The Current Role of Total Intravenous Anesthesia in Cardiac Surgery: Total Intravenous Anesthesia and Cardiopulmonary Bypass

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ALTHOUGH OVERALL mortality after cardiac surgery has decreased in recent decades, this process has been partially offset by changes in the patient population involving more complex disease and significant comorbidity.[1] Perioperative morbidity has stayed roughly the same and remains a relevant burden to health care providers. Attempts to identify independent risk factors for cardiac surgery are complex and include patient factors as expressed in the EuroSCORE or Parsonnet score, surgical technique, and the presence or absence of systematic goal-directed protocols.[2] However, the contribution of anesthesia is largely unknown.

With the availability of newer and shorter acting intravenous (IV) and volatile anesthetic agents, cardiac anesthesia fundamentally has shifted from a high-dose opioid/narcotic technique in recent years to a more balanced, synergistic approach. This shifted paradigm also has led to an emphasis on early tracheal extubation with application of multimodal analgesia including local anesthetic techniques resulting in the establishment of safe and effective fast-track protocols.[3,4] Modern anesthesia techniques for cardiac surgery need to offer qualities that go beyond safety alone.

EUROPEAN EXPERIENCE

The development of European anesthesiology has occurred concurrent with significant developments in anesthetic pharmacology. The introduction of neuroleptanalgesia, the combination of a potent phenoperidine-type opioid with a neuroleptic and later with a long-acting benzodiazepine, provided the initial basis for the concept of stress-free anesthesia and surgery,[5] becoming the preferred option for cardiac surgery. Further refinement in the pharmacology of 2 opioids, the fentanyl congeners alfentanil and sufentanil, by Janssen in the 1970s and 1980s improved the spectrum of applications of IV techniques beyond cardiac anesthesia.

After the disappointing appearance (and subsequent disappearance) of the steroid-based agents althesin, pregnanolone, and etomidate, the development of propofol[6] and the establishment of comprehensive pharmacokinetics (PK) knowledge as the basis of drug delivery[7] eventually led many European clinicians to adopt the technique of total intravenous anesthesia (TIVA).[8,9] This adoption of TIVA was enhanced by the availability of smart infusion pumps allowing target-controlled infusion (TCI) of most IV anesthetic agents suitable for TIVA based on their PK models.[10–12] With the advent of propofol TCI, most countries established formal training courses on IV pharmacology supported by academic institutions and leading researchers. In 1996, remifentanil, an even faster and better titratable opioid, was introduced into clinical practice. Supplementation with remifentanil allowed more rapid intraoperative adaptation to surgery and enhancement of recovery in patients undergoing cardiac surgery.[13] Although this drug initially was not well understood in terms of dose requirements, leading to excessive dosing at times, the knowledge gained from PK simulations and applications of TCI has improved drug delivery and made remifentanil a popular component for TIVA.[12]

It became apparent that using TCI allowed more precise titration of TIVA to clinical effect, leading to a reduction of the side effects seen with the sometimes cumbersome manual infusion regimens.[14,15] Together with the favorable effects of propofol in reducing postoperative nausea and vomiting and possibly postoperative pain,[16,17] a patient's well-being is enhanced after TIVA compared with volatile-based techniques.[18,19]

CARDIOPULMONARY BYPASS

Most physiologic studies on the effects of IV anesthetic agents during cardiopulmonary bypass (CPB) originate from the early 1990s, and only a few new PK studies have been added since that time. Propofol has been found to be a mild vasodilator[20] and reduces oxygen consumption during hypothermic CPB.[21] In contrast to volatile agents, propofol retains myocardial contractility at clinically relevant concentrations[22] and does not alter the arrythmogenic myocardial threshold, stabilizing Ca^{2+} homeostasis.[23] As a potent scavenger of oxygen free radicals,[24] propofol also attenuates ischemia-reperfusion injury, which helps to reduce oxidative stress during the intraoperative and postoperative phases.[25]

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Changes in PK behavior during CPB have been demonstrated for almost all anesthetic agents, with the choice and volume of priming fluids and temperature management essential determinants of the distribution, metabolism, and free fractions of these drugs.[26] The PK of propofol during CPB are not fully understood because results from studies are conflicting. Early studies have shown that the total concentration of propofol is likely to decrease when starting CPB secondary to hemodilution and an increase in the free fraction[27] or to remain unchanged.[28] Pre-CPB steady-state values are reestablished during rewarming. Bailey et al[29] undertook a PK analysis and were able to quantify this step-change of initiation of CPB with an increase of the central compartment from 6 to 15 L and an increase in elimination clearance. There is an offsetting effect of reduced hepatic extraction with graded levels of hypothermia because hepatic blood flow decreases by almost 20% after CPB is instituted.[30,31] Hypothermic CPB (32°C-34°C) also seems to alter the pharmacodynamics of propofol, with a higher central nervous system sensitivity during and immediately after bypass than with normothermic off-pump procedures. In a more recent study by Barbosa et al,[32] fairly similar blood concentrations were obtained most of the time using TCI, despite a higher metabolic clearance during CPB. These investigators found evidence of enhanced sensitivity to propofol using a bispectral index–guided maximum effect model of maximal drug effect. However, they also demonstrated that PK model–based TCI systems for propofol can be used safely and effectively during and after CPB. In comparison, volatile anesthetic agents show even larger variations in uptake and elimination when used on CPB[33] and depend heavily on the choice and use of oxygenators.[34]

