ABSTRACT

The interventional cardiology is growing and evolving. Many complex procedures are now performed outside the operating room to manage cardiovascular pathologies which had been traditionally treated with cardiac surgery. Appropriate sedation strategy is crucial for improved patient comfort and successful procedure while ensuring safety. Sedation for cardiovascular intervention is frequently challenging, especially in critically-ill, high-risk patients. This review addresses pre-procedure evaluation and preparation of patients, proper monitoring, commonly used sedatives and analgesics, and considerations for specific procedures. Appropriate depth of sedation and analgesia should be balanced with patient, procedural and institutional factors. Understanding of the pharmacology of sedatives/analgesics, vigilant monitoring, ability and proper preparation for management of potential complications may improve outcomes in patients undergoing sedation for cardiovascular procedures.

Keywords: Sedation; Cardiovascular interventions; Monitored anesthesia care

INTRODUCTION

The interventional cardiology is rapidly growing both in number and complexity. As an integral component of cardiologic procedures, the demand for sedation is also increasing. The goal of procedural sedation is minimizing patients’ discomfort and ensuring safety. Depending on the depth, sedation provides anxiolysis, progressive impairment of consciousness, amnesia and analgesia. Appropriate sedation enables patients’ immobility during the procedure, facilitating successful procedure while reducing the risk of complication by optimizing environment, as well as improved overall patient satisfaction. Achieving this goal is sometimes challenging, especially in case of critically ill, high-risk patients undergoing complex procedures. Adequate pre-procedural evaluation and preparation, understanding pharmacology of sedatives and analgesics, proper monitoring, ability to rescue patients from unintended deep sedation or related adverse events are mandatory to provide safe and satisfactory sedation in cardiovascular intervention.
THE DEPTH OF SEDATION

The depth of sedation is a continuum from minimal, moderate, deep sedation to general anesthesia (Table 1). Minimal sedation refers a drug-induced anxiolysis during which patients respond normally to verbal stimulation. Moderate sedation, also called as ‘conscious’ sedation, indicates an impairment of consciousness during which patients are able to respond purposefully to verbal or light tactile stimulation. During deep sedation, patients respond only after repeated or painful stimulation, and assistance to maintain patent airway may be needed. Patients under general anesthesia cannot be aroused even by painful stimulation, airway patency is usually not maintained without assistance, and spontaneous ventilation is often impaired, requiring positive pressure ventilation. In general, moderate (conscious) sedation is ideal for most percutaneous cardiovascular intervention, however, deep sedation may be required for some patients and/or procedures. More importantly, because sedation is a continuum within a wide range of levels of consciousness, transition to a deeper level may be rapid and not always predictable. Thus, the sedation provider should recognize drifting level of sedation through continuous monitoring, and also be able to rescue the patient from the deeper level of sedation and related complications.

Table 1. The continuum of sedation

| Description          | Minimal sedation                                      | Moderate sedation                                | Deep sedation                              | General anesthesia                        |
|----------------------|--------------------------------------------------------|--------------------------------------------------|--------------------------------------------|-------------------------------------------|
| Responsiveness       | Normal                                                 | Purposeful response to verbal or tactile stimulation | Purposeful response to repeated or painful stimulation | Unarousable with painful stimulation      |
| Interventions for airway patency | Not required | Not required                                      | Occasionally required                       | Frequently required                      |
| Ventilation          | Unaffected                                             | Adequate                                         | Occasionally inadequate                    | Frequently inadequate                     |
| Cardiovascular function | Unaffected                                         | Usually maintained                               | Usually maintained                         | May be impaired                          |
| Patient's perspective | Awake, calm, probably remember everything             | Sleepy, might remember things                    | Asleep, probably remember very little thing | Asleep, mostly do not remember anything   |

PRE-PROCEDURE PATIENT ASSESSMENT AND PREPARATION

The sedation provider should be aware of any medical conditions or comorbidities that potentially increase the likelihood of complications, by review of previous medical records and interview with the patients or caregivers. These include abnormalities of major organ system, any allergies, obstructive sleep apnea, morbid obesity, history of psychotropic drug use, and previous experience with sedation. The physical examination before sedation should be focused on the respiratory and cardiovascular system. The evaluation of airway is particularly important. Compromises in neck mobility and mouth opening, facial anomaly, teeth condition, neck mass, breathing sound should be checked before the administration of sedation.

