Anesthetic Management During Cardiopulmonary Bypass: A Systematic Review

Aaron E. Barry, MD,* Mark A. Chaney, MD,* and Martin J. London, MD†

Cardiopulmonary bypass (CPB) required for cardiac surgery presents unique challenges to the cardiac anesthesiologist responsible for providing the 3 most basic facets of any anesthetic: amnesia, analgesia, and muscle relaxation. Unique pathophysiologic changes during CPB result in pharmacokinetic alterations that impact the serum and tissue concentrations of IV and volatile anesthetics. Similarly, CPB causes pharmacodynamic alterations that impact anesthetic efficacy. The clinical significance of these alterations represents a "moving target" as practice evolves and the technology of CPB circuitry advances. In addition, perfusionists choose, modify, and maintain the CPB circuitry and membrane oxygenator. Thus, their significance may not be fully appreciated by the anesthesiologist. These issues have a profound impact on the anesthetic state of the patient. The delivery and maintenance of anesthesia during CPB present unique challenges. The perfusionist may be directly responsible for the delivery of anesthetic during CPB, a situation unique to the cardiac suite. In addition, monitors of anesthetic depth—assessment of clinical signs, hemodynamic indicators, the bispectral index monitor, end-tidal anesthetic concentration, or twitch monitoring—are often absent, unreliable, or directly impacted by the unique pathophysiology associated with CPB. The magnitude of these challenges is reflected in the higher incidence of intraoperative awareness during cardiac surgery. Further complicating matters are the lack of specific clinical guidelines and varying international policies regarding medical device specifications that add further layers of complexity and introduce practice variability both within institutions and among nations. We performed a systematic survey of the literature to identify where anesthetic practice during CPB is evidence based (or not), identify gaps in the literature to guide future investigations, and explore the implications of evolving surgical practice, perfusion techniques, and national policies that impact amnesia, analgesia, and muscle relaxation during CPB. (Anesth Analg 2015;120:749–69)

Clinical management of patients requiring cardiopulmonary bypass (CPB) for cardiac surgery is complex, and the cardiac anesthesiologist is faced with many challenging management issues as surgical techniques evolve, such as altered cannulation sites, minimally invasive cardiac surgery, profound hypothermic circulatory arrest, and use of mechanical assistance.[1] While busy confronting these challenges, the cardiac anesthesiologist must also ensure adequacy of the 3 basic facets of any anesthetic: amnesia, analgesia, and muscle relaxation.[2] Objective assessment of these facets is challenging during CPB because traditional clinical variables used to assess "adequacy" of anesthesia, such as heart rate, arterial blood pressure, respiratory rate/pattern, and end-tidal carbon dioxide tension, are either not available or are directly controlled by the perfusionist. A unique aspect of this period is that critical aspects of anesthetic management, such as volatile anesthetic delivery, are transferred entirely to, or at best comanaged with, the perfusionist.

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Institution of CPB induces many complex circulatory changes (pressure, flow, distribution) and profoundly alters major organ blood flow to the brain, heart, lung, kidneys, and liver.[1] Unique pathophysiologic changes accompany these alterations in circulation and blood volume, such as hemodilution, hypothermia, and the systemic inflammatory response. These alterations profoundly influence the pharmacokinetics and pharmacodynamics of IV and volatile anesthetics.[3,4] This systematic review focuses initially on the mechanics of CPB and resulting pathophysiologic alterations, influencing pharmacokinetics and pharmacodynamics of commonly used classes of anesthetics. We then attempt to synthesize high-quality studies and identify gaps in the literature pertaining to the proper maintenance of amnesia, analgesia, and muscle relaxation in patients undergoing CPB. The literature search strategy is presented in the Appendix.

CARDIOPULMONARY BYPASS CIRCUITRY

The CPB circuit (Fig. 1) consists of a venous reservoir, membrane oxygenator, and centrifugal pump designed to drain venous blood and return oxygenated blood to the arterial system.[5] Standard CPB circuits use roller pumps for suction, venting, and delivering cardioplegia and are typically equipped with a heat exchanger, filters, real-time blood gas monitors, pressure and flow monitors, and various safety mechanisms. CPB components may be coated with heparin, albumin, or other compounds designed to minimize damage to blood products and to potentially attenuate the systemic inflammatory response.[6]

During CPB, oxygen and volatile anesthetic are delivered via a membrane oxygenator inflow. Carbon dioxide and waste anesthetic gas are removed via an oxygenator

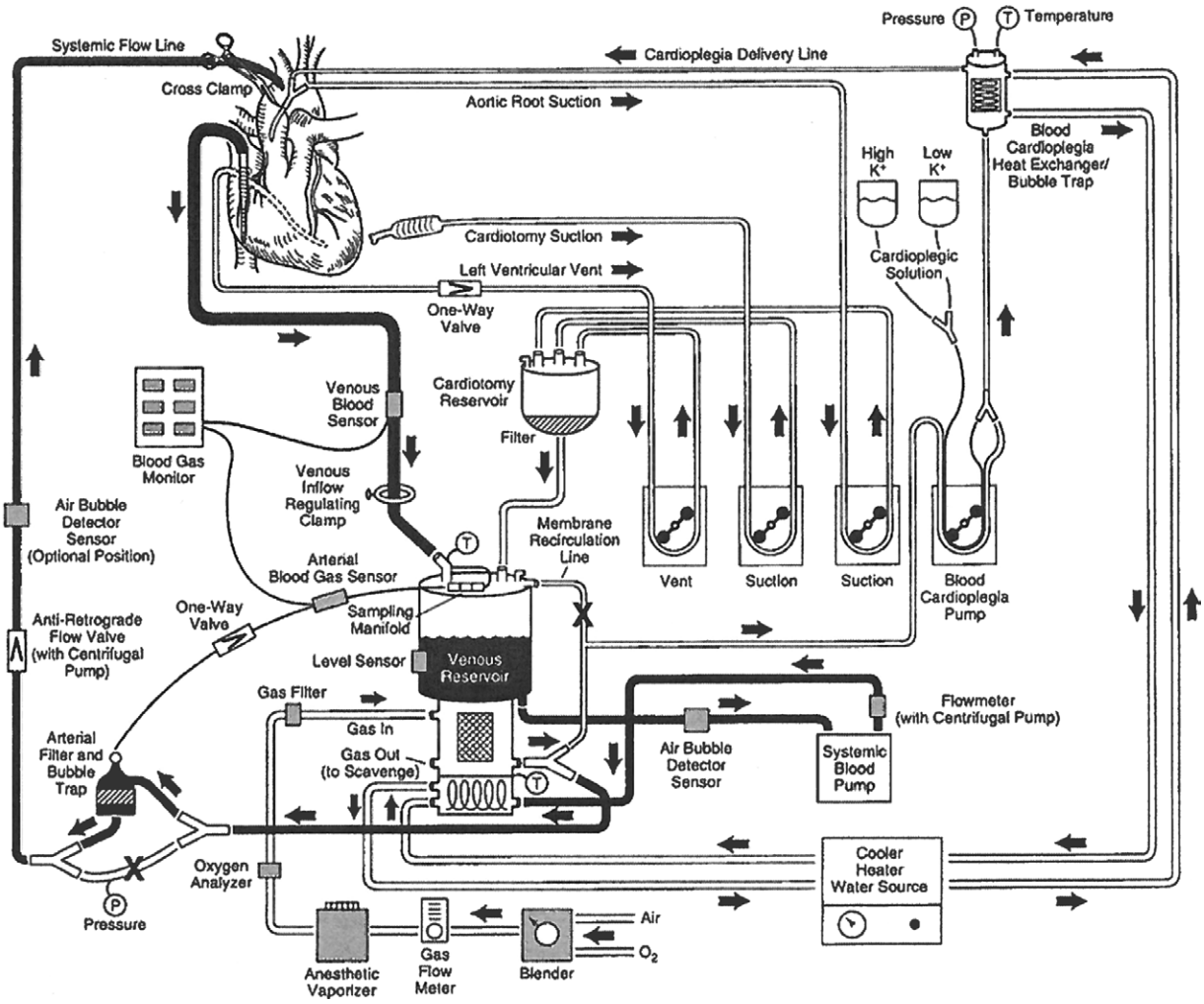

Figure 1. The cardiopulmonary bypass circuit. Reproduced with permission from Wolters Kluwer Health.[5]

Table 1. Two Types of Membrane Oxygenators in Common Use

	Membrane oxygenators	
	Polypropylene (PPL)	**Poly-(4-methyl-1-pentene) (PMP)**
Mechanism	Countercurrent exchange, capillary action	Diffusion
Gas exchange	Efficient	Efficient
Duration of use	6–8 h	Days-weeks
Microemboli	Yes	No
Blood product contact	Yes	No
Volatile anesthetics	Cross membrane	Unable to cross membrane

exhaust port. It is important to note that anesthetic vaporizers are added to the CPB circuit by perfusionists after the equipment has been purchased and without any guidance from the manufacturer.[7] This lack of standardization in anesthetic vaporizer integration into the CPB circuit may contribute to substantial variability in volatile anesthetic delivery within and between hospitals.

