

# Perioperative Pain Management in the Cardiac Patient

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**Abstract:** Pain is the perception of an unpleasant sensation to warn the body of tissue injury. Nociceptors send stimuli to the central nervous system via neurons that enter the spinal cord via the dorsal horn. The signal is then processed, integrated, and relayed to higher centres for interpretation. Surgery stimulates pain pathways due to the tissue injury that it creates and in this way a neuroendocrine cascade is set into action as a protective mechanism by the body. Cardiac patients and patients with cardiac risk factors pose a special risk when undergoing surgery. They exist in a state of altered vascular responsiveness due to endothelial injury and chronic inflammation of the vasculature. The physiologic response to pain may put cardiac patients at risk for cardiac events in the perioperative period. More recent methods in pain control, such as epidural anaesthesia, can be used to decrease the risk of cardiac events in these patients. Pain transmission and analgesia will be explored in this paper. Furthermore, the current American College of Cardiology and American Heart Association Task Force guidelines on the management of cardiac patients undergoing noncardiac surgery as well as the literature published since the release of these guidelines will be discussed.

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Pain is the perception of an unpleasant sensation from a specific region of the body. It is elicited to warn the body of impending or current trauma or injury and it represents a subjective experience resulting from the integration of nociceptive signals from specialized receptors that signal tissue damage.<sup>1</sup> There are multiple pain conducting pathways in the body through which nociceptors can alert the central nervous system (CNS) of potential injury. The painful stimulus is first processed by the CNS at the level of the spinal cord and later by higher centres.<sup>1</sup> In the spinal cord, pain signals can be amplified or dampened by local interneurons and by descending pathways.

The gate theory of pain is one of the leading hypotheses for pain modulation (Figure 1).

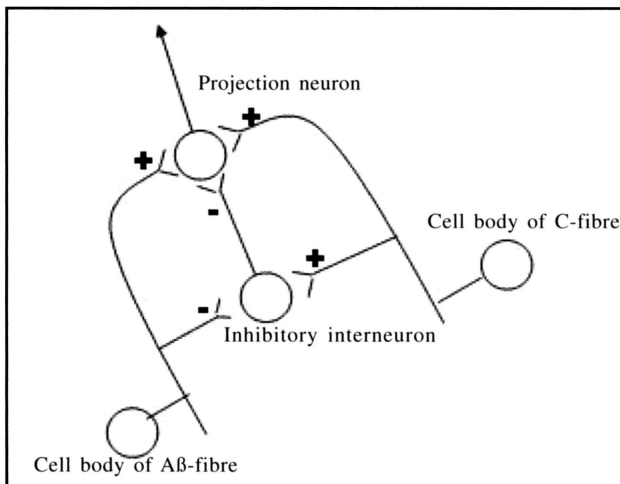


Figure 1: The gate theory of pain (adapted from Ref. 1)

When activated by a painful stimulus, C-fibres (nociceptive afferents) will inhibit the activity of the inhibitory interneuron and enhance the activity of the projection neuron with the net effect of pain transmission to higher centres. If, however, an A $\beta$ -fibre (non-nociceptive afferents) is stimulated concurrently, it will contribute to the modulation of the pain message at the level of the interneuron, thereby enhancing inhibitory interneuron

activity as well as projection neuron activity. The overall effect of A $\beta$ -fibre stimulation is decreased ascending pain transmission due to increased inhibition of ascending pain signals. The ascending pathways for pain transmission include the spinothalamic, spinoreticular and spinomesencephalic tracts.<sup>1</sup> Descending pathways originating in both the periaqueductal gray matter and the reticular formation also participate in pain modulation via interneurons in the dorsal horn.<sup>1</sup> The central nervous system contains endogenous opioid receptors which also participate in pain modulation. Mediators of pain endogenous to the CNS include the following opioid agonists: the enkephalins, the dynorphins and peptides derived from the proopioidmelanocortin family of molecules. The receptors for these naturally occurring mediators of pain are found in several areas involved in pain modulation such as the periaqueductal gray matter, the hypothalamus and the dorsal horn of the spinal cord.<sup>1</sup> Different modes of analgesia target the aforementioned areas in an effort to control the perception of pain.

