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## Awareness and Cardiopulmonary Bypass: A Meta-analysis

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<b>Abstract:</b>	Although intraoperative awareness is rare, its aftermath can be devastating. Research suggests patients undergoing cardiac surgery under cardiopulmonary bypass (CPB) are particularly vulnerable to intraoperative awareness. Anesthesia providers must be cognizant of this potential occurrence and work hard to identify and treat these patients at high risk. In this review, the authors will examine causes and clinical factors related to intraoperative awareness and discuss the potential physiological outcomes. Next, the authors will investigate anesthetic interventions utilized under CPB to prevent awareness and consider several monitoring modalities available for use in the operating room.

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Ms Sally Aquino, Managing Editor  
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Sincerely,  
Jillian E. Mouranie, RN, BSN, SRNA

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## **Awareness and Cardiopulmonary Bypass:**

### **A Meta-Analysis**

Unintended intraoperative awareness is defined as the experience of intraoperative events combined with explicit recall.<sup>1</sup> Patients undergoing procedures requiring cardiopulmonary bypass (CPB) are considered at higher risk; the occurrence of intraoperative awareness increases 10-fold and affects approximately 1% of this high risk population.<sup>2</sup> In some cases, intraoperative awareness leads to posttraumatic stress disorder (PTSD) and the associated symptoms of depression, sleep disturbances, anxiety, and flashbacks.<sup>3</sup> Furthermore, litigation associated with intraoperative recall is a significant concern for the anesthetist.

### **Possible Pathophysiological Mechanisms**

With increasing doses of anesthetic agents, the patient progresses sequentially through the stages of amnesia, sedation, unconsciousness, and ultimately, immobility and areflexia.<sup>4</sup> Difficulty in assessing the patient's level of anesthesia arises when paralysis is utilized, as intentional movement cannot be observed. Therefore, it is imperative to establish what areas of the brain and body are involved with the physiologic phenomenon of awareness, especially for the purposes of monitoring, prevention, and overall understanding.

Although there is no current consensus defining general anesthesia and the mechanism of the prevention of awareness, current hypotheses include the enhancement of the activity of the gamma-aminobutyric acid (GABA) type A, specifically  $\alpha_5$ GABA which is involved in memory impairment but not sedation or hypnosis.<sup>5,6</sup> Because these receptors are found in high concentrations in the hippocampus, this area of the brain is of particular interest in anesthesia and

intraoperative awareness. Other implicated areas of the brain associated with intraoperative awareness include the amygdala and the medial temporal lobe.<sup>5</sup>

CPB muddles the current understanding of the pathophysiology of intraoperative awareness due to multiple factors. These factors include altered pharmacodynamics and pharmacokinetics of drugs, hemodilution, and the binding of large amounts of drugs by the bypass machine.<sup>4,7</sup> Specific high risk periods during CPB can be associated with rewarming, fluid shifts, and the rapid changes in anesthetic concentrations.

### **Clinical History of Intraoperative Awareness**

As the practice of anesthesia has advanced, the incidence of intraoperative awareness in cardiac surgery has improved from up to 23% to a current estimate of approximately 1.5%.<sup>4,8</sup> Although there has been significant improvement in the identification, prevention, and understanding of intraoperative awareness, the consequences and implications of this phenomenon cannot be overlooked.

### **Psychological Sequelae**

Most commonly described memories associated with intraoperative awareness include auditory perceptions, feelings of abandonment and insecurity, fear, panic and less commonly, pain.<sup>9,10,11</sup> These experiences can lead to posttraumatic stress which is characterized by avoidance, the re-experience of the event, and hyperarousal which lasts for one month or longer.<sup>12,13</sup> Additionally, while the patient may initially deny psychological symptoms, PTSD may manifest up to one month following the awareness event.<sup>14</sup> Thus, this may delay and complicate treatment. Other long term effects associated with intraoperative awareness include

avoidance of doctors, hospitals, and future surgeries, as well as persistent impairment of one's social life.<sup>12,15</sup>

### **Clinical Factors Related to Intraoperative Awareness and CPB**

Patients undergoing cardiac surgery are at an inherently higher risk of intraoperative awareness secondary to their lower cardiac reserve, hemodynamic instability, and higher American Society of Anesthesiologists (ASA) status.<sup>18</sup> Other patient related factors include the female gender, age younger than 60, alcoholism, recreational drug, opioid, sedative, hypnotic, or antiepileptic drug use, and history of awareness under general anesthesia.<sup>3,9</sup> The complexity of cardiac surgery and its various methods, modalities, and complications can put the patient at an even higher risk of intraoperative awareness, intertwining all of these factors for the anesthesia provider to consider and compensate. Due to the low incidence of occurrence of intraoperative awareness associate with CPB, current literature does not investigate the association of increased awareness and pump time, complicated CPB separation, and CPB associated with circulatory arrest.

