Anaesthesia for ICU-based procedures: the advantages of and options available for inhalational anaesthesia

Kruger H, MBChB, DA(SA)
Registrar, Department of Anaesthesiology, University of the Free State, Bloemfontein
Correspondence to: Dr Henk Kruger, e-mail: drhlkruger@yahoo.com

Introduction

Many patients admitted to an intensive care unit (ICU) will undergo a surgical procedure for correcting the underlying cause of their disease, to deal with the complications of their disease or the treatment of their disease, or to undergo diagnostic procedures which will direct the course of their treatment. The majority of these procedures are performed in the operating theatre, but a small number of these cases will be managed in the ICU environment, which will place the anaesthetic and surgical team in an unfamiliar environment.

Many studies indicate that the outcomes of these procedures depend on the interaction of many factors, which include the extent of the procedure, the physiologic reserve of the patient, the presence of chronic pathological conditions, and the nature of the acute physiological derangements.[1] The plan for the critically ill patient should include preoperative optimisation of the general condition, a chronological plan for the intraoperative treatment, coordination with the surgical team, provision for additional equipment, expertise and resources, and a postoperative plan.

In this discussion, we shall put emphasis on the anaesthetic options, techniques and problems that we experience with the anaesthesia for procedures which will be performed in ICU.

Consideration of the surgical procedure

Critically ill patients may undergo a myriad of ICU-based surgical procedures, which could include tracheostomy for respiratory failure and long-term ventilation, surgery to remove septic or necrotic foci, application or realignment of external fixation of fractures, dressing change in the patient with burns or other extensive wounds, exploratory surgery for occult bleeding and haemorrhage control, cleaning and secondary exploration of previous laparotomy, closure of open cavities, invasive diagnostic procedures, and insertion or removal of invasive diagnostic or life support equipment.

Whether definite life saving measures should be undertaken immediately or whether the procedure should be preferably delayed and performed electively, depends on the stability of the patient and nature and urgency of the procedure, as well as the critically ill patient's condition and current treatment, which includes risks associated with transport.

The decision to proceed with ICU–based surgical intervention must be made after weighing up the associated benefits and risks, as well as evaluating the expertise and equipment available. Be aware of the principle of *primum non nocere*: first do no harm.

Timely and emergent intervention may be life saving and vital in case of certain conditions. Ideally, surgical intervention should only take place after adequate resuscitation of the patient, with all the required resources in place.

In general, the simplest intervention, resulting in the least physiologic upset, performed by the most capable and experienced personnel at the most suitable location is the best option for the critically ill patient.

Risk of patient transfer

Complicating circumstances and life threatening conditions may make the risks associated with the transfer of patients to another site of treatment unacceptable. A change in patient management, when leaving the "safety of ICU", occurs in 24–39% of cases.[2,3]

Conditions which may complicate transport include:

- Inability to oxygenate or ventilate a patient
- Haemodynamic instability
- Inadequate monitoring
- Inadequate airway control
- Ergonomic factors (e.g. elevators, power failure)
- Inadequate personnel and resources[4]

Morbidity and mortality related to the transfer of patient are due to many factors, of which the most important are:

- Haemodynamic and respiratory deterioration

- Interruption of medication
- Loss of intravascular access points
- Loss of airway or ventilatory support
- Human error[4]

The majority of incidents during transportation or transfer of a critically ill patient occurs at the destination of transfer, rather than in the ICU itself. There appears to be no correlation between the incidence of mishaps and the severity of disease. Duration of the procedure and delay at the destination site may contribute to these incidents.[4] Szem found an overall mortality rate of 26.4% for patients requiring transport, in comparison with 11.4% in the control group, although the patients requiring transport in this study may have been sicker.[5]

The Australian Incident Monitoring Study revealed that 39% of incidents were equipment related, and 61% were staff or patient issues. The majority of system-based incidents occurred because of the need to disconnect patients from ventilators, interruption of infusions while changing infusion pumps and monitors, and the limited battery life of devices used during transport.[6]

Although the anaesthesiologist is simultaneously responsible for monitoring the patient as well as making adjustments to medications to maintain haemodynamic stability, the risk for complications during patient transfer between ICU and theatre is still very high. For many ICU-based procedures there is just not time for transferring the patient to the operating room. In others patients, the procedure to be performed is just not considered serious enough to transfer the patient to the operating room when compared to the risk of transferring the unstable critically ill patient to the operating room. Limitations in ventilatory options in the operating room can also influence the decision of the location in which the patient must undergo the procedure.