Surgical procedures elicit a physiologic response similar to those triggered by tissue injury and trauma. Stimuli from the surgical incision and procedure ascend to the thalamus via the aforementioned pathways. Communications from the thalamus to the hypothalamus elicit the release of hormones such as adrenocorticotropic hormone (ACTH) and vasopressin (VP) that will act either directly or indirectly on the pituitary gland, the pancreas and the adrenal glands to trigger a stress response.<sup>2</sup> Adrenocorticotropic hormone acts on the adrenal gland resulting in increased levels of circulating cortisol, the major mediator of the metabolic responses to stress and hyperglycaemia. Vasopressin released from the posterior pituitary gland acts to increase total body water, thereby contributing to postoperative fluid shifts. VP also has effects on the vasculature which lead to an increase in peripheral vascular resistance.<sup>3</sup> Pain also stimulates the sympathetic nervous system which increases circulating catecholamines. Both epinephrine and norepinephrine contribute to the hypertension and tachycardia seen in the postoperative period. These increases

in vascular resistance and heart rate cause an increase in myocardial oxygen requirements and therefore predispose to ischemic episodes, potentially contributing to the incidence of perioperative cardiac events, defined herein as myocardial infarction (MI).<sup>4,5</sup> It has been shown that patients experiencing episodes of perioperative ischemia are 3 times more likely to suffer from a postoperative MI, which is in turn associated with increased morbidity and mortality.<sup>6</sup> Furthermore, the postoperative period is characterized by a hypercoagulable state because of changes to normal hemostatic mechanisms. There is increased platelet aggregation and activation, increased conversion of fibrinogen to fibrin and increased fibrinolysis by plasmin.<sup>7</sup> Thus, each component of the neuroendocrine response to stress has the potential to influence the stability of cardiac patients throughout the perioperative period.

Patients with cardiac risk factors pose a special risk when undergoing surgery. Hypertension, atherosclerosis and coronary artery disease can lead to states of chronic inflammation of the blood vessels and to endothelial injury. This alters the normal anticoagulant and vasoreactive properties of the blood vessels and predisposes to thrombosis and exaggerated vasoconstriction.<sup>8</sup> As previously mentioned, surgery and pain stimulate a neuroendocrine response in which catecholamine and vasoconstrictor levels are elevated. In patients suffering from cardiovascular disease this is especially pertinent as their response to circulating hormones may increase myocardial oxygen demand, which, coupled with enhanced vascular reactivity, increases the risk of coronary vasoconstriction, thrombosis and MI. Thus, while the effects of surgery itself on the stress response cannot be avoided and are highly dependent on the condition of the patient and the procedure being performed, an adequate pain relief regimen can have a large impact on the perception of pain and its associated physiologic responses and risks. Furthermore, it has been shown that adequate postoperative pain relief allows for earlier ambulation, increased lung volumes following thoracic surgery and reductions in the incidence of venous thrombosis.<sup>8</sup>

### **Managing Perioperative Pain**

There are many different approaches to pain relief beginning with the preoperative period through to the postoperative period. Some of the most common approaches including oral analgesia, intramuscular analgesia, patient controlled analgesia and epidural analgesia will be discussed here. The type of analgesia used will depend on the patient's personal preferences, the surgical procedure and whether the patient is being treated on an inpatient or an outpatient basis.

The most commonly used oral analgesics for mild to moderate pain relief are the nonsteroidal anti-inflammatory agents (NSAIDs, Table 1). They can be used alone or in combination with other analgesic agents such as opioids. Other oral analgesics include the p-aminophenols (acetaminophen), the propionic acids (ibuprofen, naproxen), and the indoles (indomethacin, ketorolac).<sup>10</sup> Oral

