medicine, Seoul, Korea. *[1553]*

Protein Kinase C-ϵ Primes the Sarcolemmal KATP Channel to Modulation by Isoflurane by Kei Aizawa, Lawrence A. Turner, Zeljko J. Bosnjak, Wai-Meng Kwok. Medical College of Wisconsin, Milwaukee. *[1554]*

Sevoflurane-induced Preconditioning Against Hypoxic Neuronal Injury Is Dose-Dependent and is Triggered by Mitochondrial K_{ATP}-channels by Franz Kehl, Ralphiel S. Payne, Thorsten Smul, Norbert Roewer, Avital Schurr. Julius-Maximilians-University, Wuerzburg, Bavaria, Germany. *[1555]*

Concentration-dependent Attenuation of Mitochondrial Respiration by Sevoflurane in Isolated Cardiac Mitochondria Is Mediated in Part by Reactive Oxygen Species by Matthias L. Riess, David F. Stowe, Michele M. Henry, Amadou K. S. Camara, Janis T. Eells. Medical College of Wisconsin, Milwaukee. *[1556]*

The Role of Nuclear Factor-kappa B in Sevoflurane Preconditioning during Myocardial Ischemia/Reperfusion by Caiyun Zhong, Yamei Zhou, Hong Liu. University of California, Davis. *[1557]*

SOAP/Journal Abstract Session: Obstetric Anesthesia Research Contributing to Several Specialties—"Innovative Research in OB Anesthesia"

Tuesday, October 14, 2003, 2:00 to 4:00 PM, in the Gateway Ballroom 102 in the Moscone Center, San Francisco, California

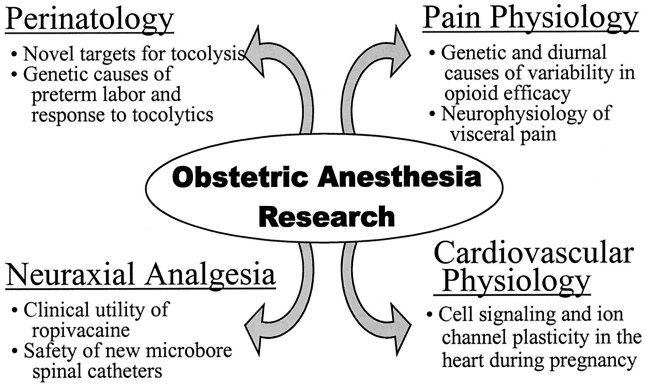

Fig. 1. Obstetric anesthesia research contributions to be highlighted at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 11–15, 2003.

Next month's Annual Meeting will highlight the first special research session sponsored jointly by the Society for Obstetric Anesthesia and Perinatology (SOAP) and ANESTHESIOLOGY. The eight abstracts (the complete list follows below) selected for oral presentation in this session reflect both outstanding science and major research contributions by obstetric anesthesiologists to several areas of medicine (fig. 1).

Perinatology

Preterm delivery remains an important cause of neonatal morbidity. Although some clues to the causes of premature labor have come from epidemiologic studies, we remain woefully ignorant regarding normal mechanisms that regulate uterine activity. Two abstracts in this session approach this problem from different angles. Yunping Li, M.D. (Abstract 1558) focuses not on mechanisms that stimulate myometrial activity, but rather on factors that maintain uterine quiescence during preterm pregnancy. She and her colleagues hypothesized that premature labor originates from activation of an enzyme, extracellular signal regulated kinase (ERK), which in turn phosphorylates a protein, Caldesmon, leading to smooth muscle activity and uterine contractions. Dr. Li will present biochemical studies that show this cascade to occur during premature labor in the rat, that administration of an experimental compound which prevents activation of ERK delays preterm delivery, and that the ERK/Caldesmon pathway represents an important novel target for tocolysis. Ruth Landau, M.D. (Abstract 1564), as part of a series of studies in collaboration with Richard Smiley, M.D., Ph.D., focuses on genetic factors that interact with pregnancy to determine the risk of preterm delivery and response to traditional tocolytics. Dr. Landau will present evidence that tocolysis with a β2-adrenoceptor agonist is more likely to be successful in delaying preterm delivery in women homozygous for the Arg16 variant of the β2-adrenoceptor, which has been associated with less desensitization on exposure to β2-agonists. Therefore, selection of class of tocolytic in the future may be based on simple genetic testing of blood.

