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Using Remifentanil in Mechanically Ventilated Rats to Provide Continuous Analgosedation

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Remifentanil is a potent synthetic opioid with sedative effects. Intravenous remifentanil provides deep sedation and analgesia in laboratory animals during experimental procedures. We hypothesized that remifentanil would provide effective analgosedation during assisted mechanical ventilation without affecting respiratory mechanics in rats. Five male Sprague–Dawley rats (weight, 400 to 450 g) were assigned to receive assisted mechanical ventilation with continuous positive airway pressure for 5 h. Remifentanil (0.4 μg/kg/min IV) was delivered for the duration of ventilation. There were no differences between baseline, 1 h, and 5 h of ventilation in the mean arterial pressure, cardiac output, heart rate, and body temperature of all rats. Similarly, no differences were observed in the tidal volume, respiratory rate and minute ventilation, and gas exchange was equal in all rats at all time points. Frequent assessment of sedation by toe pinch documented loss of the pedal withdrawal reflex in all rats. We conclude that continuous remifentanil infusion provides sufficient analgosedation for mechanically ventilated rats without compromising hemodynamics, respiratory function, or gas exchange.

Abbreviation: ABS, analgesia-based sedation.

Strategies to ensure appropriate anesthesia and analgesia in animals during and after experimental procedures are important in a laboratory setting. The use of fentanyl and other opioids for pain control and surgical anesthesia has increased in laboratory animals, owing to the clinical principle of analgesia-based sedation (ABS). In ABS, analgesics are used to maximize comfort, minimize distress, and provide deep sedation simultaneously.[21,26,31] Compared with hypnosis-based sedation, ABS is more effective for managing intensive care patients, because sedatives have little or no analgesic potency and are less effective in inducing tolerance to painful stimuli.[27]

Opioids are administered parenterally, intravenously, orally, and even intrathecally in laboratory animals.[4,5,33,35] However, the intraperitoneal application of opioids makes titrating their effects more challenging because of the risk of under- or overdosing,[9,19] thereby complicating prediction of their effects. This drawback is especially important in animals undergoing potentially harmful procedures, such as experimental sepsis[29] or lung injury, because the risks for hemodynamic deterioration and premature death are greater. For these purposes, animals need deep sedation and analgesia, where a drug-induced state of reduced consciousness limits easy arousal and response to painful stimulation. The ideal strategy would ensure effective anesthesia–sedation, analgesia, and hemodynamic stability in laboratory animals undergoing potentially painful interventions.

Remifentanil is a derivative of fentanyl, a drug widely used as a potent synthetic opioid with properties of analgesia and sedation.[12,13] Remifentanil belongs to a class of opioid analgesics known as the phenylpiperidines[22] that functions as a potent opioid receptor agonist mainly by binding to the μ receptor, but this drug also can interact with the δ and κ receptors widely expressed in the CNS.[28,31] Remifentanil is unique from other analgesic derivatives in that its molecular structure contains 2 ester linkages that are highly susceptible to various plasma and nonspecific tissue esterases.[18,28] Hydrolysis of these linkages results in the rapid metabolism of remifentanil, giving it the shortest half-life of all fentanyl derivatives, with a metabolism independent from organ function.[13,25,26,31]

The rapid onset and offset of remifentanil's effects make it an ideal candidate for an intravenous infusion protocol where continuous anesthesia and analgesia are required, regardless of the duration of the procedure.[12] This benefit is due to remifentanil's predictable termination of anesthetic and analgesic effects, thereby facilitating fast recovery when the infusion is discontinued.[18,28] In addition to delivering effective analgesia, remifentanil has been reported to produce respiratory depression, chest wall and muscular rigidity, suggesting the need for respiratory support such as mechanical ventilation.[20,24]

Due to its ease of titration, remifentanil has been used in spontaneously breathing patients needing minor procedures,[14] intensive care patients,[2] and preterm infants that required mechanical ventilation due to respiratory distress.[16] According to one report, remifentanil provided deep sedation and analgesia without causing respiratory or hemodynamic compromise.[16] A recent study similarly demonstrated that intravenous remifentanil was effective for ABS in critically ill patients, but it was not superior to fentanyl.[34] Remifentanil was effective in improving the breathing pattern of patients undergoing pressure-support ventilation because of rapid shallow breathing,[24] and remifentanil infusion decreased the respiratory rate but not tidal volume of patients during ventilation.[24] Therefore, remifentanil infusion is safe and effective for ABS in adult, pediatric, and neonatal intensive care patients for a variety of procedures, including mechanical ventilation.[1]

