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Review Article

Pain Management in Cardiac Surgery

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ABSTRACT

Aim of review: Acute or chronic pain may occur after cardiac surgeries. This overview describes the epidemiology, pathophysiology, preoperative interventions, surgical techniques, pain medications, regional anesthesia, and alternative measures to relieve pain after cardiac surgeries. This review also discusses post-sternotomy and post-thoracotomy chronic pain and their management.

Methods: The articles published in the past 2 decades in this area were reviewed.

Recent findings: Both acute and chronic pain after cardiac surgery is common and could cause significant morbidity. Opioid and non-opioid analgesics are usually used medications for pain control. Recently, neuraxial and paravertebral anesthesia have been studied in cardiac surgeries with success yet carry concerns of neuraxial hematoma due to heparin administration.

Summary: Acute pain after cardiac surgeries is common and could lead to chronic pain syndromes. Analgesics need to be administrated regularly for pain control after cardiac procedures. Regional anesthesia could be a valuable adjunct for effective pain control after cardiac surgery. (Funded by the Yangzhou Natural Science Foundation, and The Affiliated Hospital of Yangzhou University, both in China.)

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Cardiac surgeries may bring great pain to patients and a large number of patients report postoperative chest pain after cardiac surgeries. They are not limited to surgical incisions but also involve tissue injury, inflammations, prolonged sternal retraction and use of chest and mediastinal tubes (1). The management is challenging yet critical because pain control is closely associated with clinical outcomes. It has been shown that insufficient pain control after coronary artery surgery can increase the risk of myocardial ischemia or infarction via enhanced concentrations of circulatory stress hormones and increased myocardial oxygen demand (2, 3). Moreover, persistent pain after cardiac surgery may lead to pulmonary dysfunction, mainly due to difficulty in coughing. Pain during movement prevents patients from mobilization, breathing exercises and rehabilitation (1, 2, 4, 5). Eventually, uncontrolled pain after surgery may result in slower rehabilitation, longer intensive care unit and hospital stays, more readmissions, higher long-term

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morbidity (4, 5), patient dissatisfaction and negatively influence patients' daily function, relationship, sleep and general enjoyment of life. In addition, pain contributes to significant personal and financial costs for the patients and the healthcare system (6-8).

Epidemiology of Cardiac Surgery Pain

Despite the significant advances in pain management, more than 50% of patients still report moderate to severe pain after cardiac surgery (1). In Bjørnnes AK's review (9), the postoperative pain remained in the moderate to severe range for the majority of patients across all four days after surgery, 85% (day 1) to 57% (day 4). The sternotomy pain was found in approximately 70% of the patients. In addition, osteoarticular pain (29%), upper back (23%) and the lumbar region (14%) were also frequently marked out as pain locations, and with no significant differences related to sex or preoperative pain levels.

In particular, women reported greater pain intensity and interference compared to men during the first year following cardiac surgery, and pain at one month increased the probability of pain at 12 months for both men and women. Clinicians and researchers need to be aware of sex-related pain education and management differences, and women, in particular, need help to dispel concerns about pain management prior to cardiac surgery (10).

Cardiac Surgery Pain Pathophysiology

Direct trauma to sternum, ribs, muscles, and nerves plays important role in post cardiac surgery pain. However, neurotransmitter dysfunction and endocrinal disease could contribute to pain too. Costa found that 65.2% of patients with chronic cardiac surgical pain had depression or anxiety disorder (11). Neurotransmitters such as serotonin and noradrenaline act at the neurobiological level and play an important role in the modulation of pain. Interestingly, hypothyroidism is very common among patients with cardiac surgical pain (11). Hypothyroidism could lead to aminoglycan deposits on surrounding nerves, primary axonal degeneration, segmental demyelination, peripheral nerve dysfunction and chronic pain (12). Additionally, low oxygen consumption and high blood pressure among hypothyroid individuals lead to regional hypoxia, muscle spasms and eventually pain (13). Sternal wound complications may aggravate the risk of cardiac surgical pain, including superficial infections, sternal instability and mediastinitis (11). Socially, patients who have not yet retired and are not working complain of cardiac surgical pain more often (14).