**Table 1: Analgesic modalities**

Modality	Advantages	Disadvantages
Oral	Easy administration	Inadequate pain control postoperatively
Intramuscular	As needed basis	Unpredictable absorption Delay between request for analgesia and administration Cycles of high and low analgesic concentrations
Patient-Controlled	Immediate Can administer baseline infusion	No delay between request and administration
Epidural	Continuous pain relief Potential sympathetic blockade	May not be used in patient with coagulopathy Catheter is CNS portal of entry

opioids (codeine) are often used in conjunction with COX inhibitors in order to enhance analgesia while reducing adverse effects of the drugs. While the oral administration of analgesic agents is very convenient, it rarely confers adequate pain relief in the perioperative period. Intramuscular analgesia is also not ideal due to the unpredictable absorption and serum concentrations of drug and therefore unpredictable pain relief. When administered on an as needed basis there is also a delay from the moment of sensing pain to the return of blood levels within the analgesic range. This is problematic as cycles of high and low concentrations of drug in the blood lead to periods of side effects alternating with periods of suboptimal analgesia, which also leads to intermittent stimulation of the sympathetic nervous system and its potential deleterious effects on the cardiovascular system.<sup>10</sup>

Patient controlled analgesia (PCA) was designed in order to circumvent the cycling analgesia that goes with the intramuscular route of administration. Because the patient controls their own level of analgesia with PCA, superior levels of pain relief are possible as there is no delay between the request for more drug and its administration. The infusion pumps used for PCA are programmable such that a maximum dose of opioid may be delivered over a set period of time and a 'lockout' period or minimum time between doses can be specified. These features protect against high blood levels of opioids and are designed to avoid sedation and respiratory depression. In addition, a continuous infusion may be administered in order to maintain a minimum opioid blood level while sleeping. Studies have shown that not only are patients more satisfied with their pain control while using PCA, but that the total amount of drug administered is less.<sup>10</sup> Patient controlled analgesia does not avoid, however, the adverse effects associated with opioid use (e.g. nausea, vomiting and pruritis).

Lastly, epidural analgesia has been shown to be very effective. Studies have shown increased lung volumes and earlier ambulation associated with its use.<sup>10</sup> Epidural analgesia may be achieved using opioids and local

anaesthetics either alone or in combination. The use of local anaesthetics also results in blockade of the sympathetic and somatic motor systems, which may not be desirable depending on the situation. Opioids alone do not result in such blockade although they do often result in significant side effects. When used in combination, a synergistic effect is seen which allows for decreased doses of each drug and therefore fewer side effects while maintaining more optimal analgesia. Epidural anaesthesia may not be used in patients afflicted with a coagulopathy of any kind or with an infection over the site of injection.<sup>10</sup> Furthermore, a catheter must be used for continuous or intermittent administration of these agents. Thus, the catheter becomes a portal of entry for microorganisms and raises the possibility of infection.

### ***Current Guidelines for the Management of Preoperative Pain in Cardiac Patients***

In 2002, the American College of Cardiology (ACC) and the American Heart Association (AHA) Task Force on Practice Guidelines released a guideline update on the perioperative cardiovascular evaluation for noncardiac surgery. The purpose of the guidelines is to provide physicians with an approach to the cardiac patient, including when to initiate supplemental preoperative evaluations, the benefits of certain perioperative therapies and anaesthetic and analgesic considerations both during and after surgery. With respect to anaesthesia, the ACC/AHA Task Force reviewed the literature investigating the effects of anaesthetic technique and agent, perioperative pain management and perioperative patient monitoring on the occurrence of cardiac events. It was determined that there is no specific anaesthetic technique showing superior protection of the myocardium.<sup>11-16</sup> The degree of coexisting cardiac disease and the severity of surgery, however, were found to be determinants of outcome.<sup>17</sup> One randomized study showed that there was no difference in outcome when using the inhalational anaesthetics halothane, enflurane, isoflurane or sevoflurane.<sup>15</sup> Another study, however, did show an increase in the incidence of myocardial ischemia when using desflurane versus sufentanil in coronary artery bypass graft surgery.<sup>18</sup> Furthermore, multiple studies showed that there is no difference in risk between general and regional anaesthesia techniques in cardiac patients.<sup>12-16</sup>

Most cardiac events in patients undergoing noncardiac surgery occur postoperatively, a time at which adequate monitoring of the patient and suppression of the stress response is crucial. Unfortunately, no randomized controlled trials have successfully demonstrated the effects of analgesic techniques on patient outcome. It has been shown that patients using epidural analgesia postsurgically call for fewer doses of opioids and show a decreased stress response to surgery.<sup>19</sup> Studies show conflicting results with respect to the incidence of cardiac morbidity with epidural versus intravenous anaesthesia and analgesia techniques.<sup>14,15,20,21</sup> Despite the lack of decisive evidence showing superior technique for pain management, the guidelines released by

the ACC/AHA strongly reinforced the need for carefully planned anaesthesia and analgesia regimens to minimize patient discomfort in addition to blunting stress response to surgery.