In laboratory animals, continuous intravenous infusion of remifentanil was used in the ABS of swine undergoing mechanical ventilation with preserved spontaneous breathing in the presence of lung injury.[20] In addition, intravenous remifentanil was effective in providing deep sedation to facilitate mechanical

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ventilation of swine in both pressure-support and pressure-control modes.[20] When used in conjunction with isoflurane or sevoflurane in laboratory rats, intravenous remifentanil reduced the minimum alveolar concentration in a dose-dependent manner, thus providing alternative routes for effective sedation and pain relief.[11,17] These findings support the potential use of intravenous remifentanil in an ABS regimen to provide deep analgosedation in laboratory animals during various experimental procedures including mechanical ventilation.

Although remifentanil has been used for ABS in patients and animals, there is currently no well-established protocol for its use for continuous sedation of laboratory animals undergoing mechanical ventilation with spontaneous breathing. For that reason, we developed a regimen for intravenous infusion of remifentanil to maintain continuous analgosedation in laboratory rodents during assisted spontaneous breathing. We hypothesized that an ABS protocol based on remifentanil would facilitate deep sedation of rats undergoing assisted ventilation without compromising the hemodynamic stability, respiratory mechanics, and gas exchange while preserving spontaneous breathing.

Materials and Methods

Laboratory animals and husbandry. Healthy male Sprague–Dawley rats (*Rattus norvegicus*; weight, 400 to 450 g) were obtained from Charles River Laboratories (Saint-Constant, Canada). The rats were pair-housed in the Carlton Animal Care Facility at Dalhousie University on a 12:12-h light:dark cycle, at a constant room temperature of 21 to 22 °C, in conventional cages (10.5 in. × 19 in. × 8 in.) with hardwood chip bedding (Beta Chips, Northeastern Products, Warrensburg, NY) and hay. The rats received unlimited access to Prolab Rodent Chow (PMI Nutrition International, St Louis, MO) and water. All rats received daily health checks by animal care staff at Dalhousie University to ensure the wellbeing of all animals.[8]

Experimental apparatus and procedures. All experimental procedures and protocols were conducted humanely with approval from the University Committee on Laboratory Animals, the Research Ethics Board, and the Carlton Animal Care Facility at Dalhousie University.[8] Five male Sprague–Dawley rats were used, to minimize the number of animals necessary to achieve the objective of this study. To refine animal treatment in the laboratory, various measures were taken throughout experiments to ensure that the rats were treated humanely with care and respect. All experiments were conducted on a heated stainless steel operation table (Harvard Apparatus Canada, Saint-Laurent, Canada) with an internal surface heater maintained at 37 °C. Additional heat was provided by an overhead lamp (Burton Medical, Chatsworth, CA) as needed.

Rats initially were anesthetized by intraperitoneal injection of sodium pentobarbital (55 mg/kg; Ceva Sante Animale, Montreal, Canada) to provide surgical anesthesia for vessel cannulation. Once surgical anesthesia was confirmed, the rats were placed in supine position on the operation table, and the neck and femoral regions of the body were prepared for cut-down and vessel cannulation.[7] The carotid artery was cannulated to monitor mean arterial pressure by direct connection to a physiologic pressure transducer (ADInstruments, Colorado Springs, CO). The external jugular vein was cannulated to facilitate the continuous infusion of remifentanil and fluids (saline).

A thermocouple temperature probe (Physitemp Instruments, Clifton, NJ) was inserted into the aorta through the femoral artery to facilitate monitoring of body temperature and for measuring cardiac output by using the thermodilution principle. Briefly, 2 boluses of 0.5 mL each (0.9% NaCl, room temperature) were administered intravenously. Temperature changes were recorded, and cardiac output was computed according to the Stuart–Hamilton equation by using LabChart software (ChartPro 6.0, ADInstruments) from the mean of 2 consecutive measurements. Core body temperature was monitored continuously throughout all experiments and maintained between 37 to 38 °C to minimize distress and ensure the comfort of the rats. Finally, a tracheostomy was performed by securing a 14-gauge cannula in the trachea. The tracheal cannula was connected to a neonatal intensive care ventilator (Evita XL, Draeger Medical, Richmond Hill, Canada) to receive continuous positive airway pressure of 4 cm H_2O with preserved spontaneous breathing for 5 consecutive hours.[7] Airway pressures and flow rates were measured by using a pneumotachometer (Hans Rudolph, Shawnee, KS) and recorded by using LabChart. Throughout the experiments, rats were ventilated such that the fraction of inspired O_2 was 0.6, except during blood gas sampling, when this proportion was increased to 1.0 to enable calculation of the intrapulmonary shunt fraction (data not shown).