Sufentanil and remifentanil are popular opioid components used more recently for TIVA in patients undergoing cardiac surgery. Apart from providing analgesia and hemodynamic stability, these modern, potent fentanyl congeners contribute other beneficial physiologic effects during cardiac surgery. For example, activation of the delta opioid receptor can elicit preconditioning and postconditioning, contributing direct cardioprotective effects. The role of this mechanism is currently an area of active research, as the accompanying article by Irwin et al[35] explains in more detail.

Because the PK of sufentanil and remifentanil have been well characterized in past PK models,[12,36] application of both drugs using TCI has become the obvious choice for most anesthesiologists in countries where the drug label has been extended accordingly. As with propofol, adjustments in dosing with TCI during CPB have to be considered. As a highly lipophilic drug with a shallow dose-response curve, sufentanil may require adjustments during CPB based less on changes of clearance and calculated compartments than on higher unbound concentrations.[37] Although there is a 17% reduction in sufentanil concentration during initiation of CPB when using a constant infusion, this effect is short-lived, and the performance of TCI based on a PK model is affected little during the later stages.[38]

In contrast, remifentanil shows slightly different PK characteristics when used during CPB. This potent opioid, with a high metabolic clearance and tissue distribution, exhibits a significantly increased volume of distribution with institution of CPB. This increased volume of distribution remains even shortly after initiation of CPB, as noted by Michelsen et al.[39] The PK of remifentanil during CPB are described best with a 2-compartment model instead of the usual 3-compartment model description. Elimination clearance seems to be reduced proportionally to the level of hypothermia. Because metabolic clearance for remifentanil is constant and nearly infinite, the benefit of TCI models lies in the calculated loading and maintenance of the central compartment over time.

ORGAN PROTECTION

A major emphasis in the conduct of modern cardiac anesthesia is maintenance of the integrity of end organ function in general and cardiac and brain protection in particular. Although the last decade was dominated by publications advocating the cardioprotective effects of volatile agents over propofol by means of preconditioning the myocardium or minimizing ischemia-reperfusion injury,[40] these results are mainly experimental, with little convincing evidence in terms of meaningful clinical endpoints as seen in more recent, larger scale patient studies in cardiac and noncardiac surgery.[41–43] A meta-analysis suggested a possible benefit in mortality with volatile agents; however, all studies included except one were underpowered.[44] A proof-of-concept study demonstrated a reduction of inflammatory markers with cardiospecific sevoflurane exposure, but there was a lack of attenuation in markers of myocardial cell damage.[45] As risk prediction for cardiac surgery shifts toward biomarker screening alongside scoring risk factors of individual patients,[46] the likelihood that the presence or absence of one particular intervention within the highly complex perioperative process of cardiac surgery consistently will affect mortality remains highly speculative.

A more tangible outcome after cardiac surgery is the possible effects of anesthesia on the integrity of brain function and, in particular, the impact of anesthesia on neurocognitive outcome after CPB. Although stroke is still considered a rare complication after CPB, various degrees of cognitive dysfunction and decline are common and may last longer compared with noncardiac surgery.[47] Based on experimental research, there is now a possible association between exposure to volatile anesthetic agents and the formation of neurofibrillary tangles and amyloid plaques in patients with Alzheimer disease.[48,49] In contrast, propofol has been shown to elicit direct neuroprotection by attenuating inflammatory responses during CPB,[24] by scavenging hydroxyl radicals formed by brain injury,[50] and by reducing the infarct size after experimental ischemia-reperfusion (neuroapoptosis challenge) in the brain.[51]

CONCLUSIONS

TIVA has various characteristics that make it a sensible alternative to the use of volatile agents. In Europe and elsewhere in the world, the availability of TCI has made TIVA an economically viable technique that allows precise titration to clinical effect. The benefits of TIVA include organ protection; patient well-being; and enhanced recovery after cardiac surgery, especially when propofol is combined with remifentanil, which also contributes to cardioprotection. Also, there is great potential to improve neurocognitive outcomes in patients undergoing cardiac surgery. However, it remains to be seen

if early claims of improved brain protection outcomes with TIVA versus inhaled anesthetics are demonstrated in prospective and well-powered clinical research.

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