Ergonomic consideration of the facilities and equipment in ICU

Many features of non-operating room anaesthetics may impair delivery of quality anaesthetic care.
Factors that may complicate the task of the anaesthesiologist in ICU include:

- Layout of the ICU
- Unfamiliar anaesthetic equipment
- Implications of the procedure performed
- Remoteness of anaesthetic assistance
- ICU personnel less familiar with the anaesthetic aspects of intraoperative patient care

Locations outside the operating room are designed for their primary role. Space for anaesthetic equipment and anaesthetic and emergency drugs may be limited and not conveniently located.

Most ICU locations provide piped-in gases, suction and isolated electrical power. A gas cylinder supply must be readily available, and ICU personnel and anaesthesiologist must be familiar with the functioning and availability of the equipment.

Anaesthesia machines are often not available in ICU, which may call for different techniques of anaesthesia.

The positioning of the anaesthesiologist's location during the procedure must be such that the patient, the patient's airway, ventilatory equipment, and intravascular access can be easily reached, and that the anaesthesiologist can easily observe the monitor, infusion pumps and surgical field. Care must be taken not to hinder the surgeon or contaminate the surgical field.[7]

Personnel and staffing

Non-anaesthetic personnel are most often involved in ICU patient care. They are less familiar with the anaesthetic management of patients and operating room procedure. Consequently, they may not be able to provide the skilled assistance that the anaesthesiologist would take for granted in the operating room. Thus, the presence of an adequate number of anaesthetic personnel in the immediate vicinity of the ICU is vital, even if this means that they must accompany the anaesthesiologist from the operating room. Open communication between the care taking teams and the operating room must take place.

General considerations for ICU-based anaesthesia: the 6 Cs[8]

Clinical records

Ensure that these records are available, and that all information has been thoroughly studied. The most recent special investigations (including results for arterial blood gas analysis, haemoglobin and haematocrit, platelet counts, biochemistry and clotting profile) must be obtained. Clinical record keeping is also vital to ensure good continuity of care and for medicolegal purposes, so it is essential that they are as clear and complete as possible. The notes must be legible, accurate, up to date and must also have been signed. Alterations and late additions can also cause confusion. The keeping of clinical records may also assist in future medicolegal matters.

Consent

As the ICU-based procedure does not take place routinely, and is often immediate and definite, it is very important that you as anaesthesiologist make absolutely sure that informed consent has been obtained for the anaesthesia, surgery and blood product transfusion. Informed consent can be obtained from the patient, the family or the hospital authorities in case of an emergency.

Confidentiality

The patient's confidentiality must be respected at all times. Disclosure of sensitive patient information must be done in private, as there can be non-medical people in ICU, including the family members of the patient or other patients. Paper or electronic medical records must also not be left somewhere where confidentiality cannot be guaranteed.

Communication

Good communication is of utmost importance for the successful treatment of the critically ill patient. This not only refers to communication with the critically ill patient or his or her family, but also between the anaesthesiologist, the surgeon, theatre personnel, ICU personnel and the blood bank.

The anaesthesiologist and surgeon must discuss the condition of the patient, the urgency of the procedure, the purpose of the surgical procedure, the extent and duration of the surgical procedure, expected blood loss, relevant blood products and the postoperative plan.

Competence

Recognising your own limitations is the key principle here. When providing care to the critically ill, you are duty bound to work within your own professional competence, taking the time to ask for assistance when needed.

Careful anaesthetic drug prescription and dosage

In the unstable patient, the slightest adjustment in dosage of current treatment or addition of an anaesthetic drug can cause profound physiological and haemodynamic changes. Furthermore, these patients are usually being administered multiple drugs, which can cause drug interactions due to polypharmacy. The pharmacokinetic profiles of pharmacological preparations often change in the presence of severe pathology. Conversely, the incidence of awareness is greater in certain at-risk populations (as high as 43%),[9] especially when administering light anaesthesia because of haemodynamic instability. Awareness can be difficult to detect in the anaesthetised critically ill patient, due to masked autonomic responses and muscle relaxation. Amnestic drugs, like midazolam, scopolamine or even ketamine, should be considered, which can reduce the risk of awareness by 82%. Neuromonitoring, to detect awareness, is very difficult in the ICU–based anaesthesia.