### **Anesthetic Factors Related to Intraoperative Awareness and CPB**

It is commonly known that opioids alone do not suppress recall.<sup>3,16,17</sup> Current literature does not confirm that prophylactic administration of a benzodiazepine reliably reduces the incidence of intraoperative awareness.<sup>4,18</sup> However, the American Society of Anesthesiologists task force on intraoperative awareness recommends the use of benzodiazepines in cardiac surgery.<sup>18</sup> Not surprisingly, continuous infusions of benzodiazepines and narcotics during CPB provide a more reliable and consistent plasma concentration than intermittent boluses.<sup>17</sup> Because benzodiazepines and narcotics have a synergistic effect on cognitive depression, a continuous

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4 infusion during CPB may have enhanced theoretical efficacy to reduce or eliminate  
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6 intraoperative awareness due to benzodiazepines' innate ability to elicit amnesia, along with  
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8 narcotic supplementation.<sup>17</sup> Inability to reliably measure the concentration of volatile anesthetic  
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10 agent when administered via the oxygenator and the type of diffusion membrane oxygenator may  
11  
12 affect the incidence of intraoperative recall.<sup>19,20</sup> Since the permeability of the CPB circuit to  
13  
14 volatile agent is dependent on the type of oxygenator, the depth of anesthesia may not be  
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16 uniform among different oxygenator types leading to a potential increase in intraoperative  
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18 awareness.<sup>20</sup>  
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25         Given that the level of consciousness and metabolic rate are lower during cooling, there  
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27 is reason to believe that recall would be increased with normothermic CPB. Additionally,  
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29 propofol requirements needed to maintain an adequate BIS level are reduced during hypothermic  
30  
31 CPB.<sup>21</sup> However, research has failed to show an increase in recall during normothermic CPB.<sup>16</sup>  
32  
33 In an effort to reduce costs and expedite recovery facilities have been promoting fast track  
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35 cardiac anesthesia. Current research suggests that the incidence of intraoperative awareness in  
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37 fast track cardiac anesthesia is reduced possibly due to the use of a balanced anesthetic  
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39 technique.<sup>8</sup>  
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#### 44                   **Potential Monitoring Modalities for Intraoperative Awareness During CPB**

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47         Under CPB, some anesthetic drugs may be diluted, which is one component of CPB's  
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49 provocation of an enhanced risk of intraoperative awareness. To counteract such events,  
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51 intraoperative technological tools are utilized to assess anesthetic depth during surgery.  
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53 Currently, however, there is no definitive answer for what monitor(s) is/are the gold standard for  
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55 prevention of intraoperative awareness, notably during CPB. Bispectral Index (BIS), a type of  
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4 electroencephalography (EEG), is often utilized to assess level of consciousness, although its  
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6 foolproof efficacy has not been undoubtedly or consistently voiced. Some studies have argued  
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8 that BIS levels are not reliable and do not correlate with plasma concentrations of  
9  
10 benzodiazepines and narcotics.<sup>17,22</sup> The BIS monitor is also affected by many of the common  
11  
12 surgical tools utilized during cardiac surgery and CPB; electrocautery, pacemakers, and warming  
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14 devices all decrease the effectiveness of the BIS monitor.<sup>4,5</sup> Additionally, BIS can be  
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16 compromised by the onset of CPB, as a potential hypo-perfusion of clear, oxygen-poor priming  
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18 fluid reaches the brain, or when hypothermia onsets, eliciting a proportional drop in BIS.<sup>23,24</sup>  
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25 More recently, there have been new waves of technological means with which to assess  
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27 anesthetic depth. One such technology is spectral entropy, which in contrast to the BIS's single,  
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29 mathematically derived numerical value, displays numbers for both response entropy to measure  
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31 cortex and frontal brain activity, as well as state entropy for solely cortex activity.<sup>25</sup> Spectral  
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33 entropy has also been found to have less interference from surgical tools and equipment,  
34  
35 allowing for a more reliable interpretation of anesthetic depth and consequential minor  
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37 intraoperative awareness.<sup>21,26</sup> With less interference from surgical tools, spectral entropy seems  
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39 to have one advantage, especially when one considers the close proximity of cardiac surgery to  
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41 the patient's head and its monitors. Compared to the BIS's price of use and disposal, spectral  
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43 entropy is comparable.<sup>21</sup>  
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## 50 Discussion