Differences in oxygenator design also influence volatile anesthetic delivery. Table 1 presents the 2 types of membrane oxygenators in common use. Microporous polypropylene (PPL) hollow-fiber membrane oxygenators function via capillary action and countercurrent gas exchange (Fig. 2).[8,9] The hollow fibers are fragile, and these oxygenators are only rated by the Food and Drug Administration for a maximum of 6 to 8 hours of use.[10,11] Longer durations may be associated with a decreased ability to oxygenate the patient and membrane "weeping," which usually requires brief separating from CPB to replace the oxygenator. Consequently, PPL membranes are best suited for short-term applications. Although these membranes are the standard oxygenators used during CPB in the operating room, the risk of gas embolism also limits its safety.[9] Poly-(4-methyl-1-pentene) (PMP) membrane oxygenators were developed more recently to address some of the limitations of PPL oxygenators. They are also called plasma-tight or diffusion oxygenators.[12] The clinical advantages include stability for more than 6 to 8 hours, less risk of gas microembolism, and less plasma

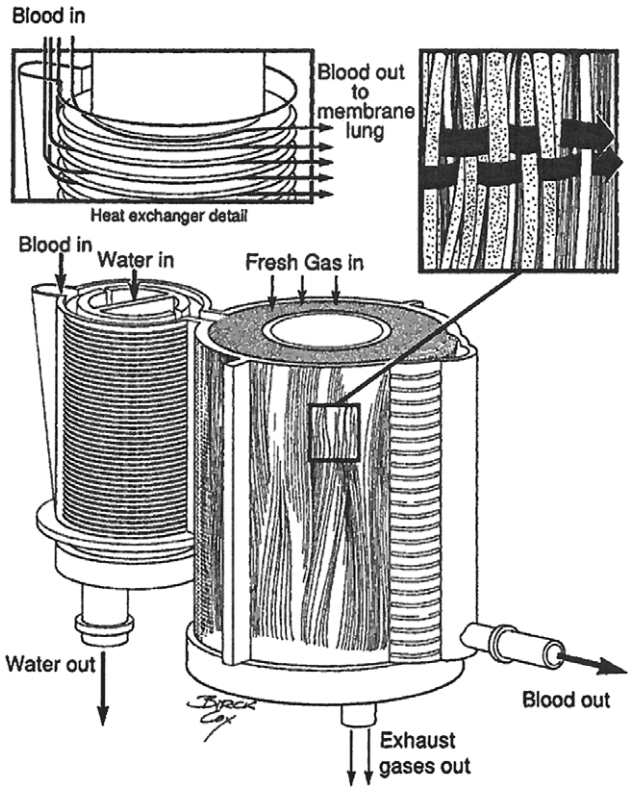

Figure 2. Membrane oxygenator. Reproduced with permission from Wolters Kluwer Health.[5]

Table 2. Clinical Factors Influencing Pharmacokinetic Changes Observed During Cardiopulmonary Bypass

IV anesthetics
Effects of hemodilution
Altered plasma protein binding
Volume of distribution
Altered drug clearance
Acid-base disturbances
Lung isolation
Drug sequestration
Systemic inflammatory response
Inhalational anesthetics
Altered blood/gas partition coefficient
Altered tissue solubility
Oxygenator design

leakage across the membrane.[11] Given their stability, PMP oxygenators are best suited for long-term applications, and they are used mainly during prolonged extracorporeal membrane oxygenation. Clinical ramifications of differences in CPB circuit or membrane oxygenator design are considered later.

PHARMACOKINETIC ALTERATIONS

Table 2 lists clinical factors influencing pharmacokinetic alterations during CPB. Previous reviews by Mets[4] in 2000 and Hall[3] in 2002 address these in detail. Herein, we provide a brief review and update with new information accumulated over the past decade. Table 3 presents an overview of important studies investigating pharmacokinetic changes observed during CPB.

IV ANESTHETICS

Effects of Hemodilution

Hemodilution is a consequence of crystalloid or colloid volume priming of the CPB circuit. This decreases blood concentrations of all IV and volatile anesthetics on initiation of CPB.[13–24] The choice of priming fluid may be important because anesthetics are less soluble in crystalloid and albumin than in blood.[25,26]

The amount of prime impacts degree of anesthetic dilution. Techniques to reduce transfusion, such as autologous priming,[27–30] aim to minimize hemodilution by restricting volume of crystalloid or colloid. Similarly, minimal extracorporeal circulation (MECC) is a new technology that aims to reduce transfusion requirements and potentially attenuate the systemic inflammatory response.[31,32] In short, MECC uses smaller CPB circuits (less blood-circuit interface), which require smaller priming volumes. "MECC" is a generic term, and each MECC circuit setup varies among individual perfusionists. MECC is not the standard of care in the United States because of the numerous clinical disadvantages of this technique, which include decreased safety (many safety devices are eliminated), inability to manipulate large volumes of fluid in and/or out of the patient, and sometimes lack of a volatile anesthetic vaporizer. Autologous priming and MECC (typical prime approximately 400 mL, in contrast to "standard" prime of 750–1000 mL) both decrease the volume of prime solution and may attenuate the effect of hemodilution on anesthetic blood concentrations. However, these techniques have only recently been introduced. Thus, their impact on anesthetic blood concentrations during CPB has not been adequately studied. Essentially, all the literature forming the basis of our understanding of the effects of hemodilution was published during the era of standard priming volumes (750–1000 mL). However, one study demonstrated that smaller priming volumes (300–360 mL vs 750–1000 mL) resulted in less hemodilution of fentanyl during pediatric cardiac surgery.[33]

Altered Plasma Protein Binding

Priming volume at onset of CPB decreases blood concentrations of albumin,[17,18,33] α_1-acid glycoprotein,[13] and red blood cells,[3,14,25] all of which bind anesthetics. This is of particular relevance for IV drugs that are highly protein bound, with high hepatic extraction ratios or low therapeutic indices.[34] Consequently, propofol, midazolam, and opioids exhibit increased free fractions of drug during CPB.[17,18,20,22,33] The free unbound component of drug is what diffuses across the blood-brain barrier, producing anesthetic effect.[35–37] The increased free fraction offsets the decrease in overall drug concentration from hemodilution (Fig. 3). Several studies have revealed that unbound drug concentrations are unaffected by initiation of CPB and in many cases may exceed pre-CPB levels, despite significant decreases in total drug concentration.[18,20,22] Decreased hepatic and renal clearance may also contribute to higher levels of unbound drug.[38,39] Thus, anesthetic depth may be preserved or even enhanced, despite decreases in total anesthetic blood concentration. Finally, given the substantial proportion of critically ill patients undergoing cardiac surgery, it is also important to consider the potential pharmacologic impact of hypoalbuminemia on concentrations of active, unbound drug. Higher

Table 3. Overview of Important Studies Investigating Pharmacokinetic Changes Observed During Cardiopulmonary Bypass

Author	Year	Study type	N	Temperature (°C)	Anesthetics measured	Surgery type	Major findings	Comments
Tarr and Snowdon[24]	1991	Prospective	10	Moderate hypothermia (24–26)	Enflurane	CABG	Blood/gas solubility and enflurane concentration decreased on initiation of bypass. Blood concentration increased throughout hypothermia. During rewarming, enflurane concentration returned to pre-cooling levels.	
Hammarén et al.[23]	1996	Prospective	15	Moderate hypothermia (30)	Propofol	CABG	Propofol concentration decreased on initiation of bypass. Unbound propofol concentration remained unchanged on initiation of bypass and was at its highest during hypothermia. Heparin did not affect propofol concentrations. Nb latency was at its maximum during hypothermia and remained prolonged throughout the remainder of the study.	
Dawson et al.[16]	1997	Prospective, randomized	24	30–32	Propofol, midazolam	Cardiac surgery	Total concentrations of propofol and midazolam fell on initiation of bypass. Unbound concentrations both increased, although the increases were not statistically significant.	Increases in unbound concentration were ~2-fold. The sample sizes were too small to be significant.
Mazoit and Samii[25]	1999	In vitro			Propofol		Propofol is tightly bound to albumin and red blood cells. The free fraction of propofol is likely to be higher in patients with hypoalbuminemia.	
Barvais et al.[21]	2000	Prospective	20	Moderate hypothermia (30)	Sufentanil, midazolam	Valve or CABG	TCI is safe and accurate before CPB for sufentanil and midazolam. When early extubation is not planned, this technique provides excellent hemodynamic stability.	Measured sufentanil and midazolam concentrations were both lower than predicted by the model during and after CPB.
Yu et al.[26]	2001	In vitro		37, 33, 29, 25, 21, 17	Desflurane, isoflurane, halothane		During normothermic CPB, blood solubility of volatile anesthetics would be unchanged when using plasma, slightly reduced when using banked blood, and markedly reduced when using crystalloids and colloids. The solubilities of anesthetics in all priming fluids increase at lower temperatures.	
Benet and Hoener[34]	2002	Review					Alterations in plasma protein binding are clinically relevant for IV drugs that are highly protein bound with narrow therapeutic indices.	
Hudson et al.[20]	2003	Prospective	61	Mild hypothermia (33)	Fentanyl	CABG	A simple, 3-compartment model used for TCI accurately predicts fentanyl concentration throughout bypass.	
Yoshitani et al.[15]	2003	Prospective, randomized	45	Normothermic	Propofol	Cardiac surgery	All patients had decreased propofol concentrations on initiation of bypass. The low-dose propofol group remained decreased, while the moderate and high-dose propofol groups had return of total concentrations back to baseline. BSR values gradually increased above baseline values in the moderate and high-dose propofol cohorts.	