Pre-sedation fasting requirements are similar with those for general anesthesia. Patients are allowed to drink clear liquid (water, sugar water, juice without pulp) until 2 hours before sedation. Minimum fasting time for light meal and non-human milk is 6 hours, and fasting 8 h or more is recommended for fatty food or meat. Routine administration
of gastrointestinal stimulants, medications that block gastric acid secretion, antacids or antiemetics are not recommended. These guidelines are mainly based on studies which investigated gastric volume and pH, and the impact of pre-sedation fasting time on patients’ outcome is not obvious. However, considering that pulmonary aspiration is a rare but frequently fatal complication, and moderate sedation can be converted to deep sedation or general anesthesia during procedure, it is generally recommended to conform the fasting guideline.

**PATIENT MONITORING**

Most of sedation-related complications are caused by drug-overdose. According to an analysis of the American Society of Anesthesiologists (ASA) Closed Claims database, respiratory depression was responsible for 21% of sedation-related claims, and almost half of these claims were judged as ‘preventable’ if proper monitoring were applied with vigilance and alarm system. It is recommended that all patients undergoing procedural sedation is monitored for respiratory function, hemodynamics and the depth of sedation. In addition to monitoring devices, it should be emphasized that a designated, trained personal for monitoring of the patient is required to attend throughout the procedure.

**Respiratory and hemodynamic monitoring**

Respiratory depression due to an overdose of sedatives is the most common adverse event during sedation. All patients undergoing procedural sedation should be monitored for hypoxemia or desaturation by pulse oximetry. Because pulse oximetry measures arterial oxygen saturation, the detection of compromised respiratory activity can be delayed, especially if patients are receiving supplemental oxygen. For early detection of hypoventilation, monitoring exhaled carbon dioxide tension is superior than pulse oximetry. Early detection enables rapid interventions to relieve respiratory depression, including adjustment of drug dosing and the depth of sedation, patient stimulation, maneuvers for airway patency, assisted ventilation and supplemental oxygen. Indeed, capnography monitoring was demonstrated to reduce respiratory complication and improve patient safety during procedural sedation with benzodiazepines and opioids. The sedation provider should also observe vigilantly for qualitative clinical signs, such as movement of chest wall, suprasternal, intercostal, and subcostal retraction, gasping for air, and stridor.

For sedation during cardiovascular procedures, non-invasive blood pressure, heart rate and electrocardiography monitoring is recommended. Invasive blood pressure monitoring is occasionally required for the patients with advanced cardiovascular dysfunction.

**Monitoring the depth of sedation**

The depth of sedation should be monitored throughout the procedure. Patient may be uncomfortable with light sedation, whereas deep sedation has greater impact on cardiopulmonary function. Thus, the margin of safety for deeper level of sedation may be narrow, especially in patients with impaired cardiopulmonary function. The dose of sedatives and analgesics are carefully titrated according to the depth of sedation as most of sedation-related complications are associated with unintended deeper level of sedation. The sedation provider can monitor the depth of sedation by periodical verbal stimulation as well as other clinical signs. However, some clinicians advocate processed, digitalized form of electroencephalogram-derived monitor to monitor the level of consciousness.
The bispectral index (BIS; Aspect Medical Systems, Norwood, MA, USA) is one of the most popular monitors of processed electroencephalogram. It receives electroencephalogram signal via a single patch sensor attached on the forehead, analyzes and processes the signal into a single number, ranging 0 (isoelectric electroencephalographic activity) to 100. A BIS value between 90 and 100 indicates fully awaken status, a value between 70 and 90 represents light to moderate sedation. A BIS value of 60 to 70 indicates superficial anesthesia, and a value between 40 and 60 is regarded as an appropriate value for general anesthesia. Monitoring with BIS is continuous and more convenient than assessment of clinical signs alone, however, for relatively short procedures, addition of BIS monitoring seems to provide little benefit over conventional assessment of clinical signs. In a study comparing the BIS monitoring with clinical assessment, awareness, propofol requirement, desaturation and need for hemodynamic and respiratory support were all similar between the study groups in patients undergoing bronchoscopy. Moreover, the correlation between the BIS and the assessed sedation level was very weak. In contrast, procedures which take long time or require moderate to deep sedation may benefit from the BIS monitoring.