### ***What has been published since the release of the ACC/AHA guidelines?***

Investigators continue to pursue the question of optimal perioperative pain relief and further studies exploring this issue have been published since the release of the ACC/AHA guidelines. In Finland, Scheinin *et al.* investigated the effects of epidural anaesthesia in elderly patients on myocardial ischemia during noncardiac surgery.<sup>22</sup> Since past research has shown that perioperative myocardial ischemia puts patients at risk for increased rates of perioperative cardiac events,<sup>23</sup> Scheinin *et al.* set out to determine whether epidural pain control throughout the perioperative period could reduce the incidence of myocardial ischemia, which would hypothetically reduce the incidence of perioperative cardiac events.<sup>24,25</sup> In this randomized controlled trial, a total of 59 patients over the age of 60 years and suffering from acute traumatic hip fracture were randomized to one of two treatment groups. Prior to randomization, patients were stratified according to “high-risk” (known coronary artery disease [CAD] and patients having 2 risk factors for CAD) or “low-risk” with respect to cardiovascular status and randomized accordingly. One group (EPI) received a continuous epidural infusion of bupivacaine and fentanyl, while the second group (OPI) received parenteral opiates for pain relief. All patients were monitored via Holter electrocardiogram (EKG) and 12-lead EKG’s were obtained both pre and postoperatively. Arterial blood oxygen saturation was measured nightly in case of hypoxaemia. Patients also rated their level of pain, itching, nausea and quality of sleep using 100 mm visual analogue scales.

Results of the study showed that during surgery the incidence of myocardial ischemia was significantly less in the EPI group (0% EPI vs. 27% OPI,  $p < 0.01$ ). There was, however, no statistical difference in the overall rates of perioperative myocardial ischemia. Furthermore, upon subjective evaluation of pain, the scores in the EPI group were approximately 40% lower than in the OPI group suggesting that epidural anaesthesia and analgesia using bupivacaine and fentanyl provides superior pain relief in an elderly patient population. It was also shown that epidural anaesthesia begun preoperatively reduces the incidence of intraoperative myocardial ischemia. Scheinin *et al.* speculate that it may be the superior analgesic efficacy of the epidural analgesia that leads to a decrease in myocardial ischemia due to reductions in the body’s natural stress response, reduced activation of the sympathetic nervous system, and therefore a decrease in oxygen demand by the heart.

The randomized nature of the study and the stratification of “high” and “low” risk patients to the different treatment groups enhanced the validity of the results obtained. A major limitation of this study, however, is the small size of

the treatment groups ( $n_{EPI}=29$ ,  $n_{OPI}=30$ ). Due to the exclusion criteria delineated at the outset of the study, it was necessary to exclude 18 patients from the study, thereby reducing the statistical power of the results. In addition, there were significantly fewer males in the OPI group (3 OPI vs. 11 EPI), which could skew the results. The authors of this study also acknowledge that they did not measure levels of cardiac enzymes in their patients. Measuring the cardiac enzymes, which are serum markers of infarction, could have provided a more sensitive method of differentiating between myocardial ischemia and infarction. Thus, the rates of myocardial ischemia and myocardial infarction may have been underestimated. Overall, further research involving larger treatment groups and more extensive cardiac evaluations are necessary before drawing firm conclusions from this study.