Most cardiac surgeons desire an analgesic technique that has an acceptable safety profile, supports rehabilitation and physical recovery and produces reasonable pain relief while promoting early discharge. Currently, this is generally accepted to be a multimodal analgesic approach rather than any individual technique as a stand-alone.

Multimodal analgesic strategies have been proposed but many options are not applicable in cardiac surgical patients (15). We aim to review different techniques to reduce the incidence and severity of cardiac surgical pain and what impact of those pain management have on longer-term surgical outcomes including bleeding complications, infective complications, cardiovascular complications, and postoperative cognitive dysfunction. The patients and surgeons alike want to know whether anesthetic and/or analgesic techniques that provide the effective postoperative analgesia for the duration of postoperation translate into improved longer-term surgical outcomes.

Preoperative Education and Interventions

A study showed that patients are overwhelmingly misinformed regarding many aspects of pain management, the meaning of pain, and the risks involved in taking medications to control pain (16). This study found the very high proportion of patients who hold the incorrect belief held by many that "people get addicted to pain medication very easily". With this in mind, it becomes increasingly apparent that patient education is the only solution to counter the misinformation that can be damaging to patient recovery after surgery, especially after cardiac surgery, for which the presence of moderate to severe pain is a recognized phenomenon with potentially significant negative side effects, such as increased risk of pneumonia, decreased mobilization, lon-

ger hospital stays, and decreased health-related quality of life. This study underlines the considerable need and absolute necessity to provide pain education to patients undergoing cardiac surgery.

At their preoperative visits, patients should be given informational folders that include detailed written information about what they can expect from their operation and perioperative care. Patients could also watch an online instructional video. Time should be dedicated in the clinic to discuss the perioperative pain management strategy, with specific attention to addressing patients' concerns. Gabapentin 300 mg and tramadol extended release 300 mg orally in the preoperative holding area within 45 minutes of the induction of anesthesia have been proposed for pain control (17).

Surgical Techniques

Surgeons should consider the feasibility of small incisions to reduce trauma and potentially pain for patients. Minimal invasive cardiac surgery and robotically assisted cardiac procedure have become a reliable and efficient alternative to conventional open full sternotomy approach for cardiac surgery (18). These usually involve right anterior thoracotomy and hemisternotomy for aortic valve surgery, right minithoracotomy and robotic-assisted thoracotomy approaches for mitral valve surgery and left thoracotomy for coronary artery bypass grafting (CABG) (19).

For these minimal invasive cardiac surgeries, the simplest adjunctive pain management technique involves the use of limited intercostal injections of local anesthetics during the surgical closure. The desire for a longer duration of local anesthesia has led many to use continuous infusions via temporary catheters and specialized pumps or longer acting liposomal bupivacaine, Exparel (Bupivacaine Liposome Injectable Suspension, Pacira Pharmaceuticals Inc., San Diego, CA). Catheters may simply be left under the subcutaneous tissue before closure and then tunneled out through the skin (20, 21). An extrapleural intercostal catheter can be placed under direct vision, which may provide improvements in pain control and pulmonary function (22). The inability to adequately strip the parietal pleura posteriorly beyond the incision may limit optimal positioning of the catheter tip. Because of the high vascularity of the chest-wall cavity, caution must be exercised when injecting local anesthetics in this region because the possibility for systemic toxicity is quite real.

Recent advancement in transcatheter aortic valve replacement and percutaneous mitral valve repair has greatly changed the landscape of cardiac surgery. In 2016, transcatheter aortic valve replacement established a strong foothold as the preferred treatment strategy in intermediate-risk patients, with clinical outcomes equal to or better than surgical aortic valve replacement (23). Generous local infiltration with local anesthetics might be all that is needed for transfemoral approach valve replacements.

Whereas thoracic epidural use has been reported during minimally invasive cardiac surgery, paramount among the concerns with epidural catheters is the risk of epidural hematoma formation and consequent spinal cord injury. Additional concerns relate to bilateral sympathectomy leading to hypotension. Finally, the successful use of unilateral continuous paravertebral blocks has been described for postoperative pain control. Investigators have shown a high level of safety, with equally effective pain control in comparison with epidural anesthesia (24, 25). Advantages of a paravertebral block over a thoracic epidural include a higher safety margin for neurologic complications and avoidance of bilateral sympathectomy (26).