(*Continued*)

Table 3. (Continued)

Author	Year	Study type	N	Temperature (°C)	Anesthetics measured	Surgery type	Major findings	Comments
Hiraoka et al.[13]	2004	Prospective	19	Normothermic	Propofol	Cardiac surgery	Unbound propofol concentration increased 2-fold during CPB without alteration of the total propofol concentration. Total propofol concentration decreased on initiation of bypass and re-equilibrated within minutes.	
Hudson et al.[19]	2004	Prospective	21	Mild hypothermia (>33)	Sufentanil	CABG	Sufentanil concentrations decrease on initiation of bypass. A simple, 3-compartment model used for TCI accurately predicts sufentanil concentration throughout bypass.	
Kussman et al.[33]	2005	Prospective	15 neonates and infants	Wide range. Average nadir reported: 16.7 ± 4.2	Fentanyl	Cardiac surgery	Fentanyl concentration decreased on initiation of bypass and had rebounded when measured 30 min later. Plasma fentanyl concentration varied little with the use of a low-volume bypass circuit.	
Takizawa et al.[14]	2006	Randomized, prospective	30	Normothermic	Propofol	Cardiac surgery	Unbound propofol concentration increased 2-fold during CPB without alteration of total propofol concentration. BIS decreased and BSR increased in correlation with unbound propofol concentration.	
Jeleazcov et al.[18]	2012	Prospective, randomized	38	Normothermic	Sufentanil	CABG	Total and unbound sufentanil concentrations deviated from the Gepts model used for TCI. Unbound sufentanil concentration increased significantly during CPB.	
Nitzschke et al.[17]	2013	Prospective	30	30–34	Sevoflurane	Cardiac surgery	Uptake of sevoflurane at the oxygenator is influenced by hypothermia, hemodilution, and the oxygenator fresh gas supply flow. Measuring oxygenator exhaust is not useful during bypass.	Nitzschke's conclusions about measuring oxygenator exhaust have been criticized.

BIS = bispectral index; BSR = burst suppression ratio; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; TCI = target-controlled infusion.

	Awake	Before heparin	After heparin, before CPB	During CPB (1 min)	During hypothermic CPB	After CPB, before protamine	After protamine
Time from awake sample (min)		87 (79–95)	96 (87–105)	113 (104–121)	142 (131–153)	210 (194–225)	228 (211–244)
Total propofol (μg ml^{-1})	NA	2.4 (2.1–2.7)	2.6 (2.3–2.8)	1.7 (1.5–2.0)†‡	2.1 (1.7–2.4)	1.7 (1.4–2.0)†‡	1.7 (1.5–2.0)†‡
Unbound propofol (μg ml^{-1})	NA	0.04 (0.03–0.04)	0.06 (0.040.07)	0.06 (0.040.07)	0.07 (0.040.10)†	0.04 (0.030.05)	0.02 (0.020.03)‡§
Plasma unbound fraction (%)	NA	1.5 (1.1–1.9)	2.3 (1.7–2.9)	3.5 (2.5–4.5)†	3.7 (2.3–5.1)†	2.6 (1.9–3.3)	1.5 (1.2–1.7)§
Blood PCV	NA	0.37 (0.35–0.39)	0.37 (0.34–0.39)	0.25 (0.23–0.27)†‡	0.25 (0.24–0.27) †‡	0.28 (0.26–0.30)†‡	0.29 (0.28–0.30)†‡§
Serum albumin (g litre^{-1})[1]	NA	36 (34–38)	37 (35–39)	22 (19–24)†‡	21 (18–23)†‡	24 (22–26)†‡§	25 (24–27)†‡§
Latency of Nb wave (ms)[2]	41 (33–48)	71 (67–74)*	67 (62–71)*	73 (68–77)*	79 (73–85)*‡	66 (65–68)*§	70 (65–76)*

Figure 3. Interplay of temperature, hemodilution, plasma protein concentration, heparin, and protamine on bound and unbound propofol concentrations and parameters indicating anesthetic depth. Plasma total and unbound propofol concentration, unbound fraction of propofol-packed cell volume (PCV), serum albumin concentration and latency of the Nb wave from the auditory-evoked potentials (mean [95% confidence interval]). n = 15 patients, unless otherwise indicated ([1]n = 14, [2]n = 12). NA = not available. *P < 0.05 versus value awake; †P < 0.05 versus value before heparin; ‡P < 0.05 versus value before cardiopulmonary bypass; §P < 0.05 versus hypothermic cardiopulmonary bypass (CPB). Reproduced with permission from Oxford University Press.[23]

levels of unbound propofol have been observed in critically ill patients with hypoalbuminemia,[40] possibly resulting in decreased propofol requirements (Fig. 4).

Heparin, particularly in the large amounts required for CPB, also affects free drug blood concentrations by initiating the release of lipoprotein lipase and hepatic lipase, each of which hydrolyzes plasma triglycerides into nonesterified fatty acids.[4,41] These bind competitively to plasma proteins, displacing protein-bound drugs and increasing free fraction of drug. This effect of heparin has been well described for many drugs,[42–46] and amounts as low as 50 International Units have been shown to increase the free fraction of propranolol.[45] This principle also likely applies to protein-bound anesthetics, with increasing free fractions potentially deepening anesthetic level. However, many of these studies were performed decades ago, and the clinical impact of heparin administration on modern anesthetics is unclear. Of note, protamine reverses heparin's impact on unbound drug blood concentrations.[23]

Volume of Distribution

Drugs with a high volume of distribution such as propofol and fentanyl distribute widely throughout blood and tissues. A high volume of distribution likely attenuates the clinical impact of hemodilution on anesthetic blood concentrations because drug distributed into tissues will rapidly re-equilibrate with plasma concentrations after initiation of CPB. Re-equilibration occurs over the course of a few minutes and has been demonstrated for many anesthetic[17,20] and nonanesthetic[47,48] drugs.

Altered Drug Clearance

Drug clearance is profoundly affected by hypothermia. Animal studies reveal that enzymatic efficiency is impacted by changes in temperature.[49,50] In humans, hypothermia-induced decreased Hoffman elimination occurs with cisatracurium[51,52] and remifentanil.[22] Degree of hypothermia also impacts rate of drug clearance.[52,53] A decrease in body

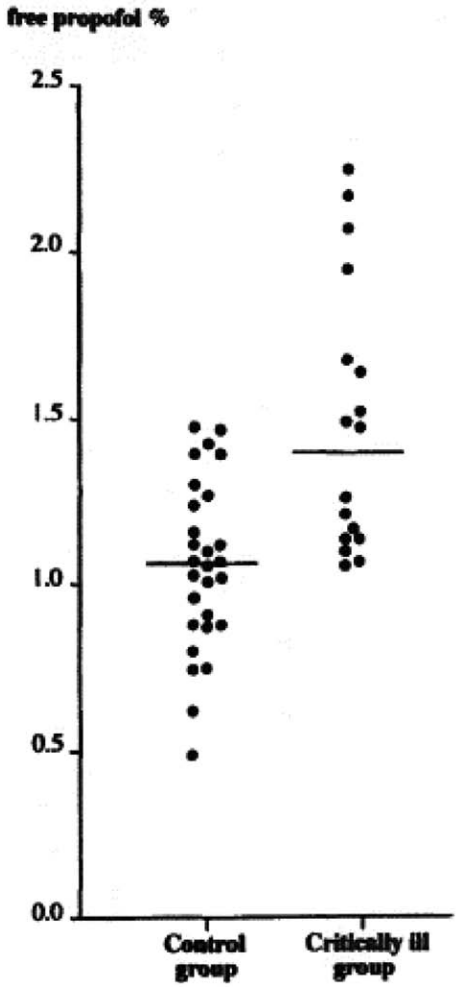

Figure 4. Unbound propofol concentrations are higher when patients are hypoalbuminemic. The percentage of free propofol in serum from control subjects and from critically ill patients; control group 1.07 (0.49–1.47%); critically ill group 1.31 (1.06–2.25%). Reproduced with permission from John Wiley and Sons.[40]

temperature of as little as 2°C may double the duration of neuromuscular blockade.[54]

Over the years, substantial change in the clinical management of hypothermia during CPB has occurred, with a shift toward "mild" hypothermia ("drifting" to 32–34°C range) and, to a lesser degree, normothermic CPB.[55] Much of the literature forming the basis of our understanding of the pharmacokinetic impact of CPB was published before this change in practice (e.g., at colder temperature). In addition, the terms "mild," "moderate," "deep," and "profound" hypothermia are often vaguely defined and vary across studies. Thus, the effects of hypothermia on drug clearance in contemporary clinical practice may not be as significant as initially reported at colder temperatures.

Drug clearance is also affected via altered organ perfusion/microcirculatory flow during CPB. Blood flow to the liver and kidney is decreased by hypothermic CPB.[3,4] This is particularly relevant for drugs with high liver extraction ratios, such as propofol.[13] However, these conclusions are based on data extrapolated from animal studies[56,57] and indirect measurements of hepatic function in humans.[58–60] Several studies have challenged these assumptions and suggest that normothermic and mild to moderate hypothermic CPB may have only minimal effects on hepatic blood flow and function.[61–64] Thus, the clinical impact of contemporary temperature management practices on hepatic and renal perfusion/function may be less than previously thought.

Drug clearance after CPB is also affected, as prolonged elimination half-lives and elevated blood drug concentrations of propofol[13,65] and midazolam[66] have been reported. While the mechanism is unclear, reduced elimination resulting from hypothermia and/or altered organ perfusion/microcirculatory flow are commonly cited as potential causes.[59]

Acid-Base Disturbances

Initiation of nonpulsatile hypothermic CPB alters microcirculatory blood flow, potentially creating physiologic areas of hypoperfusion and acidosis.[67] Basic drugs may become trapped in acidic cellular microenvironments and recirculate once perfusion improves and acidosis resolves.[4] Thus, during hypothermic CPB, there is the potential for "trapping" of basic drugs and their "release" after separation from CPB. This hypothesis is based on an old study of deltoid muscle gas tensions demonstrating decreased perfusion of muscle during hypothermic CPB,[67] and more current research on alterations in microvascular deltoid muscle blood flow during cardiac surgery supports these findings.[68] However, neither of these investigations actually confirmed that basic drugs were trapped in these cellular microenvironments because they did not measure muscle drug concentrations.