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53 Risk of awareness during CPB occurs in approximately 1% of the population undergoing  
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55 cardiac surgery. When a patient experiences awareness he or she is at risk for PTSD and the  
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57 associated symptoms of anxiety, social isolation, and reoccurring nightmares. These symptoms  
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4 can have a profound effect on daily living for the individual, along with preventing them from  
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6 going back to the hospital or other medical facilities. Risk factors for awareness have been  
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8 identified and include past awareness during anesthesia, age, gender, poor cardiac reserve,  
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10 recreational drug users or alcohol abusers, or people who take prescription narcotics, sedatives,  
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12 and antiepileptic drugs.<sup>3,9</sup>  
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17 Although there are conflicting theories regarding general anesthesia and awareness, most  
18  
19 assume there is an increase of GABA type A activity and  $\alpha 5$ GABA.<sup>5,6</sup> Since both of these  
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21 receptors are found in the hippocampus, research has been focused in this particular area of the  
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23 brain.<sup>5</sup> While significant improvement has been made to decrease the incidence of awareness  
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25 during CPB, there is still need for further research as prevention of intraoperative awareness and  
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27 associated sequelae is of great concern.  
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33 Current literature does not support the use of opioids alone to prevent recall.<sup>3,16,27</sup>  
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35 However, literature does support the use of opioids combined with benzodiazepines as a means  
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37 reducing the risk of intraoperative awareness.<sup>17</sup> The American Society of Anesthesiologists  
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39 currently recommends the use of benzodiazepines in cardiac surgery due to their abilities to  
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41 cause retrograde and antegrade amnesia.<sup>18</sup> Continuous infusions have proven to provide  
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43 consistent plasma concentrations and therefore, offer better amnestic levels than intermittent  
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45 boluses.<sup>17</sup> Another anesthetic agent, volatile anesthetics, can affect operative awareness by how  
46  
47 they are administered.<sup>19</sup> Certain oxygenators are able to produce more reliable amnesia due to  
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49 how they dispense the volatile gas.<sup>19</sup>  
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56 Advances in medical technology have provided several monitors to assess level of  
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58 consciousness, but there is no gold standard for CPB. Several research studies were conducted  
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4 using the BIS, and most concluded it to be insufficient during cardiac surgery.<sup>4,6,17,22</sup> There are  
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6 several factors that make the BIS unreliable for cardiac surgery. These factors include the  
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8 inability to correlate narcotic and benzodiazepine plasma concentrations, interference of surgical  
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10 tools used during cardiac surgery, and the hypothermia caused during CPB.<sup>4,6</sup> However, new  
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12 technology has provided a monitor that eliminates one of the problems associated with level of  
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14 consciousness monitoring and cardiac surgery. Unlike the BIS, spectral entropy has less  
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16 interference from surgical equipment. Unlike the BIS, spectral entropy has less  
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22           Despite these interventions, more studies are needed to find solutions that decrease  
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24 awareness associated with CPB and fill in the gap in the literature. Establishing evidence based  
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26 practice for prevention of intraoperative awareness associated with CPB is essential in order to  
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28 better understand the causes of intraoperative awareness and to prevent PTSD and the associated  
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30 litigation.  
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## References