Anaesthetic choices

General anaesthesia is most often utilised for surgery in the critically ill patient for reasons that may include the time needed to initiate anaesthesia, the emergent nature of the procedure, surgical and haemodynamic factors and the equipment available to administer the anaesthesia.

Regional and neuraxial anaesthesia

Regional or neuraxial techniques can play a role as valuable adjuncts to general anaesthesia. This can optimise patient comfort in the postoperative period and also reduce physiological stress.[10] Epidural analgesia is probably the regional analgesic technique most often used in the intensive care unit. It is often employed to manage pain of thoracic, abdominal, orthopaedic or cardiac origin. Studies show that measurements of lung function improve with epidural analgesia after chest trauma.[11] High levels of thoracic epidural analgesia (T1–T4) provide effective treatment of myocardial ischaemia refractory to conventional medical therapy.[12] The use of epidural analgesia is limited in patients with severe systemic or local sepsis, coagulopathy, sedated patients and patients with severe haemodymanic instability or fluid shifts. In the immediate and definite emergency situation where ICU-based anaesthesia is necessary, only an epidural catheter already in place can be used as adjunct for anaesthesia. However, as these patients are often haemodynamically unstable, epidural anaesthesia should be used with caution or not at all. No valuable time must be wasted for the placement of an epidural catheter in the emergency situation. The use of peripheral nerve blocks in ICU–based procedures as single anaesthetic technique to provide surgical anaesthesia, or even as adjunct to general anaesthesia, has a place in tracheostomy, external fixation of fractures, painful dressing changes, debridement of burns and large soft tissue wounds or painful insertion of invasive diagnostic or monitoring equipment.

General anaesthesia

The absence of anaesthetic machines in ICU makes the administration of general anaesthesia for ICU-based procedures a challenge. Intravenous anaesthetic techniques pose many problems, as the actions and side-effects of intravenous drugs are difficult to control in the critically ill patient.[13] The absence of anaesthetic administering equipment in ICU, as well as ergonomic factors, makes administration of inhalation agents a challenge.

Intravenous anaesthesia

The use of etomidate, the most haemodynamically stable and shortest acting intravenous hypnotic drug available, is precluded because of profound adrenal cortex suppression.[14]

Propofol seems to be a very good choice for either total intravenou s anaesthesia (TIVA) or target controlled infusion (TCI), and it is popular in most countries. After the report on the deaths of five children in 1992[15] and five adults in 2001,[16] propofol infusion syndrome (PRIS) was described as a severe, sometimes fatal, metabolic acidosis with rhabdomyolysis and renal and cardiac failure.[17] PRIS may also be promoted by catecholamines and corticosteroids. The "Arzneimittelkommission der deutschen Arzteschaft" issued a warning that propofol should be administered only in patients over 16 years of age, for no more than seven days, and to a maximum dose of 4 mg/kg/hour or less, if possible. They recommended frequent laboratory investigations to rule out metabolic acidosis and rhabdomyolysis, and consideration of alternative treatment options, such as benzodiazepines, in severely ill patients.[18]

Care must be taken not to increase the dosage of propofol or lengthen the duration of administration of propofol beyond these parameters when deciding on propofol for TIVA or TCI. Many anaesthetic drugs reduce the required dose or blood concentration of propofol. For example, the Cp_{50} of propofol to prevent movement on skin incision is 16 µg/ml, but this is markedly decreased by increased concentrations of fentanyl or alfentanyl.[19,20,21] This level is further reduced to 2.5 µg/ml when combined with benzodiazepines (as premedication),[22] and to 1.7 µg/ml when lorazepam has been replaced as premedication by morphine (0.15 mg/kg).[23] ICU patients are often sedated with a combination of a benzodiazepine and morphine.