Lung Isolation

Pulmonary blood inflow almost completely ceases during CPB yet continues via bronchial artery blood flow; thus the lungs are almost isolated from the systemic circulation. Opioids and neuromuscular blocking drugs are highly sequestered in the lungs during this period and are not metabolized.[23,69–71] Consequently, resumption of ventilation and reinitiation of pulmonary blood flow allow these drugs to recirculate, and increased serum concentrations of fentanyl[20] and sufentanil[19] have been demonstrated during separation from CPB (Fig. 5).

Drug Sequestration by the Cardiopulmonary Bypass Circuit

Opioids,[72] propofol,[73–76] and volatile anesthetics[8] bind tightly to the plastic components of the CPB circuit and membrane oxygenator. As much as 75% of administered propofol is absent from plasma after 120 minutes of a simulated in vitro CPB run.[75] However, CPB circuits are now routinely "coated" with a variety of substances such as heparin,[73] which decreases platelet adhesion, and phosphorylcholine,[77] which may more closely mimic the vascular wall, in an attempt to decrease damage to blood elements and attenuate the systemic inflammatory response. In vitro analyses on the impact of these coatings on propofol have not demonstrated any effect on pharmacokinetics.[23,77] There is a growing list of new "biocompatible circuit coatings"[78–81] with unknown pharmacologic implications. Thus, additional advances in CPB technology may affect pharmacokinetics. Also, the amount of drug sequestration would be expected to decrease with MECC because of smaller circuit surface area and less blood-circuit interface; however, this has yet to be studied.

Systemic Inflammatory Response

CPB induces a profound systemic inflammatory response, leading to dysregulation of cytokines, interleukins, and the cytochrome P-450 enzymatic system responsible for liver drug clearance. In addition, downregulation of enzymatic systems located in the brain may reduce drug clearance

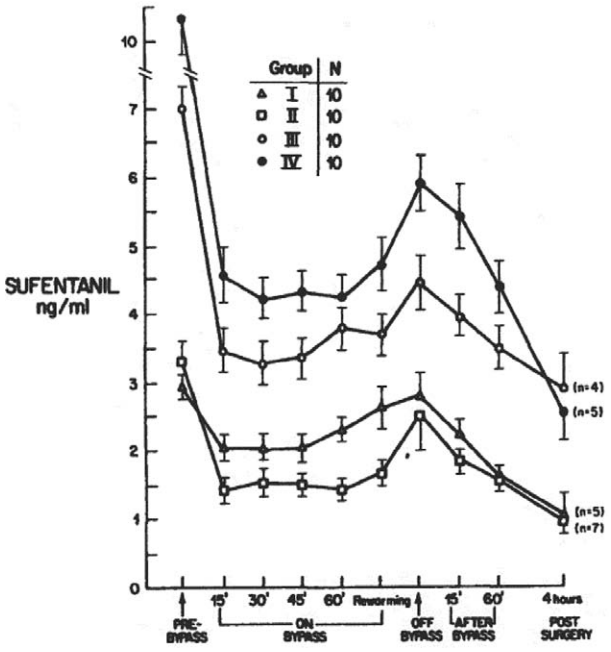

Figure 5. Increased sufentanil concentration when coming off bypass as a consequence of pulmonary arterial inflow and ventilation. Plasma sufentanil concentrations in all 4 groups. All measurements represent the mean ± SEM for 10 patients except for the last sample, 4 hours (240 minutes) after cardiopulmonary bypass. Reproduced with permission from Wolters Kluwer Health.[71]

and prolong anesthetic action centrally.[3] MECC, corticosteroids,[82] complement inhibitors,[83] and other techniques used to reduce inflammation may impact anesthetic pharmacology by such attenuation, yet this has not been formally studied. The systemic inflammatory response induced by CPB is a broad topic beyond the scope of this review, and the reader is referred elsewhere.[84–86] In general, the clinical impact of individual inflammatory mediators is poorly understood.[3] By extension, the sum effect of the inflammatory response on pharmacokinetics is even less well defined. Interestingly, a recently published small (n = 14 animals) porcine model study hints at the potential ability of anesthetic technique to alter the systemic inflammatory response.[87] Pigs administered isoflurane, in contrast to propofol, during CPB exhibited a greater increase in fluid extravasation from the intravascular to the interstitial space, resulting in dilution of interstitial fluid and a decrease in interstitial colloid osmotic pressure, implying that perhaps propofol is better than volatile anesthetics at systemic inflammatory response attenuation during CPB.

VOLATILE ANESTHETICS

The use of volatile anesthetics during CPB was first described in 1974.[88] In addition to the factors discussed above, the pharmacokinetics of volatile drugs are impacted by 3 additional factors: altered blood/gas partition coefficient,[24,26,89–96] altered tissue solubility,[90,97,98] and oxygenator design.[8,9,12,89,97,99] An important consideration when evaluating clinical studies in this arena is how the volatile anesthetic was measured. One method measures plasma concentration, which requires storage at controlled temperature and transport to a laboratory. Rapid results are not available, preventing applicability for intraoperative management. Another method is to sample the membrane exhaust port (end-tidal anesthetic concentration [ETAC]), which may offer real-time data to help guide intraoperative management.

Altered Blood/Gas Partition Coefficient

Hemodilution and hypothermia are competing physiologic factors influencing volatile anesthetics by virtue of their opposite effects on the blood/gas coefficient (hemodilution decreases, hypothermia increases). During hypothermic CPB, they act to counterbalance each other.[90] During rewarming, however, the blood/gas partition coefficient decreases.[91] Regarding desflurane and isoflurane, substantial increases in temperature during rewarming (30.4–37.5°C), with small increases in hematocrit (21%–22%), resulted in the lowest blood/gas partition coefficient measured (approximately 75% of preinduction levels for all 3 drugs).[91] This results in more rapid washin or washout of volatile anesthetic during separation from CPB and implies that anesthetic titration (changing levels) during hypothermia is slowed.[100] However, slower titration of volatile anesthetic can be partially overcome by increasing the fresh gas flow in the CPB circuit.[17,99] Practice variations regarding hemodilution and temperature management strategies will impact blood/gas partition coefficients of volatile anesthetics.

Altered Tissue Solubility

Hypothermia increases solubility of volatile anesthetics in tissues, such as the brain, resulting in increased anesthetic depth.[4] However, with alterations in the blood/gas partition coefficient noted earlier, titration (changing levels) of volatile anesthetics occurs more slowly during hypothermic conditions,[89,90,97,101] and it may take more time to reach a deeper anesthetic state.

Oxygenator Design

Oxygenator design profoundly affects anesthetic uptake. Oxygenators either absorb volatile anesthetic[8,99] or prevent passage of the agent altogether (Fig. 6).[9,12] In vitro comparison of PPL and PMP membranes confirms that while

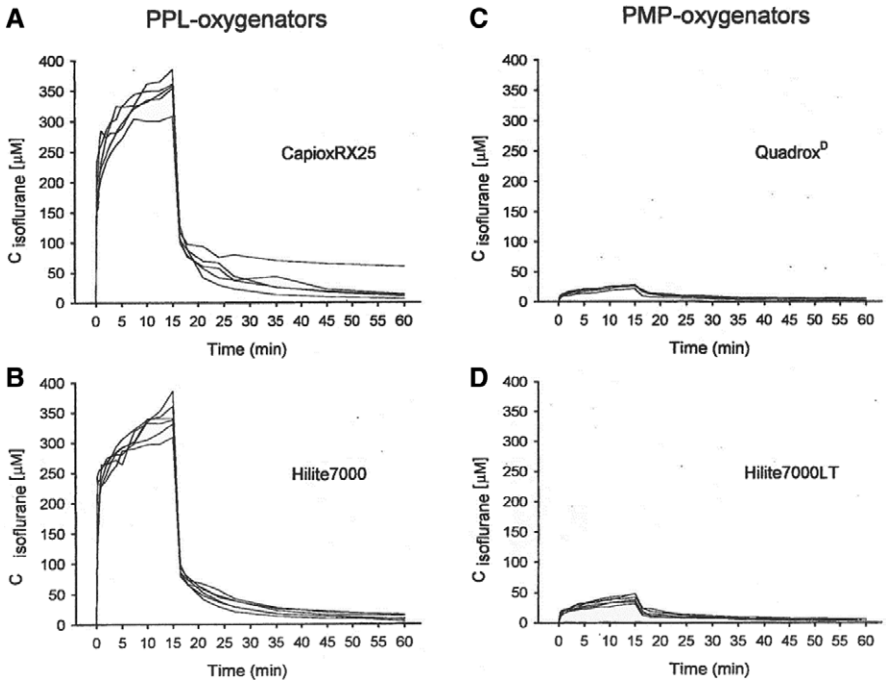

Figure 6. Isoflurane does not cross poly-(4-methyl-1-pentene) (PMP) membrane oxygenators. Isoflurane blood concentrations ($C_{isoflurane}$ [µm]) for the uptake and elimination sequence in the 4 oxygenator groups. Each line represents a single patient. (A) Capiox® RX25; (B) Hilite® 7000; (C) Quadrox^D; (D) Hilite® 7000LT.[12] PPL = polypropylene. Reproduced with permission from Wolters Kluwer Health.[12]

volatile anesthetics cross the PPL membrane, virtually no volatile anesthetic diffuses across the PMP membrane.[9] This finding has been confirmed using gas chromatographic measurement of blood isoflurane concentrations in vivo.[12] While PMP oxygenators are widely used for extracorporeal membrane oxygenation given their superior stability to fragile PPL oxygenators, they may also be used during CPB in the operating room if total IV anesthesia is the planned technique, which is common throughout Europe. Despite such issues, manufacturers of membrane oxygenators (PPL or PMP) are not required to test the impact of their design on anesthetics; they are only required to ensure biocompatibility with membrane components.[10] Consequently, the impact of membrane oxygenators on anesthetics may not be apparent until after the device comes to market.[11]

PHARMACODYNAMIC ALTERATIONS

We are still far from a complete understanding of how anesthetics initiate and maintain the anesthetic state. This fact limits our knowledge of pharmacodynamic alterations induced by CPB. Furthermore, the relative impact of hypothermia alone or CPB on pharmacodynamic alterations cannot always be separated. Altered pharmacokinetics due to hypothermia or CPB and lack of an objective assessment of adequacy of anesthesia during this time also confound evaluation of anesthetic depth. Despite these issues, several studies indicate that hypothermia and impaired cerebral function resulting from pathophysiology associated with CPB play major roles in the pharmacodynamics of IV and volatile anesthetics (Table 4).