A complete set of measurements was taken at baseline and after 1 and 5 h. The parameters measured included hemodynamics (mean arterial pressure, cardiac output, temperature, and heart rate) and respiratory mechanics (tidal volume, respiratory rate, and minute ventilation). The heart rate was calculated from continuous electrocardiographic monitoring. Tidal volume was calculated as the time integral from the flow recorded by the pneumotachometer. While the fraction of inspired oxygen was set to 1.0, arterial blood gas samples (200 µL each) were analyzed by using a blood-gas analyzer (ABL 510, Radiometer Canada, London, Ontario, Canada) and a species-adjusted cooximeter (OSM 3, Radiometer Canada).

All rats underwent regular assessment of sedation level by toe pinch and tail flick. So that flight tendency could be monitored, rats were not restrained. After the experiment, rats were euthanized by barbiturate overdose.

Sedation protocol. An initial intraperitoneal dose of sodium pentobarbital provides approximately 60 to 120 min of anesthesia.[15] After the effects of pentobarbital wear off, the need for additional analgosedation becomes prominent. Furthermore, deep sedation only might not provide sufficient analgesia for painful procedures. For these reasons, all rats received intravenous infusion of remifentanil (4 µg/mL, diluted in saline, at 0.4 µg/kg/min; Ultiva, Abbot Laboratories, Saint-Laurent, Canada) to maintain sedation and minimize pain and stress during mechanical ventilation; this dose led to no responses from the rats in response to toe pinch and tail flick stimuli in a pilot study (data not shown). The diluted remifentanil was delivered by using a 60-mL syringe attached to a syringe pump (Perfusor Space, Braun Medical, Melsungen, Germany), which was started as soon as the central venous catheter was placed. Hemodynamics, respiration, and visual appearance were monitored continuously, and the level of sedation was assessed every 30 min by using the toe pinch and tail flick methods. In case of a reaction to stimuli or spontaneous movement, a bolus dose of remifentanil (0.2 to 0.4 µg/kg) and additional pentobarbital (0.5 mg IV) were allowed as rescue medication. All rats received 0.9% NaCl (3 to 5 mL/h; Hospira, Montreal, Canada), including occasional boluses as needed to flush lines.

Statistical analysis. All data were collected and recorded by using the PowerLab operating system (ADInstruments) and LabChart 6.0 Software. Data are expressed as mean ± 1 SD. Repeated-measures ANOVA was used to compare within-subjects measurements at baseline and after 1 and 5 h of mechanical

Table 1. Cardiac and respiratory parameters (mean ± 1 SD; n = 5) of rats undergoing mechanical ventilation with spontaneous breathing

	Baseline	1 h	5 h
Mean arterial pressure (mm Hg)	145 ± 15	146 ± 21	134 ± 9
Cardiac output (mL/min)	125 ± 53	156 ± 41	131 ± 55
Heart rate (beats/min)	399 ± 32	399 ± 42	405 ± 44
Temperature (°C)	37.2 ± 0.7	37.0 ± 0.3	37.1 ± 0.3
Tidal volume (mL)	3.0 ± 0.3	3.2 ± 0.3	3.4 ± 0.9
Respiratory rate (breaths/min)	73 ± 15	87 ± 16	76 ± 17
Minute ventilation (mL/min)	219 ± 61	281 ± 55	247 ± 47
pH	7.30 ± 0.05	7.34 ± 0.12	7.32 ± 0.13
paO_2	336 ± 134	398 ± 147	379 ± 185
$paCO_2$	64 ± 7	42 ± 9	46 ± 15

ventilation and analgosedation. Significance was set at a P value of 0.05 (SPSS 10.0, Chicago, IL).

Results

Hemodynamic measurements. There were no significant changes in the mean arterial pressure, cardiac output, heart rate, and core body temperature at baseline and after 1 and 5 h of mechanical ventilation. Continuous analgosedation with remifentanil preserved hemodynamics in all rats equally and did not cause significant changes in core body temperature (Table 1).

Respiratory mechanics. The respiratory function was stable in all rats. Tidal volume, minute ventilation and respiratory rate were well controlled over the experimental period (Table 1). No episodes of apnea or hypopnea were observed in any of the rats.