COMMONLY USED SEDATIVES AND ANALGESICS

Midazolam
Midazolam is a benzodiazepine with a rapid onset (1 to 5 minutes) and short duration of action ([Table 2](#)). It is the most commonly used agent for short procedures requiring light to moderate sedation. It confers anxiolysis and antegrade amnesia. Because it has no analgesic property, it is usually used in combination with opioids. It blunts central respiratory drive response to hypercapnia or hypoxia. The respiratory depressant effect is dose-dependent and might be increased with rapid intravenous bolus administration. A reduced dose is recommended for old age and patients with impaired cardiopulmonary function. Midazolam is thought to have minimal effect in terms of hemodynamic deterioration. Midazolam has negligible direct myocardial depressive effect and modest decrease in blood pressure can occur due to mild vasodilation and sympatholytic effect. However, both respiratory and cardiovascular effects are synergistic when midazolam is used in combination of other sedatives and analgesics, for example opioids, leading to severe respiratory depression and hypotension greater than expected by the effect of each drug. Midazolam is metabolized in liver, and the main metabolite, which possesses sedative activity, is rapidly cleared via kidney. Thus, in patients with liver cirrhosis or renal impairment, midazolam administration can result in profound sedation for longer duration.

Midazolam may induce agitation, restlessness, aggressiveness or hallucinations. This paradoxical disinhibitory reactions develop within several minutes after intravenous administration following transient sedation. It is reported to occur in <1% of midazolam administrations and thought to be associated with loss of cortical resistance and reduced serotonin control. Patient with alcohol abuse or psychologic disturbances are at increased risk of paradoxical reactions. The paradoxical reactions may be attenuated with flumazenil or haloperidol.

Propofol
Propofol is a sedative-hypnotic agent with no analgesic effect. It has rapid onset (<1 minute) and relatively short context-sensitive half-time, which enables smooth and quick recovery even after prolonged continuous infusion ([Table 2](#)). Propofol has little paradoxical excitatory effect and low incidence of nausea and vomiting. These favorable pharmacokinetic and
pharmacodynamics profile made it one of the most popular intravenous agents in modern anesthetic practice.

The pharmacokinetic model of propofol is described as a 3-compartmental model which consists of central, peripheral (lean tissues) and deep (fat tissues) compartment.\textsuperscript{29} Following intravenous bolus administration, propofol is rapidly redistributed to a peripheral compartment, resulting in fast offset of its clinical effect (5–10 minutes). Because propofol is lipophilic, the fat compartment acts as a reservoir after prolonged infusion. Redistribution from the fat compartment may delay the offset of action especially in obese patients.\textsuperscript{30} Time required for decrease in plasma concentrations are also significantly longer in the elderly.\textsuperscript{29} Nonetheless, recovery after prolonged infusion is relatively quicker compared with other hypnotics such as midazolam, because the rate of metabolism and excretion is faster than the rate of redistribution. The context-sensitive half-time of propofol is 25 minutes after 3 hour-long infusion, whereas midazolam has a context-sensitive half-time of 70 minutes for a similar duration of infusion.\textsuperscript{31} Propofol is mainly metabolized in liver, and the metabolites, which have no hypnotic effect, are excreted via kidney.\textsuperscript{30}

Propofol is a potent respiratory depressant. An intravascular bolus administration may result in apnea. The dose, speed of injection and co-administered drugs, especially opioids, are associated with the incidence and duration of apnea.\textsuperscript{32} Propofol infusion at 100 µg/kg/min induces a 40% decrease in tidal volume and a 20% increase in respiratory rate.\textsuperscript{33} Propofol also induces cardiovascular depression, with a greater extent compared with other intravascular sedative agents.\textsuperscript{34} Even in healthy individual with no cardiovascular impairment, propofol produces 25% to 40% decrease in systemic blood pressure. In addition to vasodilatory effect, it also decreases cardiac output and stroke volume. These cardiovascular effects are associated with sympatholytic activity and whether propofol has direct myocardial depressive effect is still controversial.\textsuperscript{35} Notably, peak hemodynamic effect of propofol tends to follow behind the hypnotic effect.\textsuperscript{36} So profound hypotension may manifest a few minutes after the patients fall into deeper level of sedation.