Other pharmacokinetic factors which may complicate the effects of propofol in the critically ill include:

- Reduced protein binding due to the inflammatory response or catabolic state
- Smaller volume of distribution and intravascular volume of critically ill patients
- Reduced cardiac output
- Age of the patient
- Metabolism and excretion

Propofol has detrimental effects on the haemodynamic status[24,25,26,27] as well as the advantage of lung protection in the critically ill,[28] which must be seriously considered when deciding on this anaesthetic technique. This requires starting with low dosages and titrating up to the necessary response.

Prolonged use of other drugs, like benzodiazepines, for ICU sedation is associated with accumulation and poor control of action. For benzodiazepines, a quick onset of tolerance and a ceiling effect are characteristic.[13] Caution in the administration of induction dosages of benzodiazepines must be practised when administering these drugs to patients who are already being sedated with benzodiazipines. Midazolam is the benzodiazepine of choice to induce anaesthesia. The rate of induction by midazolam is influenced by:

- Dosage
- Speed of injection
- Degree of premedication or sedation
- Age
- ASA classification
- Physical status
- Concurrent anaesthetic drugs[29,30]

The stresses of intubation and surgery are not suppressed by midazolam, which calls for the combination with adjuvants, usually opioids.[31] The usual induction dose of midazolam in pre-sedated patients is 0.05–0.15 mg/kg, which is reduced to less than 0.1 mg/kg when used in coinduction with synergistic drugs.[32,33] The emerging time after an induction bolus of midazolam is 15–20 minutes, and midazolam is only used for shorter, less invasive ICU-based procedures. Accumulation with repeated bolus administration or with continuous infusion prolongs arousal time. This is less of a problem with midazolam than with diazepam or lorazepam.[34] The chief advantages of benzodiazepines are amnesia (1–2 hours after induction dosages) and haemodynamic stability. However, midazolam is not a good intravenous induction drug in the critically ill.

Although widely used throughout the world for the maintenance of anaesthesia, little concentration-effect data for continuous infusion of ketamine are available. Most studies suggest hypnotic and analgesic thresholds at 1.5–2.5 µg/mL and 150–200 ng/mL, respectively.[35,367] As sole agent, infusion rates of 60–80 µg/kg/minute will provide clinical anaesthesia. Bowdle et al[35] showed a good correlation between the targeted and observed drug concentrations. Greater psychedelic effects for a variety of symptoms were associated with increased ketamine concentrations. No apparent threshold concentration could be demonstrated for these effects, and also no concentration at which these effects plateau. Ketamine is often used as the analgesic component of different TIVA techniques with propofol (described by Gray et al,[36] Wieber et al,[37] Roberts et al[38] and Schuttler et al[39]), and also with midazolam (described by Donner et al[40]).

Dexmedetomedine interacts with both opiates and hypnotics to reduce drug requirements needed to maintain sedation or anaesthesia.[41] Peden et al examined the combination of dexmedetomidine and propofol.[42] They found that an infusion of 3 ng/kg/minute of dexmedetomidine reduces the median effect (ED) infusion rate of propofol for loss of consciousness from 5.79 to 3.45 mg/kg/hour. However, at these infusion rates, dexmedetomidine caused significant side effects (sinus arrest and severe postural hypotension). This, as well as the long activation time of dexmedetomidine, makes its use for anaesthesia in ICU unpopular. In the patient already on dexmedetomidine, careful continuation of the infusion can be considered.

Inhalational anaesthesia

Protection from the consequences of ischaemia of the heart, brain, kidneys and other organs will obviously be a major advantage for the critically ill patient with haemodynamic instability.[13] The concept of pharmacological preconditioning of the myocardium for tolerance to ischaemia has renewed the interest in the use of volatile anaesthetics in cardiac anaesthesia.[43,44] The number of distressing experiences in ICU correlates with poor physiological outcome.[45] Volatile anaesthetics act primarily on the rostral brain structures like the cerebral cortex and, even at low concentrations, may completely depress consciousness (MAC_{awake}) while leaving many autonomic functions (such as temperature control, blood pressure regulation or respiration) undisturbed.[13]