Gas exchange. Arterial blood gas measures (pH, paO_2, and $paCO_2$) were similar between all rats at baseline and did not change significantly over the course of the experiments at the 1- and 5-h measurements (Table 1).

Discussion

The purpose of this study was to investigate the feasibility of using remifentanil in an ABS regimen to provide tolerance to mechanical ventilation. Hemodynamics and respiratory stability were preserved in all rats receiving continuous positive airway pressure by means of a tracheostomy tube (Table 1). Similarly, gas exchange remained stable throughout the duration of ventilation (Table 1).

Various factors must be considered when administering sedatives to laboratory animals. Such factors include (but are not limited to) experimental time course, the drug delivery system chosen for the type of experimental procedure,[7] and animal size. Because most mechanically ventilated animals remain in a supine position throughout the ventilation period, an intravenous delivery system is appropriate.

Intravenous sedation has several advantages for studies using mechanical ventilation because, unlike inhaled anesthetics, it does not interfere with the gas mixtures used for ventilation. Furthermore, only few advanced ventilators permitting assisted-ventilation modes (such as those used in the critical care setting) have the capability to provide inhalational anesthesia. In addition, inhaled anesthetics have been associated with hemodynamic instability through vasodilation.[30] From an ecologic standpoint, inhaled anesthetics (as halogenated fluorocarbon pollutants) potentially have negative effects on ambient air.[3]

During prolonged experiments, repeated dosing of intraperitoneal or intravenous sedatives with long half-lives carries a grave risk for overdosing upon reapplication. Hemodynamic instability and respiratory arrest are frequent consequences of inadvertent overdosing. Conversely, remifentanil seems to be an ideal sedative in this case because continuous delivery ensures effective analgosedation, and the drug's specific metabolism allows quick clearance from the organism and titration to the desired level of sedation.[12,28] In experiments with multiple drugs, it is important to consider potential drug interactions. In the present study, pentobarbital was used to induce surgical anesthesia. The sedating effect of pentobarbital is approximately 60 to 120 min,[15] at which point our protocol provided remifentanil sedation for tolerance of mechanical ventilation. For that reason, the effects of pentobarbital and remifentanil did not interfere to alter the outcomes during mechanical ventilation, but we cannot exclude the possibility that pentobarbital prolonged the efficacy of remifentanil beyond its pharmacologic duration of action. Some studies[36] have used much higher doses (up to 2 μg/kg/min) of remifentanil with isoflurane than we used here, although the rats in the previous study underwent particularly invasive surgery requiring deeper anesthesia. In addition, it is important to note that our experiment did not involve injury to the rats, meaning that any procedure causing increased sympathetic reaction and pain is likely to require a higher dose of remifentanil than that used in the current experiment.

Depending on the state of the laboratory animal during the procedure (stable as compared with the presence of trauma or injury), intravenous drug administration will ensure that the drug takes effect (causing fast relief) immediately without the need to wait for its onset. Remifentanil has strong analgesic potency that provides fast effects.[18,28] The use of a syringe pump to infuse remifentanil intravenously facilitated the delivery of continuous infusions at controllable rates or bolus delivery when necessary. This method of delivery is effective for mechanical ventilation protocols, which can be either short or long-term. Furthermore, the dose can be titrated to effect and may need to be adjusted once prior sedation with barbiturates or α1-agonists dissipates.

The size of typical laboratory rats (300 to 500 g) imposes no problem to cannulation of a major blood vessel (the jugular vein was used in the current study) through which remifentanil can be delivered. Using our infusion protocol, we monitored the sedation level and wellbeing of the rats during the procedure.[8] In addition, our experimental set-up allowed for real-time monitoring of mean arterial pressure, cardiac output, heart rate, and core body temperature to ensure the hematologic and respiratory stability of the rats during mechanical ventilation.

However, some limitations apply in generalizing our current results. Although we did not observe movement or tendency to flee in our rats, we did not systematically construct dose-

response relations required for various levels of sedation. Much higher self-administered doses of remifentanil in rats have been reported[26] without causing unconsciousness; however, it must be noted that continuous infusion of a drug will increase the context-sensitive half-life, likely increasing the sedative effect. We cannot rule out that prevailing low levels of pentobarbital in fact contributed to the remifentanil-associated sedation. Monosedation with remifentanil in humans has been applied successfully in minor procedures, such as awake fiberoptic intubation,[23] in vitro fertilization,[32] and radiofrequency ablation. Importantly, these procedures produce more discomfort rather than pain, such that increased dosage of remifentanil or co-medication with other sedatives has to be considered for rodent sedation during painful procedures.