Opioids

Most cardiac surgeons desire an analgesic technique that has an acceptable safety profile, supports rehabilitation and physical recovery and produces reasonable pain relief while promoting early discharge. Currently, this is generally accepted to be a multimodal analgesic approach rather than any individual technique as a standalone. The most common modality is still through opioids. However, serious safety issues and increased mortality and morbidity with opioids have been raised recently. The American Society of Anesthesiologists has endorsed multimodal analgesia, involving multiple analgesics with differing modes of action, to reduce the overreliance on opioid-based postsurgical analgesic regimens and the associated adverse effects (e.

g., nausea, vomiting, respiratory depression). Unfortunately, substantial doses of opioid analgesics are still needed to provide sufficient analgesia for cardiac surgery.

Most patients are provided with patient-controlled analgesia narcotics, such as morphine, hydromorphone, sufentanil or remifentanil. Whether one is better than the other one is undetermined. Morphine is the most used pain medication during patients' hospital stay (9). The recommended oral starting dose is approximately 90-120 mg / 24 hr. (30-40 mg intravenously) for adults > 50 Kg and could provide a tolerable post-operative pain score of less than 3 (9). Activation of N-Methyl-D-Aspartate (NMDA) receptors by remifentanil could theoretically result in the clinical development of hyperalgesia and acute tolerance (27). However, P. Florkiewicz found that remifentanil is safe in cardiac surgery patients, providing hemodynamic stability without predisposing to exaggerated postoperative pain or increased opioid consumption (28). Alavi et al. demonstrated that both remifentanil and sufentanil patient-controlled analgesia can provide acceptable analgesia after coronary artery bypass (29). The difference between their efficacies was inconspicuous until 24 h postoperatively. Remifentanil seems to result in better pain relief at 24 h postoperatively (29).

Non-Opioid Pain Medication

In recent years, intravenous acetaminophen and ketorolac have become popular in cardiac operating rooms and intensive care units (30). Intravenous (IV) acetaminophen has drawn special interest due to lack of renal effects in cardiac patients compared to ketorolac. Two randomized controlled trials in cardiac surgery patients failed to demonstrate an opioid-sparing effect of either IV acetaminophen or propacetamol (31, 32). The prodrug of acetaminophen is hydrolyzed by plasma esterases to acetaminophen (2 g of propacetamol is hydrolyzed into 1 g of acetaminophen). Interestingly, a recent double-blind, randomized, placebo-controlled trial showed the administration of IV acetaminophen during cardiac surgery and for the first 24 hours postoperatively reduced opioid consumption and improved patient satisfaction with their overall patient experience but did not reduce opioid side effects (33).

Post-operatively, naproxen could also be administered in the absence of specific contraindications, following the usual institutional protocol (34). Parenteral and oral ketobemidone, oral oxycodone and paracetamol with codeine are also standard procedures to patients for postoperative pain relief (9). However, paracetamol and NSAIDs as part of a multimodal analgesic approach for treating postoperative pain after sternotomy have been reported to be ineffective (3, 4).

Anesthesia Drugs and Pain after Cardiac Surgery

Recent studies suggest that choice of anesthetics may influence postoperative opioid consumption and pain. Propofol was shown to inhibit NMDA receptors and pain after surgery (35). Ketamine is also an NMDA receptor antagonist and has been proposed to use as adjuncts to improve analgesia after thoracic surgery. A systemic review of 15 randomized controlled trials evaluated the efficacy of ketamine in the treatment of acute post-thoracotomy pain; fewer studies assessed its effect on attenuating chronic post-thoracotomy pain (36). The majority of reviewed studies demonstrated that ketamine has efficacy in reduction of acute pain, but the evidence is limited on the long-term benefits of ketamine to prevent post-thoracotomy pain syndrome, regardless of the route of administration. A nested analytical study found there is a statistically significant reduction in acute post-thoracotomy pain with intravenous or epidural ketamine (36). However, currently, the evidence for the role of ketamine as a preventative agent for chronic post-thoracotomy pain is insufficient due to the heterogeneity of the studies reviewed with regard to the route of administration, dosage, and outcome measures (36). There is no study found in the literature regarding whether the use of other common cardiac anesthesia medications, such as etomidate, dexmedetomidine or inhalational anesthesia agents, will affect pain after cardiac surgery.