Onset of action is usually rapid, especially when delivery systems like the AnaConDa® or Zeus® are used. The wash-in kinetics of sevoflurane using the AnaConDa® proved to be less than that observed with a normal vaporiser, but 80% of maximum tension was reached after 8 minutes in both groups.[46] The end-tidal fraction (Fet) of the volatile anaesthetic can be monitored, a precise indicator of the drug's concentration in the target organ which is much more reliable than any target-controlled infusion algorithm.[47-51] End–tidal tension in the AnaConDa® and vaporiser mirror arterial tension in both groups.[52] Volatile anaesthetics accumulate very little, and elimination is less dependent on liver and kidney function. With the exception of halothane, volatile anaesthetics interfere very little with haemodynamics, especially in low concentrations. Ebert et al showed that the regulation of heart rate (baroreceptor reflex) and the peripheral sympathetic nerve activity were hardly disturbed at 0.5 MAC desflurane compared with the awake state.[53] The AnaConDa® can be used with any ICU ventilator. It includes a heat and moisture exchanger which is intended for single patient use and should be changed after 24 hours for hygiene reasons. It consists of a dead space of 100 mL. The AnaConDa® can be used with isoflurane or sevoflurane.

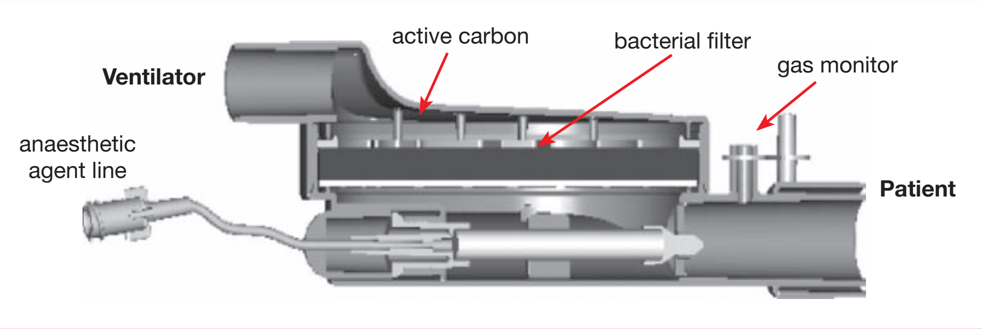
The AnaConDa® is a very promising tool for inhalational sedation and anaesthesia in the ICU, because it enables the use of standard ICU ventilators. The only technical modification is connection to a form of anaesthetic gas scavenging (AGS) system. If active AGS is applied with suction, the performance of the ventilator must be checked before a patient is connected.

Several points must be considered when using the AnaConDa®:

- The volatile anaesthetics, sevoflurane and isoflurane are drawn up into a 50 mL syringe from the bottle with a specific adapter. Only special syringes and tubings may be used, as unsuitable plastic materials may be dissolved by the volatile anaesthetics.
- Care must be taken to avoid bubbles in the syringe. When volatile anaesthetics are stored in a refrigerator, other gases may dissolve and later may form bubbles when warming up. Due to their high vapour pressure, volatile anaesthetics will evaporate into these bubbles and make them expand. Additionally, because of their high density (1.5 g/mL), volatile anaesthetics may exert a negative pressure if the syringe pump is fixed high above the patient's head. These will lower the boiling point inside the syringe, which is 49.8ºC for isoflurane and 59.8ºC for sevoflurane, at normal pressure. The growing bubbles may pump liquid volatile anaesthetics into the device, a mechanism referred to as autopumping. Autopumping may lead to a severe overdose.
- Therefore:
  - Volatile anaesthetics should be stored at room temperature
  - The syringe should be filled up without bubbles
  - The syringe pump should be at the level of the patient's head or below; and, obviously
  - Heat sources must always be kept away from the syringe
- When bubbles are detected, the device should be disconnected from the patient and the reason investigated.

When starting the administration, a rate of 25 mL/hour is recommended until the volatile anaesthetic reaches the evaporator. This can be determined by carefully watching the infusion line, or by the first signal detected by the gas monitor. Depending on the minute volume and the desired concentration, the rate should then be selected according to a dosing table. After one hour, the rate may be slightly lowered again. In our experience over up to 28 days, the rate of isoflurane very rarely needs to be modified. If sedation or hypnosis is not adequate, a bolus of 0.5 mL liquid isoflurane can be injected and onset of action will be more rapid than with any intravenous drug. Usually rates of 2–5 mL/hour are enough to achieve an Fet of 0.3–0.5 vol%. In a study

Figure 1: The AnaConDa® volatile delivery system



conducted by Endlun et al,[54] it was concluded that the administration of sevoflurane via a syringe pump was as convenient as with a vaporiser. Concentration changes could be performed rapidly and with ease. Care must be exercised in case of respiratory depression, when inadvertent deepening of anaesthesia could take place. Therefore, controlled ventilation is recommended.