Another limitation lies in the fact that our rats were euthanized at the end of the experiment, so that we were unable to study the previously reported effects of hyperalgesia after remifentanil use.[6,10] The rats were euthanized to eliminate any potential suffering after the invasive procedures. A low number of rats was tested to minimize the use of animals but was sufficient for proof of concept.

The current study demonstrated that the continuous intravenous infusion of remifentanil by using a conventional syringe pump provides sufficient analgosedation of laboratory rats for tolerance of minimally painful procedures such as mechanical ventilation. Furthermore, the continuous infusion protocol was effective for mechanical ventilation with assisted spontaneous breathing without compromising hemodynamic stability, respiratory mechanics, or gas exchange. Our current protocol may prove effective for rodent sedation and analgesia during experimental mechanical ventilation in a laboratory setting.

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The authors declare no conflicts of interest.

References

1. **Abdel Hamid AM, Abo Shady AF, Abdel Azeem ES.** 2010. Remifentanil infusion as a modality for opioid-based anaesthesia in paediatric practice. Indian J Anaesth. **54:**318–323.
2. **Battershill AJ, Keating GM.** 2006. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. Drugs **66:**365–385.
3. **Berton J, Sargentini C, Nguye JL, Belii A, Beydon L.** 2007. AnaConDa reflection filter: bench and patient evaluation of safe and volatile anesthetic conservation. Anesth Analg **104:**130–134.
4. **Buerkle H, Yaksh TL.** 1996. Comparison of the spinal actions of the μ opioid remifentanil with alfentanil and morphine in the rat. Anesthesiology **84:**94–102.
5. **Buerkle H, Yaksh TL.** 1996. Continuous intrathecal administration of short-lasting μ opioids remifentanil and alfentanil in the rat. Anesthesiology **84:**926–935.
6. **Cabañero D, Campillo A, Célèrier E, Romero A, Puig MM.** 2009. Pronociceptive effects of remifentanil in a mouse model of postsurgical pain: effect of a second surgery. Anesthesiology **111:**1334–1345.
7. **Canadian Council on Animal Care.** 1993. Categories of invasiveness in animal experiments, appendix XV-B. In: Guide to the care and use of experimental animals, vol 1, 2nd ed. Ottawa (Canada): Canadian Council on Animal Care.
8. **Canadian Council on Animal Care.** 1993. Ethics of animal investigation, appendix XV-A. In: Guide to the care and use of experimental animals, vol 1, 2nd ed. Ottawa (Canada): Canadian Council on Animal Care.
9. **Cannon CZ, Kisslin GE, Hoenerhoff MJ, King-Herbert AP, Blankenship-Paris T.** 2010. Evaluation of dosages and routes of administration of tramadol analgesia in rats using hot-plate and tail-flick tests. Lab Anim (NY) **39:**342–351.
10. **Célèrier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G.** 2000. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology **92:**465–472.
11. **Criado AB, Gomez de Segura IA.** 2003. Reduction of isoflurane MAC by fentanyl or remifentanil in rats. Vet Anaesth Analg **30:**250–256.
12. **Egan TD.** 1995. Remifentanil pharmacokinetics and pharmacodynamics: a preliminary appraisal. Clin Pharmacokinet **29:**80–94.
13. **Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanksi DR, Shafer SL.** 1993. The pharmacokinetics of the new short-acting opioid remifentanil (GI187084B) in healthy adult male volunteers. Anesthesiology **79:**881–892.
14. **Eichhorn V, Henzler D, Murphy MF.** 2010. Standardizing care and monitoring for anesthesia or procedural sedation delivered outside of the operating room. Curr Opin Anaesthesiol **23:**494–499.
15. **Gaertner DJ, Hallman TM, Hankenson FC, Batchelder MA.** 2008. Anesthesia and analgesia for laboratory rodents, p 240–288. In: Fish RE, Brown MJ, Danneman PJ, Karas AZ, editors. Anesthesia and analgesia in laboratory animals, 2nd ed. New York (NY): Elsevier.
16. **Giannantonio C, Sammartino M, Valente E, Cota F, Floretti M, Papacci P.** 2009. Remifentanil analgosedation in preterm newborns during mechanical ventilation. Acta Paediatr **98:**1111–1115.
17. **Gomez de Segura IA, de la Vibora JB, Aguado D.** 2009. Opioid tolerance blunts the reduction in the sevoflurane minimum alveolar concentration produced by remifentanil in the rat. Anesthesiology **110:**1133–1138.
18. **Heavner JE, Cooper DM.** 2008. Pharmacology of analgesics, p 98–118. In: Fish RE, Brown MJ, Danneman PJ, Karas AZ, editors. Anesthesia and analgesia in laboratory animals, 2nd ed. New York (NY): Elsevier.
19. **Hedenqvist P, Roughan JV, Flecknell PA.** 2000. Sufentanil and medetomidine anaesthesia in the rat and its reversal with atipamezole and butorphanol. Lab Anim **34:**244–251.
20. **Henzler D, Pelosi P, Bensberg R, Dembinski R, Quintel M, Pielen V, Rossaint R, Kuhlen R.** 2006. Effects of partial ventilator support modalities on respiratory function in severe hypoxemic lung injury. Crit Care Med **34:**1738–1745.
21. **Karabinis A, Mandragos K, Stergiopoulos S, Komnos A, Soukup J, Speelberg B, Kirkham AJ.** 2004. Safety and efficacy of analgesia-based sedation with remifentanil versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: a randomized, controlled trial. Crit Care **8:**R268–R280.
22. **Katzung B, Masters S, Trevor A, editors.** 2009. Basic and clinical pharmacology, 11th ed. New York (NY): McGraw Hill Companies.
23. **Mazères JE, Lefranc A, Cropet C, Steghens A, Bachmann P, Pérol O, Rosay H.** 2011. Evaluation of the Bonfils intubating fibrescope for predicted difficult intubation in awake patients with ear, nose, and throat cancer. Eur J Anaesthesiol **28:**646–650.
24. **Natalini G, Dimaio A, Rosano A, Ferretti P, Bertelli M, Bernardini A.** 2011. Remifentanil improves breathing pattern and reduces inspiratory workload in tachypneic patients. Respir Care **56:**827–833.
25. **Olofsen E, Dahan A.** 2005. Population pharmacokinetics–pharmacodynamics of anesthetics. AAPS J **7:**E383–E389.
26. **Panlilio LV, Schindler CW.** 2000. Self-administration of remifentanil, an ultrashort-acting opioid, under continuous and progressive-ratio schedules of reinforcement in rats. Psychopharmacology (Berl) **150:**61–66.
27. **Park G, Lane M, Rogers S, Bassett P.** 2007. A comparison of hypnotic and analgesic based sedation in a general intensive care unit. Br J Anaesth **98:**76–82.
28. **Patel SS, Spencer CM.** 1996. Remifentanil. Drugs **52:**417–427.
29. **Royse CF.** 2009. Anaesthesia in septic patients: good preparation and making the right choice? Crit Care **13:**1001.
30. **Royse CF, Liew DF, Wright CE, Royse AG, Angus JA.** 2008. Persistent depression of contractility and vasodilation with propofol but not with sevoflurance or desflurane in rabbits. Anesthesiology **108:**87–93.