Pain Physiology

Most fundamental research and current commercial development in pain today targets neuropathic pain, yet other major pain problems remain practically ignored. Three abstracts in this session explore such unstudied areas. There is a tremendous interindividual variability in potency and efficacy of opioid treatment for pain. Ruth Landau, M.D. (Abstract 1559) examined one possible genetic basis for this variability, that of a polymorphism of the μ-opioid receptor, with one allele expressing a receptor with higher affinity for μ-opioid receptor ligands than the other. This genetic polymorphism had previously been studied only in drug-addicted populations, where the higher affinity allele occurs with a frequency of 10–18%. Dr. Landau will present a large study in nonaddicted pregnant women in whom this allele frequency is much higher (30%), suggesting a lower opioid dose requirement for analgesia and possibly indicating a difference in genetic expression of μ-opioid receptors between addicted and nonaddicted populations.

Variability in opioid efficacy depends not only on genetic factors, but also on a complex interplay with neurophysiologic factors that change with time. Diurnal patterns of hormonal release and neuro-immune functions have previously been described, but little attention has been paid to pain and opioid efficacy. As part of a series of studies addressing diurnal patterns in pain and analgesic efficacy, Richard Debon, M.D. (Abstract 1563) examined the duration of analgesia from intrathecal sufentanil injection in laboring women. He will present evidence of a strong diurnal influence, significantly different from that previously observed in chronic pain patients receiving oral morphine, and will discuss the need to account for this pattern when examining analgesic efficacy in future studies.

Most of our understanding of peripheral mechanisms of pain comes from study of somatic structures, primarily the skin. The neurophysiologic basis for pain from the lower uterine segment and endocervix, the site of labor and many types of gynecologic pain, remains virtually unexplored. Chuanyao Tong, M.D. (Abstract 1562) utilized a newly described animal model of pain resulting from dilatation of the uterine cervix. He will present data showing the efficacy of a highly selective κ-opioid receptor peptide agonist in this model and will discuss the possibility that intravenously administered peptide agonists of this type may, in the future, effectively treat pain from the first stage of labor with minimal maternal or fetal effects.

Neuraxial Analgesia

The local anesthetic, ropivacaine, has been marketed for several years, yet controversy persists regarding its most fundamental properties, especially its relative potency for sensory and motor block compared to bupivacaine. This has particular relevance in obstetrics: a meta-analysis has suggested that ropivacaine produces less motor block than bupivacaine in laboring women, accompanied by a reduced rate of instrumental delivery. Peter Szmuk, M.D. (Abstract 1565) performed a randomized, prospective, large trial of 565 laboring women randomized to self-titrated bupivacaine, 0.125% or ropivacaine, 0.2% for analgesia. On the basis of these results, it seems that ropivacaine is less potent than bupivacaine and at similar doses it does indeed produce less motor block, but this has no influence on rate of instrumental delivery.

Microbore spinal catheters, developed over 15 yr ago, were rapidly applied to obstetric and peri-operative settings, and allowed rapid, flexible, and effective titration of analgesia and anesthesia with minimal doses of drug. Shortly after their introduction, a series of permanent neural injuries, mostly associated with injection of 5% lidocaine, led the Food and Drug Administration to withdraw these devices from the market. In a landmark study, Valerie A. Arkoosh, M.D. (Abstract 1561) will present a large, multicenter study of intrathecal sufentanil, administered through a 28-gauge catheter, compared to epidural bupivacaine plus sufentanil for labor analgesia. Preliminary data indicate that headache rates were similar between these methods and that neurologic injury did not occur.