Xenon seems to have the ideal properties to become the inhalational agent of choice for ICU sedation or anaesthetics. In the study of Bedi et al,[55] 30 vol% Xenon was sufficient, and patients were haemodynamically more stable than with propofol. There are a few arguments against the use of xenon in the ICU, namely its price and difficulty to administer, and the need to apply high oxygen concentrations in some patients. Whether the use of xenon will become widespread depends on the availability and handiness of closed breathing systems, methods of recycling, or discoveries of more natural resources that will lower the price.

Postoperative care and handover to the ICU personnel

The critically ill patient must not be handed over by the anaesthetist in ICU after the procedure, until proper care has been taken about the patient's condition regarding the haemodynamic status, airway and respiratory and metabolic stability. A proper adequate airway must always be in place and ventilatory settings must be optimal for the patient's condition and requirements. The ICU personnel must be aware of any treatment changes which were made during the course of the procedure. Emergency drugs, ample oxygen cylinders, manual ventilatory equipment and supplies for airway management must always be available. There must be sufficient vascular access, and the necessary time must be spent to explain the different intravascular routes and monitoring requirements. Infusion pumps must all be in place and activated and pointed out. Treatment targets must also be explained. The post-operative carers must always be informed of any problems or complications experienced during the procedures, as well as those expected in the course of the postoperative treatment. The patient must be kept under anaesthesia or very efficient sedation until muscle relaxants are reversed, and the procedure completed. Postoperative pain relief and sedation must be prescribed. Medical records must be updated in terms of the medical history, monitoring and intravascular lines, anaesthesia technique and drugs administered, amounts of these drugs given, fluid and blood requirements, the surgical procedure and complications, anaesthetic complications and other issues (e.g. allergies and isolation requirements).

The anaesthesia team is responsible for the care of the patient until a full verbal report is given to the ICU team, and the latter accepts the care of the patient. There must be good communication between the ICU team and the anaesthesiologist and surgical team at all times. The contact information of everyone involved with the procedure must be available to the ICU team.

Conclusion

Anaesthesia for the ICU-based procedure will always be difficult and have a high risk for complications. Care must be taken, through good communication and careful planning, not to complicate matters further. The risks of transport and patient stability, as well as the urgency of the procedure, will weigh the most in the decision in favour of an ICU-based procedure. In many cases, the anaesthesiologist will have the most insight and experience in the handling of these patients and must always assist in the decision making.

References

1. Aitkenhead AR. Injuries associated with anesthesia. A global perspective. Br J Anaesth. 2005;95:95.
2. Hurst JM, Davies K, Johnson DJ, et al. Cost and complications during in-hospital transport of critical ill patients: a prospective cohort study. J Trauma. 1992;33:582–585.
3. Indeck M, Peterson S, Smith J, et al. Risk, cost and benefit of transporting ICU patients for special study. J Trauma. 1988;28:1020–1025.
4. Longnecker DE, Fitzsimons MG, Sims N, et al. Monitoring and transport of the critically ill. Anesthesiology 2008;80:1812–1813.
5. Szem JW, Hydo LJ, Fischer E, et al. High risk intra-hospital transport of critically ill patients: safety and outcome of the necessary "road trip". Crit Care Med 1995;23:1660–1666.
6. Becmann U, Gillies DM, Berenholtz SM, et al. Incidents relating to the intra-hospital transfer of critically ill patients. Analyses of the reports submitted to the Australian Incident Monitoring in Intensive Care. Intensive Care Med. 2004;30:1579–1585.
7. Stensrud PE. Anesthesia at remote locations. Millers Ans; 7 th edit, 79: 2461–2462.
8. Gillespie G. Putting the stress on anxiety. MPS Casebook. 2009.17;(2):7.
9. Kwo, J. Developing an anesthetic plan for the critically ill patient. Anesthesiology, Longnecker DE 2008, 79:1808.
10. Schultz-Stubner S, Boezaart A, Hata S. Regional anaesthesia in the critically ill. Crit Care Med 2005;33:1400.
11. Moon MR, Luchette FA, Gibson SW, et al. Prospective, randomized comparison of epidural versus parenteral opioid analgesia in thoracic trauma. Ann Surg. 1999;229:684.
12. Gramling-Babb P, Miller MJ, Reeves ST, et al. Treatment of medically and surgically refractory angina pectoris with high thoracic epidural analgesia: initial clinical experience. Am Heart J 1997;133:648.
13. Meiser A, Labenthal H. Inhalational anesthetics in ICU: theory and practice of inhalational sedation in the ICU, economics, risk-benefit. Best Prac Res Clin Anaesth. 2005;19:523–538.
14. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. Lancet. 1983;1(8336):1270.
15. Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. BMJ 1992;305:613–616.