31. **Sammartino M, Garra R, Sbaraglia F, De Riso M, Continolo N.** 2010. Remifentanil in children. Paediatr Anaesth **20:**246–255.
32. **Sarikaya HB, Iyilikci L, Gulekli B, Posaci C, Erbil Dogan O, Ok E, Eglen M, Ellidokuz H, Gunerli A.** 2011. Comparison of the effects of 2 different doses of remifentanil infusion for sedation during in-vitro fertilization procedure. Saudi Med J **32:**689–694.
33. **Sessler CN, Pedram S.** 2009. Protocolized and target-based sedation and analgesia in the ICU. Crit Care Clin **25:**489–513.
34. **Spies C, Macguill M, Heymann A, Ganea C, Krahne D, Assman A, Kosiek HR, Scholtz K, Wernecke KD, Martin J.** 2011. A prospective, randomized, double blind, multicenter study comparing remifentanil with fentanyl in mechanically ventilated patients. Intensive Care Med **37:**469–476.
35. **Thompson AC, Kristal MB, Sallaj A, Acheson A, Martin LB, Martin T.** 2004. Analgesic efficacy of orally administered buprenorphine in rats: methodologic considerations. Comp Med **54:**293–300.
36. **Vianna PT, Castiglia YM, Braz JR, Viero RM, Beier S, Vianna Filho PT, Vitória A, Reinoldes Bizarria Guilherme G, de Assis Golim M, Deffune E.** 2009. Remifentanil, isoflurane, and preconditioning attenuate renal ischemia–reperfusion injury in rats. Transplant Proc **41:**4080–4082.