HYPOTHERMIA

Hypothermia clearly impacts anesthetic requirements. Studies on the effect of temperature reveal that less propofol is required to maintain a constant bispectral index (BIS) level during normothermic CPB.[102] Patients exposed to hypothermic CPB require even less propofol,[23,103] suggesting that hypothermia increases its potency.[14,15] Studies on volatile anesthetics assessing anesthetic depth with electroencephalography or ETAC report decreased anesthetic requirement during hypothermia[15,104,105] and increased anesthetic requirement during rewarming.[106,107] This has been consistently demonstrated in adult patients for sevoflurane[106] and isoflurane,[107,108] in pediatric patients,[108,109] and in animals.[110] One investigation in children measured isoflurane minimum alveolar concentration requirements and isoflurane lipid solubility and suggested that anesthetic solubility alone is not enough to explain the decreased minimum alveolar concentration requirement observed during cooling. These investigators postulate that their results imply a potential amnestic effect of hypothermia.[108]

Hypothermia induces both pharmacokinetic and pharmacodynamic alterations. Some investigators have attempted to control these pharmacokinetic changes to delineate the potential impact of hypothermia alone on pharmacodynamics, by assessing isoflurane lipid solubility, not blood concentration, yet this is challenging.[108] In reality, it remains quite difficult to distinguish clinically whether changes in anesthetic depth are due to altered pharmacokinetics or pharmacodynamics (or both).

Hypothermia also confounds studies that rely on BIS monitoring to assess anesthetic depth because BIS independently decreases with hypothermia[103,104,111–114] and increases during rewarming.[14,17,107,114] It is unclear whether these electroencephalographic changes represent the anesthetic state or are an artifact of changing temperature. In addition, the response of BIS to changes in temperature is highly variable among patients.[109,115–117] This information, along with the demonstration of decreased minimum alveolar concentration requirement during hypothermia,[108,110] would propose that electroencephalographic changes in response to hypothermia may indeed reflect changes in anesthetic depth, potentially lending validity to studies reliant on electroencephalographic monitoring.

Hypothermia also impacts analgesia and the density of neuromuscular blockade. Analgesia may be affected via decreased morphine binding at opioid receptors under hypothermic conditions.[118] Neuromuscular blockade density is enhanced during hypothermia; muscle strength is impaired by as much as 10% with each decreasing degree Celsius in the absence of muscle relaxant.[54] Whether the result of pharmacokinetic or pharmacodynamic alterations (or both), studies clearly demonstrate that decreased doses of vecuronium[119,120] and rocuronium[121] are required during hypothermic CPB.

Table 4. Clinical Factors Influencing Pharmacodynamic Changes Observed During Cardiopulmonary Bypass

Hypothermia
Increased IV anesthetic potency during hypothermia
Increased inhaled anesthetic potency during hypothermia
Decreased inhaled anesthetic potency during rewarming?
Increased sensitivity to neuromuscular blockade during hypothermia
Decreased morphine binding to opioid receptors?
Impaired cerebral function
Microembolic phenomenon/systemic inflammatory response
Cerebral edema/brain inflammation
Decreased cytochrome P-450 activity
Increased intracranial pressure
Postoperative cognitive dysfunction

IMPAIRED CEREBRAL FUNCTION

Exposure to CPB alone (with or without hypothermia) has been implicated as a reason for decreased minimum alveolar concentration requirement. While the mechanism is unclear, impaired cerebral function as a consequence of CPB has been the focus of many animal studies.[110,122–126] However, such observational studies have lacked control groups and report inconsistent results. Several human studies during hypothermic CPB implicate CPB as an independent factor responsible for decreased anesthetic requirements.[103,107,127] Specifically, initiation of CPB decreases the magnitude of propofol requirements, and the effect of hypothermic CPB is significantly more than that of normothermic CPB.[103] Isoflurane requirements are also reduced during hypothermic CPB[107] and isoflurane requirements are reduced after, compared with before, hypothermic CPB.[127]

One randomized, controlled trial assessed minimum alveolar concentration of rats exposed to normothermic CPB.[126] Ten rats were cannulated and exposed to CPB and

compared with a control group that underwent sham cannulation without CPB. Although isoflurane requirements remained unchanged in the sham CPB group, minimum alveolar concentration after 20 minutes in the CPB group was 10% lower than pre-CPB measurements and remained below baseline at the last measurement 2 hours after CPB. This is consistent with a study in goats demonstrating a 20% decrease in minimum alveolar concentration requirements after CPB exposure.[110]

Other investigations have sought to compare anesthetic requirements in patients during CPB and off-pump coronary artery bypass patients to determine the potential hypnotic impact of CPB. One study showed no difference in propofol requirements between CPB and off-pump coronary artery bypass patients.[128] However, the off-pump coronary artery bypass procedures took significantly longer, and equivalent propofol consumption was only noted after correcting for time. More recently, other investigators have compared CPB with off-pump coronary artery bypass procedures and found that less propofol is required during CPB to maintain a constant BIS.[129] However, these investigators did not measure serum propofol concentrations and were unable to account for the effects of altered pharmacokinetics due to CPB.

Although it appears that anesthetic requirements decrease during CPB, the mechanism of such an effect remains unclear. Numerous models of CPB-induced neurologic injury, such as microembolic load, cerebral edema, brain inflammation, decreased brain cytochrome P-450 activity, or increased intracranial pressure, have all been invoked to explain why anesthetic requirements may decrease.[3,130–132] New avenues of study have identified surgical trauma as a potential source of exaggerated and persistent neuroinflammation, perhaps leading to postoperative cognitive dysfunction in elderly patients.[133,134] While the etiology of postoperative cognitive dysfunction is certainly multifactorial, the systemic inflammatory response observed during cardiac surgery has also been used to explain the frequent incidence of postoperative cognitive dysfunction in this surgical population.[135]

HOW DO THESE ALTERATIONS AFFECT ANESTHETIC MANAGEMENT?

To the novice, initiation of CPB is the start of a mandatory "downtime" for anesthesiologists, when workload appears to diminish. However, the experienced cardiac anesthesiologist appreciates that initiation of CPB begins a unique period in which management of the patient's physiologic and anesthetic state is shared with the perfusionist. Given the pharmacokinetic and pharmacodynamic alterations discussed earlier, physiologic controversies related to appropriate mean arterial blood pressure, flow rates, degree of anticoagulation, and absence of traditional clinical variables used to assess adequacy of anesthesia, such as changes in heart rate, pulsatile blood pressure, and the de facto delegation of several key anesthetic processes such as volatile anesthetic delivery to the perfusionist, this should be appreciated as a period of maintained vigilance for the anesthesiologist. Unfortunately, ensuring that the 3 basic tenets of anesthesia are met (amnesia, analgesia, muscle relaxation) during CPB remains challenging.

ENSURING AMNESIA DURING CARDIOPULMONARY BYPASS

Ensuring amnesia requires an accurate assessment of anesthetic depth, which is quite complicated with or without CPB. The use of BIS (discussed later) remains controversial. Monitoring anesthetic depth based on autonomic signs is challenging during CPB because these signs are largely absent. However, hypertension during normal CPB flows may indicate that anesthetic depth or the degree of neuromuscular blockade is inadequate. Traditional methods of measuring ETAC are also impractical because of the minimal blood flow through the lungs during CPB. Several studies suggest measuring the oxygenator membrane exhaust gas for halogenated anesthetic as a surrogate for ETAC.[12,90,97,106,107,136] However, this is not a standard practice. Consequently, routine monitoring of patients during CPB cannot ensure that adequate anesthesia to prevent awareness is being delivered or to exclude equipment malfunction such as cracked tubing or damaged vaporizers. With the use of total IV anesthesia during CPB, there is no real-time monitor of IV anesthetic serum concentration. Empiric dosing regimens based on target-controlled infusions are distorted by pharmacokinetic and pharmacodynamic alterations during CPB.[18,21,22,53,119,137,138] In addition, cardiac patients may not tolerate traditional amnestic doses without adverse hemodynamic consequences. Finally, practitioners may be hesitant to use appropriate doses of anesthetics while separating from CPB because of perceived depressant effects on the myocardium.[139,140]

Thus, considering all the above, it may not be surprising that cardiac surgery patients exhibit an increased incidence of recall when compared with other surgical cohorts.[141–148] Initial reports of awareness using a high-dose opioid technique during the early days of cardiac surgery were common, and the incidence was reported to be as high as 23%.[149] High-dose opioid techniques blunt hemodynamic responses traditionally used to assess anesthetic depth without ensuring amnesia.[150] A significant decrease in the incidence of awareness in cardiac surgery occurred once high-dose opioid techniques were supplemented with benzodiazepines or volatile anesthetics.[151] More contemporary methods using balanced anesthetic techniques based on the combination of low- to moderate-dose opioids, benzodiazepines, volatile anesthetics, or propofol infusions have decreased the incidence of awareness during cardiac surgery to 0.2% to 2.3%.[141,142,144–148] This incidence remains significantly higher than the reported rate in the general surgical population.[144,152]

However, the 5th National Audit Project on accidental awareness during general anesthesia in the United Kingdom and Ireland published simultaneously in *Anaesthesia* and the *British Journal of Anaesthesia* may change our thinking regarding awareness. The incidence of certain/probable and possible accidental awareness cases was much lower than previously reported (approximately 1:19,000). Although cardiac cases remained "high risk" (approximately 1:10,000), most of the reports involved either brief interruption of drug delivery caused by human error or technical problems or the use of intentionally low doses of anesthetic drugs in high-risk patients, such as those with cardiovascular instability. The full report can be found at http://www.nationalauditprojects.org.uk/NAP5_home.

