Review Article

Remifentanil in critically ill cardiac patients

Laura Ruggeri, Giovanni Landoni, Fabio Guarracino[1], Sabino Scolletta[2], Elena Bignami, Alberto Zangrillo

Department of Anesthesia and Intensive Care Medicine, Università Vita-Salute San Raffaele, Milan, [1]Department of Cardiothoracic, Cardiothoracic Anesthesia and Intensive Care Medicine, University Hospital of Pisa, Pisa, [2]Department of Surgery and Bioengineering, Unit of Cardiothoracic Anesthesia and Intensive Care, University of Siena, Siena, Italy

ABSTRACT

Remifentanil has a unique pharmacokinetic profile, with a rapid onset and offset of action and a plasmatic metabolism. Its use can be recommended even in patients with renal impairment, hepatic dysfunction or poor cardiovascular function. A potential protective cardiac preconditioning effect has been suggested. Drug-related adverse effects seem to be comparable with other opioids. In cardiac surgery, many randomized controlled trials demonstrated that the potential benefits of the use of remifentanil not only include a profound protection against intraoperative stressful stimuli, but also rapid postoperative recovery, early weaning from mechanical ventilation, and extubation. Remifentanil shows ideal properties of sedative agents being often employed for minimally invasive cardiologic techniques, such as transcatheter aortic valve implantation and radio frequency treatment of atrial flutter, or diagnostic procedures such as transesophageal echocardiography. In intensive care units remifentanil is associated with a reduction in the time to tracheal extubation after cessation of the continuous infusion; other advantages could be more evident in patients with organ dysfunction. Effective and safe analgesia can be provided in case of short and painful procedures (i.e. chest drain removal). In conclusion, thanks to its peculiar properties, remifentanil will probably play a major role in critically ill cardiac patients.

Received: 26-11-10
Accepted: 09-12-10

Key words: Anaesthesia, cardiac anaesthesia, intensive care, remifentanil, sedation

Access this article online

Website: www.annals.in

PMID: ***

DOI: 10.4103/0971-9784.74393

Quick Response Code:

Remifentanil provides analgesia and has unique pharmacokinetic properties, with a rapid onset and rapid offset, irrespective of the duration of its administration. Thanks to these properties, remifentanil can be administered in different settings including surgery, off-site sedation for minimally invasive procedures and intensive care units (ICUs). For these reasons remifentanil fits very well with the need of fast-track cardiac anaesthesia which is used in many institutes, due to the possible clinical and economical advantages. We systematically reviewed the major studies of remifentanil analgesic and sedative effects in the contest of cardiac anaesthesia, cardiac intensive care, and minimally invasive cardiac procedures.

PHARMACOLOGY AND SIDE EFFECTS

Remifentanil is a piperidine derivative, with a strong affinity for the mu-opioid receptor and few effects on the delta and kappa receptors. It is 250 times more potent than morphine. The pharmacokinetic profile of remifentanil is unique among opioids, being characterized by a rapid onset and offset. Infusion of remifentanil has an onset of action of 1 min and rapidly achieves steady-state plasma levels. Its action dissipates within 3–10 min after discontinuation of infusion. Remifentanil has a $t_{1/2}\beta$ of approximately 10–20 min and a contest sensitive half-time of 3–4 min, regardless of the duration of infusion.[1]

Remifentanil is metabolized directly in the plasma by nonspecific esterases. Its primary metabolite is remifentanil acid, which has negligible pharmacologic activity. It similarly binds the mu, delta, and kappa receptors, but with much lower affinity. Present binding studies indicate that this metabolite is 800–2000 times less potent than the parent compound.