1. Preventing, and managing the impact of, anesthesia awareness, *Sentinel Event Alert*. 2004 Oct 6; (32): 1-3. Available at: [http://www.jointcommission.org/assets/1/18/SEA\\_32.PDF](http://www.jointcommission.org/assets/1/18/SEA_32.PDF). Accessed February 3, 2012.
2. Avidan MS, Jacobsohn E, Glick D, et al. Prevention of intraoperative awareness in a high-risk surgical population. *N Engl J Med*. 2011; 365(7): 591-600.
3. Forman SA. Awareness during general anesthesia: Concepts and controversies. *Semin Anesth, Perioperative Med and Pain*. 2006; 25: 211-218.
4. Serfontein L. Awareness in cardiac anesthesia. *Curr Opin Anaesthesiol*. 2010; 23: 103-108.
5. Mashour GA, Orser BA, Avidan MS. Intraoperative awareness: From neurobiology to clinical practice. *Anesthesiology*. 2011; 114: 1218-33.
6. Mashour GA. Monitoring consciousness: EEG-based measures of anesthetic depth. *Semin Anesth, Perioperative Med and Pain*. 2006; 25: 205-210.
7. Yoshitani K, Kawaguchi M, Takahashi M, Kitaguchi K, Furuya H. Plasma propofol concentration and EEG burst suppression ratio during normothermic cardiopulmonary bypass. *Br J Anaesth*. 2003; 90: 120-126.
8. Dowd NP, Cheng DCH, Karski JM, Wong DT, Munro JAC, Sandler AN. Intraoperative awareness in fast-track cardiac anesthesia. *Anesthesiology*. 1998; 89: 1068-1073.
9. Sigalovski N. Awareness under general anesthesia. *AANA J*. 2003; 71(5): 373-379.
10. Moerman N, Bonke B, Oosting J. Awareness and recall during general anesthesia. *Anesthesiology*. 1993; 79: 454-464.
11. Domino KB, Posner KL, Caplan RA, Cheney FW. Awareness during anesthesia. *Anesthesiology*. 1999; 90: 1053-1061.
12. Osterman JE, Hopper J, Heran WJ, Keane TM, van der Kolk BA. Awareness under anesthesia and the development of posttraumatic stress disorder. *Gen Hosp Psychiatry*. 2001; 23: 198-204.
13. Mashour GA, Wang LY-J, Esaki RK, Naughton NN. Operating room desensitization as a novel treatment for post-traumatic stress disorder after intraoperative awareness. *Anesthesiology*. 2008; 109: 927-929.
14. Myles PS, Leslie K, McNeil J, Forbes A, Chan MTV. Bispectral index monitoring to prevent awareness during anesthesia: the B-Aware randomized control trial. *Lancet*. 2004; 363: 1757-1763.
15. Lennmarken C, Bildfors K, Enlund G, Samuelsson P, Sandin R. Victims of awareness. *Acta Anaesthesiol Scand*. 2002; 46: 229-231.
16. Phillips AA, McLean RF, Devitt DH, Harrington, EM. Recall of intraoperative events after general anesthesia and cardiopulmonary bypass. *Can J Anaesth*. 1993; 40: 922-926.
17. Barr G, Anderson RE, Samuelsson S, Owall A, Jakobsson JG. Fentanyl and midazolam anesthesia for coronary bypass surgery: A clinical study of bispectral electroencephalogram analysis, drug concentrations and recall. *Br J Anaesth*. 2000; 84(6): 749-752.
18. American Society of Anesthesiologists Task Force on Intraoperative Awareness. Practice advisory for intraoperative awareness and brain function monitoring. *Anesthesiology*. 2006; 104: 847-864.

19. Marks RRD. Which anesthetic agent for maintenance during normothermic cardiopulmonary bypass? *Br J Anaesth.* 2003; 90(2): 118-21.
20. Phillip A, Wiesenack C, Behr R, Schmid FX, Birnbaum DE. High risk of intraoperative awareness during cardiopulmonary bypass with isoflurane administration via diffusion membrane oxygenators. *Perfusion.* 2000; 17: 175-78.
21. Kamel IR, Drum ET, Koch SA, et al. The use of somatosensory evoked potentials to determine the relationship between patient positioning and impending upper extremity nerve injury during spine surgery: A retrospective analysis. *Anesth Analg.* 2006; 102: 1538-1542.
22. Monk TG, Weldon BC. Does depth of anesthesia monitoring improve postoperative outcomes? *Curr Opin Anaesthesiol.* 2011; 24: 665-669.
23. Sinha CA, Ramesh BGS, Singh BVP. Changes in bispectral index (BiSs) values during cardiopulmonary bypass (CPB). *MJAFI.* 2011; 67: 38-40.
24. Mathew JP, Weatherwax KJ, East CJ, White WD, Reves JG. Bispectral analysis during cardiopulmonary bypass: The effect of hypothermia on the hypnotic state. *J Clin Anesth.* 2001; 13: 301-305.
25. Baulig W, Seifert B, Schmid ER, Schwarz U. Comparison of spectral entropy and bispectral index electroencephalography in coronary artery bypass graft surgery. *J Cardiothoracic Vasc Anesth.* 2010; 24(4): 544-549.
26. Baughman VL, Hoffman WE, Koenig HM, Wheeler PL, Ananda RC, Wang M. Recovery from paralysis with succinylcholine increase response entropy and EMG but not state entropy. *Jour Clin Monitoring Computing.* 2005; 19: 201-205.
27. Fioratou E, Flin R, Glavin R, Patey R. Beyond monitoring: Distributed situational awareness in anesthesia. *Br J Anaesth.* 2010; 105(1): 83-90.