ANESTHETIC DELIVERY

In North America, the perfusionist typically delivers volatile anesthetic during CPB. The use of volatile anesthetic during CPB was initiated approximately 20 years ago in an attempt to decrease administration of long-acting opioids and sedatives to allow patients to emerge more rapidly from anesthesia and persists, in part, due to the presumed clinical benefits of volatile anesthetic preconditioning.[153,154] An additional factor perhaps favoring volatile anesthetics is the anecdotal reporting of a propofol "biofilm" or "foam" that may develop on the oxygenator membrane after long CPB runs or during low-flow CPB, prompting fears of oxygenator failure and leading to hesitation or even refusal by many perfusionists to deliver propofol directly through the CPB circuit (Robert Groom, MS, CCP, Maine Medical Center, personal communication, December 16, 2013; Joerge Ender, MD, Leipzig Heart Center, University of Leipzig, personal communication, December 19, 2013). However, there is the potential for biofilm development independent of whether propofol is administered IV or directly into the oxygenator. Despite these concerns regarding propofol, we were unable to find any case report(s) or original investigations regarding this potential problem. In contrast, 1 in vitro study supports the use of propofol during CPB, concluding that there is no effect of propofol on gas exchange properties of membrane oxygenators, even at high doses (Fig. 7).[77] This study makes no mention of a propofol biofilm or foam accumulating on the membrane oxygenator. Of note, older CPB circuits may not promote adequate mixing. Thus, propofol delivered directly into the CPB circuit may float to the top of the reservoir.[155] This can be avoided by delivering propofol IV during CPB.

In contrast to practice in North America, Europeans favor total IV anesthetic techniques during CPB. This preference has been driven by European Council Directive 93/42/EEC, which prohibits the routine use of volatile anesthetics while on CPB.[156,157] This directive bans the supplementary incorporation of an anesthetic vaporizer into the extracorporeal circuit because this would add complementary safety and performance-related device features. France and Germany, for instance, use this directive to mandate that any modification performed on CPB circuits must pass a technical approval process to ensure device safety (Joerge Ender, MD, Leipzig Heart Center, University of Leipzig, personal communication, December 17, 2013). This becomes problematic because manufacturers of CPB circuits do not build them with vaporizers, requiring perfusionists to modify them.[11] Thus, anesthesiologists in many European countries routinely administer propofol during CPB to avoid the device approval process (Joerge Ender, MD, Leipzig Heart Center, University of Leipzig, personal communication, December 17, 2013). Notably, the application of this directive to CPB circuits is variable across nations. For instance, the United Kingdom does not enforce it (Joerge Ender, MD, Leipzig Heart Center, University of Leipzig, personal communication, December 17, 2013).[7] The combination of this directive and the literature regarding the presumed clinical benefits of volatile anesthetic preconditioning[153,154] has prompted European practitioners to alternative approaches. For instance, one protocol uses MECC circuits to minimize drug sequestration and PMP membranes (prevent passage of volatile anesthetic) to maximize recirculation of tissue stores of sevoflurane accumulated before CPB in an attempt to achieve the potential benefits of volatile anesthetic preconditioning during CPB.[156]

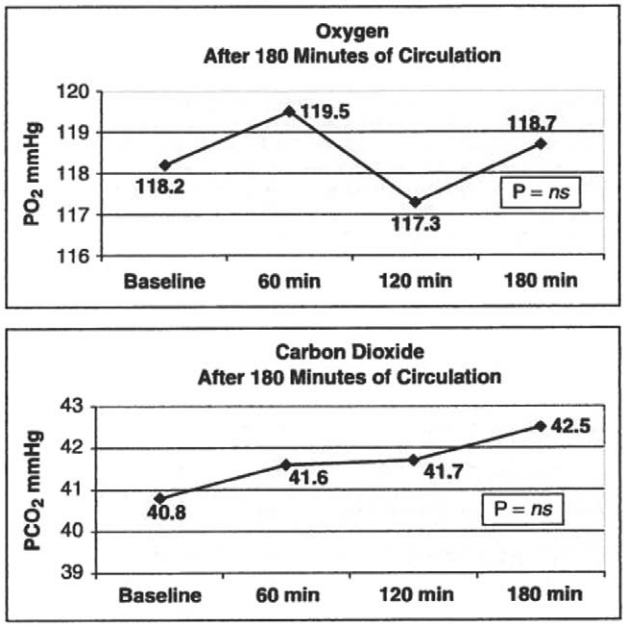

Figure 7. Gas exchange properties of polypropylene membrane oxygenators after exposure to propofol. Partial pressure of carbon dioxide after 180 minutes of circulation (4.0 L/min) and 400 mg of propofol exposure. The changes were not statistically significant.[77] PO_2 = partial pressure of oxygen. Reproduced with permission from SAGE Publications Ltd.[77]

In addition to variability in international practice, several hazards associated with the delivery of volatile anesthetic during CPB must be considered. Accumulation of toxic sevoflurane metabolites during CPB has been reported.[158] Case reports also describe severe damage to the plastic components of the circuit by spillage of liquid volatile anesthetic (Fig. 8; video supplied on request).[159–162] Figure 9 demonstrates insertion of a vaporizer on a contemporary CPB machine well away from the plastic CPB components in an effort to reduce this potential hazard. However, there are no specific instructions from device manufacturers ensuring that vaporizers are placed in a safe position. Finally, scavenging systems should be connected to the membrane oxygenator exhaust to reduce occupational exposure to volatile anesthetic (Fig. 10).[163,164] Notably, the Occupational Safety and Health Administration does not offer any recommendations for scavenging from the CPB apparatus.[165]

Guidelines from the medical community regarding occupational safety are also lacking. Several studies and organized initiatives regarding patient safety in the cardiac operating room and systematic reviews[166–169] do not address occupational health and safety for operating room personnel.[170] Similarly, these publications do not address safety with regard to occupational exposure to volatile drugs during CPB for health care providers. A recent anesthesiologist-led review provides commentary on equipment design and operating room layout yet does not provide design specifications for CPB circuits regarding

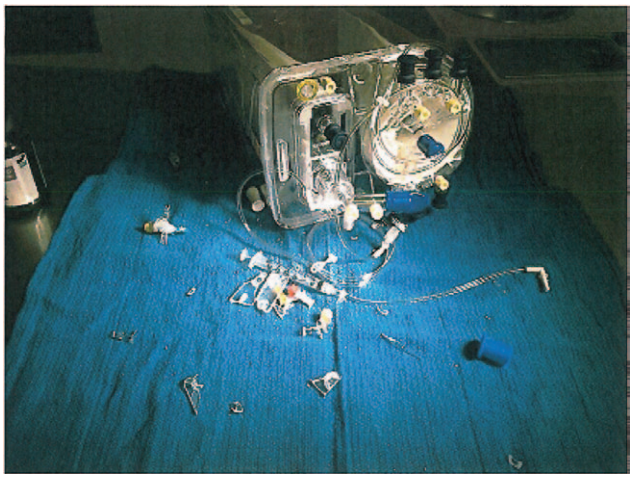

Figure 8. Damage to plastic components by liquid volatile anesthetic.

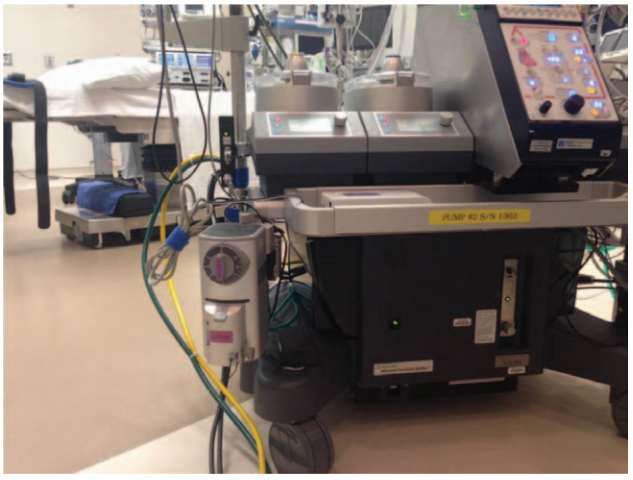

Figure 9. Recommended anesthetic vaporizer placement well away from plastic cardiopulmonary bypass components.