Epidural and Spinal Anesthesia

Regional anesthetic techniques have expanded

dramatically over the last decades. Multiple regional anesthetics and analgesic techniques have been used in children undergoing cardiac surgery. Local anesthetics and opioids injected into the epidural or subarachnoid space could block pain transmission locally and centrally, decrease or eliminate the need for systemic opioids and possible side effects. Medications can be delivered via single injection or continuous indwelling catheter through epidural approach. Earlier tracheal extubation then may be feasible, time and risk of mechanical ventilation and hospital lengths of stay (LOS) thus decreased. Spinal and thoracic epidural anesthesia has been reported in multiple studies with good success in cardiac surgery (37-40).

In a retrospective review of 220 pediatric cardiac surgery patients who had general anesthesia combined with a variety of regional techniques, Peterson et al. reported that the number of patients who had tracheal extubation in the operating room was significantly increased and the number of patients who required reintubation within the first 24 hours was significantly decreased (41). Likewise, mechanical ventilation time was significantly reduced in patients who received caudal block anesthesia for cardiac surgery versus noncaudal group (42). A Cochrane meta-analysis of 3, 000 adults undergoing cardiac surgeries found that thoracic epidural anesthesia combined with general anesthesia produced a lower risk of atrial arrhythmias and pulmonary complications compared with general anesthesia alone, but with no difference in the major outcomes of mortality, myocardial infarction, or stroke (43).

In comparison to thoracic epidural anesthesia, some anesthesiologists favor the concept of spinal anesthesia and consider the risk of spinal hematoma remote (44). However, this remains an area of ongoing investigation and debate. High spinal anesthesia using local anesthetics supplemented to general anesthesia for cardiac surgery generates much discussion among cardiac anesthesiologists. High spinal anesthesia can decrease post-operative pain in patients undergoing cardiac surgeries (45-47). Lee TW et al. (34) applied high spinal anesthesia before anesthesia induction and placed patients supine in a slight head down position to modulate the spinal blockade to T-1 level.

Unfortunately, risks associated with regional anesthesia are significant and potentially devastating in cardiac patients. A major concern is possible peridural hematoma after systemic heparinization, which is almost always required during cardiac surgery (48, 49). The reported incidence of peridural hematoma in adult cardiac surgery is about 1:150,000 to 220,000 (50). Epidural anesthesia-related paralysis in a patient with full anticoagulation during cardiopulmonary bypass has been reported (51). Especially, the peridural hematoma is difficult to detect in patients who are sedated and paralyzed after cardiac surgery and could delay diagnosis and treatment for these devastating neurologic injuries.

In pediatric cardiac patients, risks of peridural or spinal hematoma after regional anesthesia may be more worrisome due to the often-needed anticoagulation to maintain shunt patency or treat thrombotic complications post-surgery, increased vascularity, and high venous pressure in this patient population. Impressively, Peterson reported zero incidences of peridural hematoma in pediatric cardiac patients with regional anesthesia, and the author applied a 60-minute window between peridural puncture and heparinization, which might be helpful to minimize such risks (41). Emerging data on the possible neurotoxicity of inhalational anesthetics on infant brains triggered renewed interest in regional techniques as a part of a balanced anesthetic approach for children undergoing cardiac surgery.

According to the Consensus Statement of the American Society of Regional Anesthesia (ASRA), neuraxial block for patients requiring intraoperative heparin administration remains controversial (52), and it is important to balance the risk of epidural hematoma and analgesia benefit. Surgeries should be delayed 24 hours when a traumatic tap occurs; time from instrumentation to systemic heparinization should exceed 60 minutes; heparin effect and reversal should be controlled strictly; epidural catheter should be removed when normal coagulation function is regained; and patients should be monitored closely postoperatively for signs and symptoms of epidural hematoma formation (52).

Paravertebral Block (PCB)

PVB is another effective alternative for pain re-

lief after cardiac surgery with the advantages of easy learning, less risk of a failed block, the equally effective postoperative pain control in thoracic and cardiac surgeries, improved postoperative pulmonary function, and less risk of spinal cord injury from epidural hematoma compared with neuraxial anesthesia (53). The postoperative efficacy of PVB has been demonstrated in patients who underwent minimally invasive coronary artery bypass, robotic-assisted coronary artery bypass surgery, and robotic mitral valve repair. PVB use in robotic mitral valve repair was associated with more extubation in the operating room, better postoperative pain relief and decreased intensive care unit stay and the total length of stay (54). Another recent study found that intraoperative bolus injection into the paravertebral space significantly decreased remifentanil administration during transapical transcatheter aortic valve replacement without causing hypotension or any other obvious adverse events (55).