16. Cremer OL, Moons KGM, Bouman EAC, et al. Long-term propofol infusion and cardiac failure in adult head-injured patients. Lancet. 2001;357:117–118.
17. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med. 2003;29:1417–1425.
18. Arzneimittelkommission der deutschen Arzteschaft: Schwere unerwunschte Arzneimittelwirkungen nach
    a. Propofol-Infusionen zur Sedierung. Deutsches Arzteblatt 2004;101:3447–3448.
19. Smith C, McEwan A, Jhaveri R. Reduction of Propofol Cp_{50} by fentanyl. Anesthesiology. 1992:77: A340.
20. Vuyj J, Engbers FH, Lemmens HJ, et al. Pharmacodynamic effects of propofol in female patients. Anesthesiology. 1992;77:3–9.
21. Forrest FC, Tooley MA, Saunders PA, Prys-Roberts C. Propofol infusion and suppression of consciousness: the EEG and dose requirements. Br J Anaesth. 1994;72:35–41.
22. Hafer A, Doze VA, Shafer SL, White PF. Pharmacokinetics and pharmacodynamics of propofol during general anesthesia. Anesthesiology. 1998;69:348–356.
23. Spelina KR, Coates DP, Monk CR, et al. Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man. I: Patients pre-medicated with morphine sulphate. Br J Anaesth. 1986;58:10801084.
24. Larsen R, Rathgeber J, Bagdahn A, et al. Effects of propofol on cardiovascular dynamics and coronary bloodflow in geriatric patients: a comparison with etomidate. Anaesthesia. 1988;43(Suppl):1988;25–31.
25. Coates D, Prys-Roberts C, Spelina K. Propofol(Diprivan) by intravenous infusion with nitrous oxide: dose requirements and hemodynamic effects. Postgrad Med J. 1985; 61 Suppl 3:76–9.
26. Van Aken H, Meinshausen E, Prien T, et al. The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N_2O in humans. Anesthesiology 1988;68:157–163.
27. Whar JA, Plunkett JJ, Ramsay JG, et al. Cardiovascular responses during sedation after coronary revascularisation: incidence of myocardial ischemia and hemodynamic episodes with propofol versus midazolam. Anesthesiology. 1996;84:1350–1360.
28. Basu S, Mutschler DK, Larson AO, et al. Propofol (Diprivan-EDTA) counteracts oxidative injury and deterioration of the arterial oxygen tension during experimental septic shock. Resuscitation. 2001;50;341–348.
29. Reeves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology. 1985;62:310–324.
30. Kanto J, Sjovall S, Vuori A. The effects of different kinds of premedication on the induction properties of midazolam. Br J Aaesth. 1984;54:507–511.
31. Sameulson PN, Reves JG, Kouchoukos NT, et al. Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. Anesth Analg. 1981;60:802–809.
32. Brown CR, Sarnquist FH, Canup CA, Pedley TA. Clinical, electroencephalographic, and pharmacokinetic studies og a water-soluble benzodiazepine, midazolam maleate. Anesthesiology. 1979;50:467–470.
33. Theil DR, Stanley TE 3rd, White WD, et al. Midazolam and fentanyl continuous infusion anesthesia for cardiac surgery: a comparison of computer-assisted versus manual infusion systems. J Cardiothorac Vasc Anesth. 1993;7:300–306.
34. Reves JG, Glass PSA, David A, et al. Miller's Anesthesia 7th ed; 26:740.
35. Bowdle TA, Radant AD, Cowley TS, et al. Psycedelic effects of ketamine in healthy volunteers. Relationship to steady-state plasma concentrations. Anesthesiology. 1998;88:82–88.