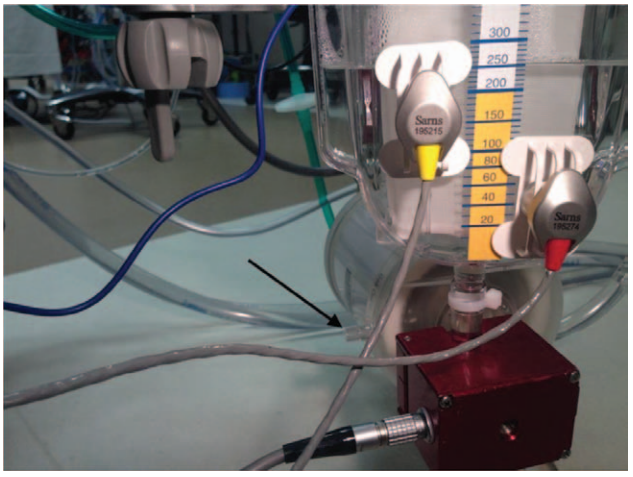

Figure 10. Membrane oxygenator gas exhaust port (indicated by arrow). This can be a source of occupational exposure to waste anesthetic gas (should be scavenged) and can also be used to monitor anesthetic gas concentration.

anesthetic vaporizer placement or scavenging systems for waste anesthetic gas.[171]

The American Society of Extracorporeal Technology's recently revised internal standards and guidelines for perfusion practice are the only guidelines available that recommend scavenging waste anesthetic gas and routine maintenance of anesthetic vaporizers.[6] Notably absent are details regarding how vaporizers should be integrated into the circuit, scavenging system specifications, recommendations for titration of volatile or IV anesthetics, how and when anesthetic-related issues should be communicated to the anesthesiologist, monitoring adequacy of anesthetic delivery, or assessment of anesthetic depth.

THE BISPECTRAL INDEX

The BIS monitor (Aspect Medical Systems, Natick, MA) is the only U.S. Food and Drug Administration–approved monitor to assess the anesthetic state of the central nervous system. However, its use during cardiac surgery[172] and in the general surgical population[148] in preventing awareness is unreliable. Patients may report awareness, despite "appropriate" BIS levels (<60).[143,173,174] However, in the absence of effect-site concentration monitors or a surrogate such as ETAC, the BIS monitor may have applicability in potentially reducing the incidence of awareness.[141,173,175,176] Table 5 outlines important studies evaluating the potential applicability of BIS in preventing awareness.

Additional potential clinical applications of BIS monitoring outside the CPB setting have recently been reviewed.[149,172] These include more appropriate anesthetic dosing, potentially improving recovery times and facilitating fast-track techniques. Preventing anesthetic overdose and reducing hemodynamic instability from unnecessarily high anesthetic concentrations may also potentially decrease morbidity and mortality. In addition, the BIS monitor may have applicability as a monitor of cerebral ischemia (prevention of catastrophic neurologic events). However, BIS-guided anesthetic dosing has not been shown to decrease extubation/recovery time,[177–180] improve morbidity or mortality,[149,172,181–183] nor is it an effective monitor of cerebral ischemia.[184–186] It may help alleviate postoperative delirium in older patients, by preventing too "deep" an anesthetic state (BIS values <20; noncardiac surgery).[187–189]

The American Society of Anesthesiologists Practice Advisory on Awareness and Brain Monitoring currently recommends that the decision to use a brain monitor should be made on a case-by-case basis and should not be considered the standard of care.[190] In the United Kingdom, the National Institute for Health and Care Excellence recommends that BIS may be useful in guiding anesthetic dosing in patients at high risk for adverse consequences of anesthetics and that BIS is useful for total IV anesthesia.[191] However, the National Institute for Health and Care Excellence also states that electroencephalographic-based monitors are not associated with a statistically significant reduction in intraoperative awareness in patients classified at high risk and that available evidence on the impact of these technologies in reducing awareness is limited.[192] The American Society of Extracorporeal Technology's recently revised internal standards and guidelines for perfusion practice recommend the routine use of cerebral oximetry yet do not address use of

Table 5. Important Studies Evaluating Applicability of Bispectral Index (BIS) in Preventing Awareness

Study	Year	N	% Cardiac surgeries	Anesthetic technique	Interviews (no., timing)	Awareness, possible awareness (no. of patients, %)	Major conclusions	Comments
Dowd et al.[147]	1998	617	100%	Inhaled and TIVA, all fast-track	1, 18 hours postextubation	2, (0.3%)	The lowest reported incidence of awareness in cardiac anesthesia. Fast-track techniques do not increase the incidence of awareness.	A single postoperative interview will likely underestimate the incidence of awareness. The interview is also not as comprehensive as those done in other studies.
Sandin et al.[144]	2000	11,785	NR	Inhaled and TIVA	3, PACU/1–3 days postoperative/ 7–14 days postoperative	19 0.18% with NMB 0.10% no NMB	Incidence of awareness is 1–2/1000 patients, muscle relaxant is associated with a higher incidence of awareness.	First prospective study of awareness with modern anesthetic techniques in Europe.
Ranta et al.[148]	2002	929	100%	Inhaled and TIVA	1, 1–18 days postoperative	5, (0.5%) definite 21, (2.3%) definite or possible	Lower incidence of awareness with more midazolam.	Results encourage providers to administer midazolam to patients at high risk of awareness.
Sebel et al.[152]	2004	19,575	NR	Inhaled and TIVA	2, PACU/>1 week postoperative	25, (0.13%) definite 71 definite or possible (0.36%)	Incidence of awareness is 1–2/1000 patients.	Validates findings of the European study with anesthetic practices in North America.
B-Aware[141]	2004	2463	49%	Inhaled and TIVA	3, 2–6 h postoperative/ 24–36 h postoperative/ 30 days postoperative	22, (1.8%) in BIS group 27, (2.2%) in routine care Factored out patients. 2, (0.17%) in BIS group 11, (0.91%) in routine care	BIS monitoring decreases the incidence of awareness when compared with evaluation of clinical signs.	ETAC monitoring became routine during the course of this study, altering the definition of "conventional" depth of anesthesia monitoring.
Punjasawadwong et al.[176]	2007	4056 (20 trials)	NR	Inhaled and TIVA	Variable	N/A	BIS monitoring may decrease the incidence of awareness compared with clinical signs. ETAC-guided protocols may also decrease the incidence of awareness.	First strong evidence encouraging the use of BIS during TIVA.
B-unaware[142]	2008	1941	27%	Inhaled	3, <24 h postoperative/ 24–72 h postoperative/ 30 days postoperative	4, (0.21%) definite 2 with BIS 2 with ETAC 9, (0.46%) definite or possible 6, (0.62%) definite or possible with BIS 3, (0.31%) definite or possible with ETAC	BIS and ETAC-guided protocols are equally efficacious in preventing awareness.	Many anesthesiologists chose not to increase anesthetic depth in response to BIS and ETAC values outside those suggested by the study parameters.
BAG-RECALL[143]	2011	5713	36%	Inhaled	2, <72 h postoperative/ 30 days postextubation	9, (0.16%) definite 7, (0.12%) definite in BIS 2, (0.04%) definite in ETAC 27, (0.47%) definite or possible 19, (0.33%) definite or possible in BIS 8, (0.14%) definite or possible in ETAC	BIS and ETAC-guided protocols are equally efficacious in preventing awareness.	Alarms strongly encouraged anesthesiologists to increase anesthetic depth in response to BIS and ETAC values outside study parameters.
Zhang et al.[173]	2011	4951	0.9%	TIVA	2, POD1/POD4	4, (0.14%) definite in BIS group 15, (0.65%) definite in control group 8, (0.3%) definite or possible in BIS group 21, (0.9%) definite or possible in control group	BIS monitoring decreases the incidence of awareness in TIVA.	There is no correlate monitor of effect-site concentrations for IV anesthetics.
MACS[175]	2012	18,836	NR	Inhaled	1, 28–30 days postoperative	8, (0.08%) definite in BIS group 11, (0.12%) definite in ETAC group 5, (0.15%) definite in no intervention group	There is no difference in the incidence of awareness between BIS and ETAC-guided protocols.	Ad hoc analysis suggests that BIS is superior to evaluation of clinical signs in the prevention of awareness.

BAG-RECALL = BIS (bispectral index) or anesthesia gas to reduce explicit recall; BIS = bispectral index; ETAC = end-tidal anesthetic concentration; MACS = minimum alveolar concentration study; N/A = not applicable; NMB = neuromuscular blockade; NR = not reported; PACU = postanesthesia care unit; POD1 = postoperative day 1; POD4 = postoperative day 4; TIVA = total IV anesthesia.

processed electroencephalographic monitors (BIS) or the assessment of anesthetic depth.[6]

END-TIDAL ANESTHETIC CONCENTRATION

When volatile anesthetics are used, ETAC may be clinically useful during CPB. This is not routine practice despite being tested and advocated by many investigators, demonstrating that monitoring of ETAC at the membrane exhaust port accurately reflects serum anesthetic concentrations.[12,90,97,106,107,136] Others caution against this practice, reporting that exhaust gas concentrations do not correlate with serum concentrations.[17] This may be due to room air admixture as a result of new safety mechanisms designed to prevent negative pressure across the oxygenator membrane.[17] This conclusion was challenged by an accompanying editorial asserting that the protocol for measuring serum anesthetic concentration was flawed.[193] While the sum of the literature advocates monitoring of ETAC during CPB, it is worth noting that evolving CPB circuit technology has the potential to impact the reliability of this practice.