The most common postoperative complication after the extremely invasive thoracoabdominal aortic aneurysm (TAAA) surgery is respiratory failure. The large thoracoabdominal incisions, a huge sigmoid-shaped incision from behind the left scapula, along the seventh rib, across the costal margin, and toward the left periumbilical region, are associated with severe postoperative pain, which would suppress patients' respiratory function (56, 57). Utilization of PVB significantly decreased postoperative pain scores at rest and while coughing, reintubation rate, the incidence of noninvasive positive-pressure ventilation use, and postoperative pneumonia after TAAA repair (58). Plus, it would be less likely to compress the spinal cord even if paravertebral hematoma formed because the paravertebral space, unlike the epidural space, is not surrounded by rigid bone.

Wound Infusion of Local Anesthetics

In recent years, long-lasting peripheral blocks that involve the use of continuous infusion of local anesthetic solution at the operative site have shown promising results both in adults and in children (59). Tirotta and co-workers showed that continuous infusion of 0.25% levobupivacaine or bupivacaine significantly reduced postoperative morphine consumption in children who were undergoing median sternotomy (59). Local anesthetic administered to an operative site may also attenuate the local inflammatory stress response in addition to its analgesic action.

A prospective, randomized trial demonstrated that continuous wound infusion with 0.2% ropivacaine after median sternotomy in children undergoing atrial septal defect (ASD) closure did not diminish morphine consumption or improve analgesia compared with placebo (59). However, pain after cardiac surgery is most often related to the median sternotomy or the chest drain. A continuous subcutaneous infusion may provide pain relief but only at the level of the wound. Therefore, in this study, local anesthesia may have been only partly effective and the mediastinal drain may have caused major discomfort in patients. The mediastinal drain sites should be injected with local anesthetics too.

Recently approved extra-long lasting local anesthetic, liposome encapsulated bupivacaine, Exparel (Bupivacaine Liposome Injectable Suspension, Pacira Pharmaceuticals Inc., San Diego, CA), was found to be able to reduce the mean pain intensity scores, amounts of postsurgical opioids used, and incidence of postoperative nausea and vomiting by port sites infiltration after robotic cardiac surgeries (60). Lidocaine 5% patches were expected to be helpful to treat post-thoracotomy pain, while Vrooman et al. found them to be ineffective in reducing acute and chronic pain after robotic cardiac valve surgery (61). It may be in part due to the fact that the intercostal nerves commonly affected by surgical thoracotomy lie between the ribs and well below the skin surface and thus cannot receive the potential benefits of lidocaine absorption.

Alternative Measures for Pain Control after Cardiac Surgeries

In a recent study, the authors applied electric acupuncture combined with dexmedetomidine to patients undergoing cardiac surgeries. They found that the supplemental utilization of acupuncture significantly decreased the doses of dexmedetomidine and morphine post-operatively compared with dexmedetomidine only group,

Table 1. Pros and Cons of Pain Management Techniques in Cardiac Surgery

Techniques	Advantages	Disadvantages
Preop Education Interventions (16, 17)	Better prepared & realistic expectations for pain. Minimal side effects with preop medications.	None
Surgical Techniques (18, 19, 23)	Minimal invasive incisions, less trauma, consider transcatheter valve repair/replacements.	Advanced training required. The device costs more.
Opioids (9, 29)	Reliable pain relief.	Respiratory depression, nausea, vomiting.
Non-Opioids (9, 30, 33, 34)	No respiratory depression.	Less effective for pain relief, long-term use could cause renal and liver issues.
Choice of Anesthesia Medications (35, 36)	Propofol/Ketamine inhibits NMDA receptors and attenuates pain.	None
Epidural/Spinal Anesthesia (34, 37-43, 45-47, 50, 51)	Excellent pain control, early extubation, fewer opioids.	Risk of peridural hematoma after heparinization.
Paravertebral Block (53-55, 58)	Easy learning, less risk of failed block, less risk of peridural hematoma, improve respiratory status.	Paravertebral hematoma after heparinization.
Wound Infusion Local Anesthetics (59, 60)	Easy to perform.	Less effective for pain control, need to address chest tube sites.
Acupuncture TENS (62-64)	Decrease opioids usage, reduce pain.	Efficacy less well defined.