The most frequent complaints in patients who receive propofol is pain at injection site, which can be managed with concomitant use of lidocaine at the start of injection.\textsuperscript{37,38} Propofol has no physical dependence, however, it may result in euphoria with sense of ‘general well-being’, predisposing a risk of addiction or abuse.\textsuperscript{39} Lipid-based formulation of propofol is susceptible to bacterial contamination and can induce life-threatening sepsis unless stored and handled appropriately in a sterile and aseptic manner.\textsuperscript{40}

**Dexmedetomidine**

Dexmedetomidine is an α-2 adrenergic receptor agonist which has anxiolytic, sedative and analgesic property (Table 2).\textsuperscript{41} Compared with clonidine, it is more selective and efficacious.

| Sedatives     | Dose                  | Onset         | Hypnosis | Analgesia | Side effects                                      |
|---------------|-----------------------|---------------|----------|-----------|--------------------------------------------------|
| Midazolam     | 0.01–0.1 mg/kg        | 1–5 min       | ++       | –         | Respiratory depression, paradoxical excitation    |
| Propofol      | Bolus: 1–1.5 mg/kg    | <1 min        | ++       | –         | Respiratory depression, hypotension, bradycardia  |
|               | Infusion: 25–100 µg/kg/min | 10–15 min | +        | +         | Biphasic hemodynamic effect: hypotension, hypertension, bradycardia |
| Dexmedetomidine | 1 µg/kg over 10 min followed by infusion at 0.2–0.7 µg/kg/h | 10–15 min | +        | +         | Biphasic hemodynamic effect: hypotension, hypertension, bradycardia |
| Remifentanil  | 0.05–2 µg/kg/min      | <1 min        | –        | ++        | Respiratory depression, chest wall rigidity, bradycardia, hypotension |

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It exerts sedative effect by binding to α-2 receptors in the locus coeruleus and analgesic effect by an action on α-2 receptors in spinal cord as well as locus coeruleus. Unlike other sedative drugs such as propofol and benzodiazepines, dexmedetomidine induces sedation through the endogenous sleep-promoting pathway. Thus, it produces a natural sleep-like patterns of the electroencephalogram, and patients receiving dexmedetomidine usually fall asleep when undisturbed, while they are easily arousable and cooperative. Dexmedetomidine has minimal respiratory depressive effect. Sedation with dexmedetomidine induces modest reduction in minute ventilation, however, ventilatory response to hypercapnia is unaffected even in deep sedation. Dexmedetomidine reduces the release of norepinephrine and sympathetic tone in the central nervous system, thus it can induce severe bradycardia. Transient hypertension can occur due to stimulation of peripheral α-2 receptors. Slow initial loading over 20 minutes may reduce the transient hypertension. In case of hypertension during initial loading, it is recommended to decrease subsequent continuous infusion rate. Hypotension can also occur, especially in old age, history of diabetes or hypertension, or with a large loading dose. Dexmedetomidine can be used alone or in combination with other sedatives/analgesics. Because dexmedetomidine exerts minimal respiratory depression, combined administration with other sedatives/analgesics provide excellent results without increased risk of respiratory complication.

Opioids
Owing to their strong analgesic efficacy, addition of opioids can ameliorate procedure-related discomfort. Opioids have no hypnotic effect, however, it can reduce the requirements of other hypnotics when used in combination. Because the risk of respiratory and cardiovascular depression increases synergistically with other sedatives, special attention is needed in patients receiving opioids in combination with propofol or midazolam. Remifentanil is an ultra-short acting synthetic opioid, which has gained popularity recently for conscious sedation during painful procedures. It has rapid onset and short context-sensitive half time regardless of the duration of infusion. Recovery is rapid even after prolonged infusion and not affected by hepatic or renal function. Initial loading dose is not necessary, and an infusion at 0.05–2 µg/kg/min provides sufficient analgesia for most procedures (Table 2). However, respiratory depression is not infrequent even at subtherapeutic doses. Like other opioids, remifentanil infusion occasionally induces chest wall rigidity which impairs ventilation.