ENSURING ANALGESIA DURING CARDIOPULMONARY BYPASS

While the focus of anesthetic studies during CPB has primarily been directed at amnesia, very little has been published regarding analgesia during CPB. Unlike amnesia, there is no potential monitor of "analgesic depth."[2] Lack of real-time monitoring of plasma drug concentrations forces anesthesiologists to rely on clinical signs of pain, such as tachycardia, hypertension, and tachypnea. These clinical signs are usually unreliable or absent before, during, and after CPB (pacemakers, vasoactive drugs, paralytic drugs). Thus, opioid dosing during CPB is empirically driven. In the past, high-dose opioid techniques likely provided some reliable degree of early postoperative analgesia. However, fast-track early extubation protocols using low-dose opioid supplementation are now the norm in clinical practice. Their implications for postoperative analgesia are complex and may vary with the type of opioid used, as well as adjuvant sedation used (e.g., potential opioid-sparing effects of dexmedetomidine) and other potential nonopioid drugs (e.g., nonsteroidal anti-inflammatory drugs).[194,195]

ENSURING MUSCLE RELAXATION DURING CARDIOPULMONARY BYPASS

Neuromuscular blockade during CPB may be desirable, yet there is no definitive evidence that it is absolutely required; therefore, there is wide variability in the practice of neuromuscular blockade during cardiac surgery.[196–199] Historically, high-dose opioid techniques allowed practitioners to use high doses of long-acting nondepolarizing drugs because patients had return of motor function long before amnestic and analgesic drugs were metabolized. Current fast-track early extubation techniques and the potential association between awareness and neuromuscular blockade[200] have encouraged practitioners to use less paralytic drug during CPB. Optimizing neuromuscular blockade becomes even more challenging in the face of the aforementioned pharmacokinetic and pharmacodynamic alterations due to CPB. If neuromuscular blockade is planned, careful dosing should be guided by peripheral nerve stimulation with a twitch monitor. It is important to note that muscle strength decreases substantially during hypothermia, even in the absence of muscle relaxants.[54] This is likely to affect the amplitude of muscle twitches seen with peripheral nerve stimulation.

CONCLUSIONS/FUTURE DIRECTIONS

The unique pharmacokinetic and pharmacodynamic alterations associated with CPB, lack of traditional clinical signs of "adequate" anesthesia, and lack of a reliable monitor of anesthetic depth make the cardiac anesthesiologist's job of ensuring amnesia, analgesia, and muscle relaxation during CPB difficult to impossible. Much of our knowledge is based on clinical investigations performed many years ago under much different clinical management strategies (profound hypothermia, profound hemodilution, no circuit coating) than exist today (normal to mild/moderate hypothermia, autologous priming, MECC, circuit coating). Further complicating clinical management is lack of any regulatory oversight regarding after-market modification of the CPB circuit by perfusionists or occupational health and safety concerns. Last, lack of consensus regarding how to deliver anesthetics during CPB is perhaps best highlighted by the difference in clinical practice between North American practitioners (with a strong preference for volatile anesthetics) and European practitioners (generally favoring total IV anesthesia).

Strategic areas for future research include evaluating the pharmacokinetic and pharmacodynamic alterations induced by modern CPB circuitry (smaller, coated) under near-normothermic conditions, clinical ramifications of neuroinflammation associated with CPB, and development of a reliable clinical monitor of anesthetic depth. Finally, regulatory oversight mechanisms need to be developed to standardize not only CPB circuitry but also after-market modifications.

DISCLOSURES

Name: Aaron E. Barry, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Aaron E. Barry approved the final manuscript.
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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Mark A. Chaney approved the final manuscript.
Name: Martin J. London, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Martin J. London approved the final manuscript.

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APPENDIX

Systematic Literature Review Search Strategy

We performed a systematic review of the effects of cardiopulmonary bypass on pharmacokinetics of anesthetic drugs and unintended awareness during cardiac surgery. A list of pertinent keywords was derived, and a PubMed database search was performed for each topic, anesthetic awareness and pharmacokinetics. To assess the feasibility of this technique, we began with the topic perceived to be more focused: anesthetic awareness and cardiac surgery. Search terms were "Cardiac Surgery" OR "Cardiopulmonary Bypass" AND Awareness OR Recall OR BIS AND Anesthesia NOT "General Anesthesia" NOT Epidural NOT "General Anesthesia" NOT Spinal NOT Epilepsy (12/11/13). Results of this search were reviewed, and titles and abstracts related to the topic were highlighted. Recently published, highly cited, and review articles were considered "high-yield" articles, and the PubMed "related citations" query was applied to each. Articles related to the topic highlighted during this round were added to the list. The "related citations" query was also applied to "high-yield" articles from this round. Any related articles identified during this final round were added to the list. Articles in languages other than English were excluded from our search.

A similar search strategy was used for pharmacokinetics. The only notable difference in technique was restricting the initial screen to articles published from 2000 to the present. Search terms were "Cardiac Surgery" OR "Cardiopulmonary Bypass" OR "Open Heart" AND Pharmacokinetics OR Pharmacodynamics AND Anesthesia OR Anesthetic NOT Cardioprotection NOT Epidural NOT Spinal NOT Non-Cardiac NOT Preconditioning NOT Cardioplegia NOT Transfusion, Filters: Publication date from 2000/01/01 to 2013/12/31; Humans; English (12/17/13).

The search on awareness and cardiac surgery yielded 1349 results. Titles and abstracts related to the topic narrowed the list to 54. Seven "high-yield" articles were identified in this round.[149,172,176,179,201–203] As expected, there was

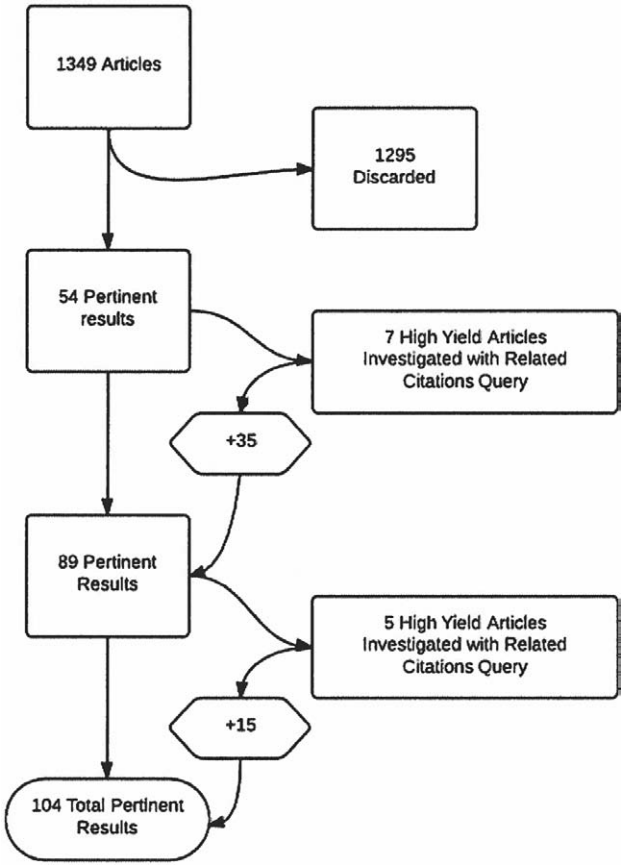

Figure 11. Systematic literature review search results for awareness and cardiac surgery.

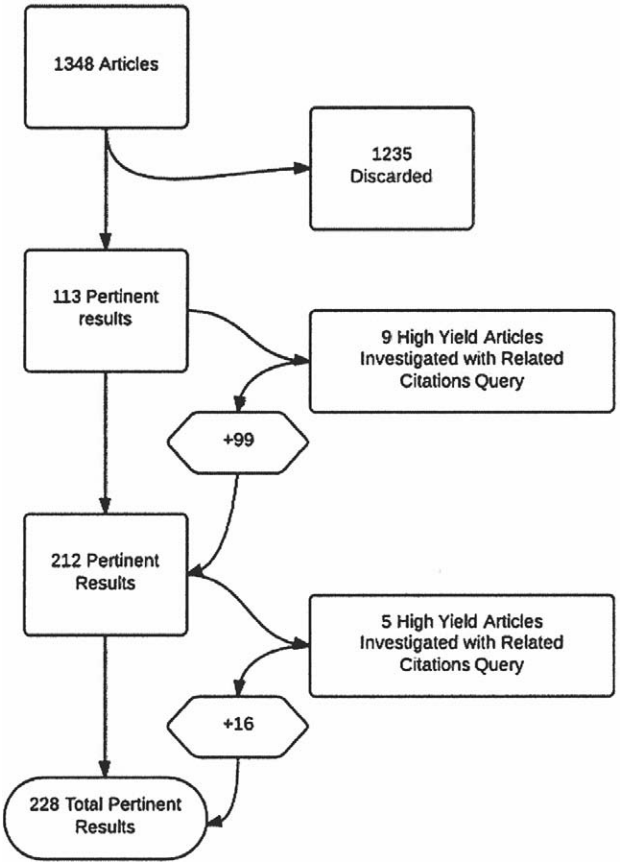

Figure 12. Systematic literature review search for pharmacokinetics and cardiopulmonary bypass.

significant overlap in studies found using the "related citations" query. However, 35 additional articles were identified. Five articles from during this round were considered "high yield," and the "related citations" query was applied to each.[141,143,175,181,182] Fifteen additional relevant studies were discovered and added to the total. In summary, 104 articles pertinent to the topic of anesthetic awareness during cardiac surgery were identified and obtained for full review.

The same systematic approach was then turned to pharmacokinetics and CPB. The initial screen yielded 1348 results. Titles and abstracts related to the topic narrowed the list to 113. Nine "high-yield" articles were identified in this round.[3,4,14,17,18,51,96,103,120] The "related citations" query yielded 99 more articles. Five more "high-yield" articles were analyzed.[7,193,204–206] Sixteen additional studies were identified. In summary, 228 articles pertinent to the topic of pharmacokinetics and CPB were identified and obtained for full review. Bibliographies of all articles obtained for review were used to identify seminal papers for historical context.

The search strategy and results are depicted in Figures 11 and 12.