In 2001, Park *et al.* studied the effect of epidural anesthesia and analgesia on perioperative outcome in a randomized controlled trial.<sup>26</sup> The aim of their research was to determine whether the combination of epidural anaesthesia and analgesia could decrease the incidence of major complications and death during all or any one of aortic, gastric, biliary and colon surgeries. The trial included 1021 patients randomly assigned to one of two treatment groups: 1) general anaesthesia and postoperative analgesia using parenteral opioids (intramuscular or intravenous) or 2) epidural and general anaesthesia and postoperative analgesia using epidural opioids. Prognostic variables such as surgical type, age and Goldman index were balanced between the groups and there were no other significant differences between the groups. Patients were assessed preoperatively by medical history, physical examination, laboratory tests, chest radiography, EKG and percutaneous oxygen saturation. Postoperatively, a 12-lead EKG was performed, and total creatinine phosphokinase and MB isoenzymes were measured. Postoperative pain and physical performance were assessed using visual analogue scales. Both primary endpoints (death, new myocardial infarction, worsened heart failure, persistent ventricular tachycardia, complete A-V block, severe hypotension, pulmonary embolism, respiratory failure, cerebral hypoxia, thrombosis, haemorrhage and renal failure) and secondary endpoints (pneumonia, sepsis, gastrointestinal bleeding, new angina pectoris, epidural haematoma, respiratory depression and reoperation for complications) were measured for up to 30 days following surgery. Although the investigators were not blind to the treatment group, the endpoints measured and the visual analogue scales used were well defined prior to the initiation of the study which reduces the possibility of bias influencing the experimental outcome.

The results of the Veterans Affairs Cooperative Study showed that there was no overall difference in the rates of death or major complications between the two groups. When looking specifically at aortic surgery, however, there was a significant reduction in death and major complications in group 2 (epidural anaesthesia, 22%) versus group 1 (parenteral anaesthesia, 37%;  $p<0.01$ ). Group 1 showed a

higher incidence of new myocardial infarction ( $p<0.01$ ), stroke ( $p<0.05$ ) and respiratory failure ( $p<0.01$ ). Thus, in this study the positive effects of anaesthetic and analgesic technique on outcome appears to be limited to patients undergoing high risk surgery, i.e. abdominal aortic surgery. When considering pain management, patients randomized to group 2 required significantly less medication than group 1 while maintaining superior levels of analgesia the day following surgery as measured by a visual analogue scale ( $p<0.01$ ).<sup>26</sup>

The results of this trial are relevant to patient care. The fact that the study groups were large in size and that the study took place at multiple institutions increases its applicability and reduces the probability of spurious results due to a single institution's approach to patient care. Unfortunately, the study was limited to male patients, which raises the question of how female patients would respond to the same treatment regimen. The endpoints measured include aspects of patient care important to the physician and to the patient. Furthermore, not only did the study consider the medical aspects of anaesthesia and analgesia (e.g. cardiovascular function), but it also considered elements of patient satisfaction (e.g. degree of pain and physical performance).

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## CONCLUSION

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Surgery stimulates multiple physiologic reactions within the body, which can be managed with the use of anaesthetic and analgesic agents. When dealing with patients that have cardiac risk factors it is essential to take into account the results from preoperative cardiovascular investigations in order to plan for effective pain relief and to reduce the risk of intra and postoperative cardiac events. At this time, it is difficult to draw general conclusions regarding the use of epidural anaesthesia in cardiac patients undergoing noncardiac surgery. Based on the 2001 study by Park *et al.*, however, it appears that epidural anaesthesia is of benefit in cardiac patients undergoing high risk noncardiac surgeries such as abdominal aortic repair. In this study, patients undergoing aortic surgery and treated using epidural anaesthesia showed decreased incidence of new myocardial infarction, stroke and respiratory failure up to 30 days postoperatively.

Based on the available literature, Park *et al.* suggested that their observed reductions in myocardial ischemia could possibly be explained by nonanalgesic effects of epidural analgesia such as alterations in preload and afterload and more stable haemodynamics. It has also been suggested that the sympatholytic effects of epidural anaesthesia and analgesia may reduce the stress response and influence the hypercoagulable state normally seen after surgery.<sup>22</sup> It would be interesting to investigate why this difference in outcome is observed. Is it due solely to the improved analgesia with epidural analgesic techniques or are there additional underlying explanations for this effect?

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