Cardiovascular Physiology

Cardiac hypertrophy, arrhythmias, and prolonged QT intervals can occur during pregnancy, as well as in nonpregnant individuals, and the mechanisms by which these occur may differ. Manoureh Eghbali, Ph.D. (Abstract 1560) examined, in heart tissue of nonpregnant and pregnant rats and mice, the expression and function of a cell signaling pathway beginning with the tyrosine kinase c-Src ending in extracellular signal regulated kinase activation and those of potassium channel subtypes known to be down-regulated in cardiac hypertrophy and leading to a prolonged QT interval. He will show that pregnancy is associated with no change in c-Src protein expression, but with an increase in its activity, along with a reduction in the expression of mRNA for one potassium channel subtype, Kv4.3, and that processes activated in the heart during pregnancy and high estrogen exposure differ significantly from those of pathologic cardiac hypertrophy.

Not long ago, one of us opined that obstetric anesthesia research was retreating from major contributions to medical understanding and practice.[1] Judging from the exciting work to be presented next month, this assessment was most certainly premature. Please join us in what should be a fascinating and lively series of presentations and discussions.

A total of eight talks will be presented and available for discussion. The text for each abstract can be found on the ASA-Abstract Web site or in the CD-ROM that is included with this issue of the Journal.

Chronobiology of Intrathecal Sufentanil: Periodic Variations in Duration of Action by Richard Debon, Emmanuel Boselli, Bjorn Lemmer, Bernard Allaouchiche, Dominique Chassard. Hotel-Dieu Hospital, Lyon, France. *[1563]*

A Novel Kappa Opioid Receptor Agonist Inhibits Response to Visceral Nociception in Rats by Chuanyao Tong, Dongping Du, James C. Eisenach. Wake Forest University School of Medicine, Winston-Salem, North Carolina. *[1562]*

ERK Inhibition Delays the Onset of Labor in a Rat Model of Preterm Labor by Yunping Li, Hyun-Dong Je, Sabah Malek, Kathleen G. Morgan. Beth Israel Deaconess Medical Center, Boston, Massachusetts. *[1558]*

Genetic Variability of the μ-Opioid Receptor in an Obstetric Population by Ruth Landau, Richard M. Smiley, Stylianos E. Antonarakis, Jean-Louis Blouin. University Hospital of Geneva, Switzerland. *[1559]*

β-2-Adrenergic Receptor Genotype Determines Response to Tocolysis by Ruth Landau, Michel A. Morales, Richard M. Smiley, Stylianos E. Antonarakis, Jean-Louis Blouin. University Hospital of Geneva, Switzerland. *[1564]*

Epidural Analgesia for Labor Pain with Bupivacaine Versus Ropivacaine: Effect on Labor and Delivery and Neonatal Outcome by Peter Szmuk, Shmuel Evron, Marek Glezerman, Oscar Sadan, Tiberiu Ezri. University of Texas Medical School, Houston, Texas. *[1565]*

Molecular Signature of Heart Functional Hypertrophy during Pregnancy by Mansoureh Eghbali, Abderrahmane Alioua, Ligia Toro, Enrico Stefani. David Geffen School of Medicine at UCLA, Los Angeles, California. *[1560]*

Continuous Spinal Labor Analgesia: Safety and Efficacy by Valerie A. Arkoosh, Craig M. Palmer, Esther Yun, Richard N. Wissler. Drexel University College of Medicine, Philadelphia, Pennsylvania. *[1561]*

Interested readers should also not overlook the myriad other science-related presentations at this year's Annual Meeting, including, on Monday, October 13, 2003, the Rovenstine Lecture, the 1st Annual Celebration of Research Session (to follow the Rovenstine Lecture—with lunch provided!), and the 3rd Annual FAER Honorary Research Lecture (on Monday afternoon, October 13, 2003), as well as the many excellent posters that will be presented throughout the meeting.

Reference

1. Eisenach JC: Obstetric anesthesia: What have you done for us lately? ANESTHESIOLOGY 1999; 91:907–8