NMDA, N-Methyl-D-Aspartate; TENS, transcutaneous electrical nerve stimulation.

and decreased the side effects of dexmedetomidine and morphine (62).

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive technique that is effective for postoperative pain management. It has been demonstrated to produce effective analgesia and reduce postoperative opioid requirements in patients undergoing cardiac surgery without side effects. It is a comfortable, noninvasive, and nonpharmacological method, which can be easily performed. There are several studies demonstrating that TENS is effective in controlling post-sternotomy and post-thoracotomy pain (63, 64). Although TENS decreased postoperative opioid requirements, it was not found to be as effective as the parasternal block for the management of postoperative pain after median sternotomy for CABG (65). Parasternal block reduced pain scores better than postoperative intermittent TENS protocol for the first 4 h to 8 h postoperatively.

The pros and cons of pain management techniques in cardiac surgery are shown in Table 1.

Chronic Pain after Cardiac Surgery

Chronic postoperative pain is defined as new onset pain after a surgical procedure and persisting for more than 2 months without other apparent causes (66). Chronic post-sternotomy pain (CPSP) is defined as the persistence or recurrence of pain along with a sternotomy scar for at least 3 months following surgical procedures, according to the International Association for the Study of Pain (IASP) (67). CPSP is usually under-recognized and under-treated. Its incidence varies between 17% and 56%. CPSP can decrease mobility, affect sleep patterns, reduce the quality of life, impair the patients' working ability and cause depression and anxiety (68).

CPSP is notoriously difficult to treat; standard pain management techniques often fail, including opioids, anticonvulsants, and antidepressants (69-71). Paracetamol is the most commonly prescribed drug. NSAIDs are also frequently prescribed and should be used with caution in cardiac patients due to risks of cardiac events and renal compromises (72, 73). Patients can also receive rectal acetaminophen at the end of the operation. Only patients with higher pain scores were treated with World Health Organization step III medications. Other alternatives, including oral antidepressants and anticonvulsants, are suboptimal with substantial systemic effects.

A large multicenter Italian survey indicated that one out of five patients complain pain 3 years after cardiac surgery, mainly at the sternotomy

site, of which one-quarter was severe (67). Unfortunately, the authors did not have pain information in the acute postoperative and rehabilitation phases to demonstrate correlations. Preoperative pain, anxiety, female sex, young age, and inadequate analgesic consumption are the most significant predictors of postoperative pain intensity (74). Adequate control of acute pain may limit the progression to chronic pain.

Multiple mechanisms have been developed to explain pain after thoracotomy or sternotomy: entrapment neuropathy, musculoskeletal trauma during surgery, sternal pseudoarthrosis, painful sternal wires (musculoskeletal nociceptive pain), postoperative infection, and intercostal neuralgia due to nerve damage (75, 76). CPSP is primarily neuropathic, with the characteristics of shooting, burning sensations or numbness. Persistent pain could result from partial or complete intercostal nerve damage due to mechanical trauma such as nerve traction and compression (77). One of the most common causes is the use of the internal mammary artery for coronary artery bypass grafting. About 67.4% of the patients with CPSP had received an internal mammary graft (11). Mailis A et al. also reported that the use of internal mammary grafts resulted in a higher incidence of CPSP (78). Alston RP and Pechon P affirmed that damage to the intercostal nerves could occur during the dissection of the internal mammary artery bed using diathermy (79).

Conclusion

Pain after cardiac surgery is common and could lead to significant morbidities and chronic pain syndromes. Appropriate way should be applied to different patients according to different conditions to relieve pain after cardiac surgeries. A multimodal analgesic approach would be preferred. Analgesics need to be administrated regularly for pain control after cardiac procedures. Non-opioid agents can be added to reduce the doses and side effects of opioid drugs. Regional anesthesia could be a valuable adjunct for effective pain control after cardiac surgery.

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