CONSIDERATIONS FOR SPECIFIC PROCEDURES

Catheter ablation for arrhythmias
Depending on the complexity of procedures, moderate sedation is feasible for most of cases, either with benzodiazepine, propofol, opioids or dexmedetomidine. However, in case of complex procedures, deep sedation or general anesthesia is occasionally required because the procedures can be lengthy and patient immobility is crucial for the induction and accurate mapping of the arrhythmogenic foci. In a trial comparing sedation versus general anesthesia for ablation of atrial fibrillation, general anesthesia was associated with shorter procedure time and higher arrhythmia-free rate. However, general anesthesia may predispose high incidence of esophageal injury, likely due to reduced esophageal motility and swallowing during general anesthesia. In addition, absence of feedback from patients might delay the detection of complications during the procedure.
There has been a concern that sedatives/anesthetics have a potential to suppress arrhythmia inducibility, interfering successful ablation of supraventricular tachyarrhythmia. Most of sedatives/anesthetics including volatile anesthetics, propofol, remifentanil and dexmedetomidine may slow cardiac conduction, exert sympatholytic effect and reduce the ability to elicit arrhythmia, especially in deep sedation with high doses.\textsuperscript{57-59} A combination of benzodiazepine and fentanyl is thought to have less impact on arrhythmia inducibility.\textsuperscript{60} However, a concrete evidence for superiority of any particular agent in regard to the ability to elicit arrhythmia and impact on success rate of the procedure is lacking so far, thus sedative strategy should be chosen upon a balance of patient comfort, preference and experience of sedation provider, and arrhythmia inducibility.

**Electrical cardioversion**

Electrical cardioversion is highly stimulating and requires deep sedation to alleviate patient discomfort. However, because the period of stimulation is brief, short-acting agents are recommended for rapid recovery. Either benzodiazepines, opioids, and propofol can be used.\textsuperscript{61,62} Propofol may have advantage in terms of quick onset and offset of sedation, ease of titration, less nausea and vomiting, whereas it is associated with more frequent episode of apnea and hypotension.\textsuperscript{63} Despite the theoretical advantage of propofol, benzodiazepines are widely used due to its practitioner familiarity and minimal hemodynamic effects.

**Pacemakers and implantable cardiac defibrillators**

The insertion of pacemakers and implantable cardiac defibrillators can be performed under minimal to moderate sedation. Tunneling of leads to a subcutaneous pocket needs adequate local anesthesia. Like electrical cardioversion, defibrillation threshold test requires deep sedation. Some patients with advanced heart failure may not be able to tolerate the supine position due to orthopnea and these patients are extremely sensitive to sedatives and opioids. Deep sedation in patients with advanced hear failure frequently results in hemodynamic deterioration due to reduced sympathetic tone. Moreover, retention of carbon dioxide may worsen pulmonary hypertension and lead to right ventricular failure.

**Percutaneous transluminal angioplasty**

The prevalence of peripheral artery disease and need for an appropriated sedation analgesia for percutaneous transluminal angioplasty is increasing.\textsuperscript{64} Patients undergoing percutaneous transluminal angioplasty are usually old and at increased risk of cardiovascular event. Peripheral artery disease provokes broad spectrums of pain, and balloonng may elicit significant ischemic pain. Thus, adequate pain control is crucial. Opioids alone may provide sufficient analgesia. Combination of opioids such as remifentanil with benzodiazepines or propofol may improve sedation experience, however, it can increase a risk of respiratory depression.\textsuperscript{65} Addition of dexmedetomidine can confer both sedation and analgesia while sparing the dose of opioids and preserving the respiratory function.\textsuperscript{66}

**CONCLUSION**

Sedation for cardiovascular interventions is frequently challenging. To facilitate successful procedure and improve patients’ experience and safety, appropriate depth of sedation and analgesia should be balanced with patient, procedural and institutional factors. Understanding the pharmacology of sedatives/analgesics, ability and proper setting for managing potential
complications, and clear communication between sedation provider and interventionist may improve outcomes in patients undergoing sedation for cardiovascular procedures.

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