36. Gray C, Swinhoe CF, Myint Y, Mason D. Target controlled infusion of ketamine as analgesia for TIVA with propofol. Can J Anesth. 1999;46:957–961.
37. Wieber J, Gugler R, Hengstmann JH, Dengler HJ. Pharmacokinetcs of ketamine in man. Anaesthetist. 1975;24:260–263.
38. Roberts FL, Dixon J, Lewis GTR, et al. Induction and maintenance of anaesthesia. A manual infusion scheme. Anaesthesia. 1988; 43 Suppl:14–17.
39. Schuttler J, Schutler M, Kloos S, et al. Optimal dosage strategies in total intravenous anesthesia using propofol and ketamine. Anaesthesist. 1991;40:199–204.
40. Donner B, Tryba M, Kurz-Muller K, et al. Anesthesia and Intensive care Management of severely burned children of Jehova's Witnesses. Der Anaesthetist. 1996;45:171–175.
41. Sear J. Total Intravenous Anesthesia. Anesthesiology, Longnecker et al. 2008;42:910
42. Peden CJ, Cloote AH, Stafford N, Prys-Roberts C. The effect of intravenous dexmedetomedine premedication on the dose requirement of propofol to reduce the loss of consciousness in patients receiving alfentanil. Anesthesia. 2001;56:408–413.
43. Zaugg M, Lucchinetti E, Garcia C, et al. Anaesthetics and cardiac pre-conditioning. Part II. Clinical implications. Br J Anaesth. 2003;91:566–576.
44. Zaugg M, Lucchinetti E, Uecker M, et al. Anaesthetics and cardiac pre-conditioning. Part I. signaling and cytoprotective mechanisms. Br J Anaesth. 2003;91:551–565.
45. Shelling S, Stoll C, Haller M, et al. Health-related quality of life and post-traumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med 1998;26:651–659.
46. Sturensson LW, Johansson A, Bodelsson M, Malmkvist G. Wash-in kinetics for sevoflurane using a disposable delivery system (AnaConDa) in cardiac surgery patients. Brit J Anaesth. 2009;102(4):470–476.
47. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. BMJ. 1989;298:1277–1989.
48. Millane DE, Bennet ED, Grounds RM. Isoflurane and propofol for long-term sedation in the intensive care unit: a crossover study. Anesthesia. 1992;47:768–774.
49. Spencer EM, Willats SM. Isoflurane for prolonged safety. Intensive Care Med. 1992;18:415–421.
50. Bedi A, Murray JM, Dingley J, et al. Use of xenon as a sedative for patients receiving critical care. Crit Care Med. 2003;31:2470–2477.
51. Meiser A, Sirtl C, Bellgardt M, et al. Desflurane compared to propofol for post-operative sedation in the intensive care unit. Br J Aneasth. 2003;90:273–280.
52. Sturensson LW, Johansson A, Bodelsson M, Malmkvist G. Wash-in kinetics for sevoflurane using a disposable delivery system (AnaConDa) in cardiac surgery patients. Brit J Anaesth. 2009;102(4):470–476.
53. Ebert TJ, Perez F, Uhrich TD, Deshur MA. Desflurane-mediated sympathetic activation occurs in humans despite preventing hypotension and baroreceptor unloading. Anesthesiology. 1998;88:1227–1232.
54. Bedi A, Murray JM, Dingley J, et al. Use of xenon as a sedative for patients receiving critical care. Critical Care Med. 2003;31:2470–2477.
55. Edlun M, Krietzmann D, Bouillon T, Zuchner K, Meineke I. Population pharmacokinetics of sevoflurane in conjunction with the AnaConDa's: towards target controlled infusion of volatiles into the breathing system. Acta Anaesthiol Scand. 2008;52:553–560.