Address for correspondence: Dr. Giovanni Landoni, Department of Cardiothoracic Anesthesia and Intensive Care, Istituto Scientifico San Raffaele, Via Olgettina 60, Milan, 20132, Italy. E-mail: landoni.giovanni@hsr.it

Thus, although remifentanil acid is eliminated by the kidneys, its action is not prolonged to a significant extent even in the presence of renal dysfunction or by prolonged infusion (e.g. ICU patients). Dose adjustments are not required in patients with hepatic dysfunction, but patients with liver disease can be more sensitive to the ventilatory depressant effects of remifentanil. In contrast to other opioids such as morphine and fentanyl, which can accumulate in patients with organ dysfunction, a continuous infusion of remifentanil is not associated with a prolongation of effect after discontinuation. An infusion of remifentanil for 33 days with recovery within 10 min after discontinuation was reported.[1]

A strong analgesia causing a decreased sympathetic and increased vagal tone contribute to maintaining adequate heart rate and blood pressure intraoperatively. Despite initial concerns about the negative effects on cardiovascular function, such as hemodynamic instability,[2,3] remifentanil is now considered the standard of care in patients with poor cardiovascular function including patients with severely reduced left ventricular function undergoing implantation of a cardiovascular defibrillator[4] and high-risk patients undergoing transcatheter aortic valve implantation.[5] Interestingly, a recent study by Wong *et al.*[6] suggested that remifentanil preconditioning has cardiac protective properties in coronary artery bypass graft (CABG) surgery patients receiving a standard fentanyl (25 μg/kg in total) and propofol anaesthesia: the addition of remifentanil reduced the degree of myocardial damage in term of postoperative cardiac troponin release, MB isoenzyme of creatine kinase, heart-type fatty-acid-binding protein and in reduction of ischaemia-modified albumin.

According to Egan *et al.*, high doses remifentanil administered over a short period of time might be associated with thorax/truncal rigidity, rendering facemask ventilation during induction is difficult or impossible. [7] Similarly, in rats a dose-dependent activation of central l-receptors by opioids can cause muscle rigidity.[8] On the other hand, evidences in human beings suggest that probably the difficult facemask ventilation occurring during anaesthesia induction with high doses of opioids over a short period of time is likely due to vocal cord closure, thus questioning the role of thorax/truncal rigidity.[9] A major evidence is derived from a recent meta analysis published by Komatsu *et al.*,[10] in the context of general anaesthesia, demonstrated that remifentanil does not influence the incidence of thorax/truncal rigidity. Even if the precise mechanism of impairment on ventilation is still unclear, we think that bolus injections of remifentanil should be avoided as a matter of precaution.

Since the clinical requirements for the maintenance of anaesthesia with hypnotic drugs (volatile anaesthetics or propofol) are generally adjusted according to heart rate and blood pressure, patients receiving remifentanil can be titrated to lower hypnotic doses than those treated with other drugs, with a theoretical risk for intra-operative awareness. However, Komatsu *et al.*[10] found that about half of many patients among those treated with remifentanil had recall for intra-operative awareness, compared to patients treated with other opioids, thus concluding that remifentanil is not associated with an increased incidence of awareness .

Patients using remifentanil only intraoperatively have higher postoperative analgesic requirements. Nonetheless, postoperative respiratory depression and naloxone use in these patients is lower than in patients receiving other opioids intraoperatively.[10]

The occurrence of postoperative nausea and vomiting was similar in patients receiving remifentanil or other opioids.[10] The higher incidence of postoperative shivering when compared to other opioids could be explained by the shorter inhibition of thermoregulatory response and pain.[10]

Several cases of acute withdrawal syndrome were reported after cessation of remifentanil infusion in the ICU: tachycardia, hypertension, sweating, mydriasis and myoclonus occurred within 10 min after discontinuation of remifentanil-based sedation. Symptoms persisted after administration of morphine and clonidine and disappeared only after reinitiating remifentanil. Gradual tapering of the infusion (24–48 h) may decrease the incidence of withdrawal syndrome.[1]

The interaction between opioids and volatile anaesthetics in reducing minimum alveolar concentration is similar to that previously demonstrated between isoflurane and other opioids.[11]

Remifentanil profoundly decreases propofol needs for loss of responsiveness. Notably, in the presence of propofol, remifentanil reaches much higher concentrations during the first 15 min of infusion compared with those obtained when it is infused alone. This is caused by a reduction in the central volume

of distribution and initial distribution clearance of remifentanil, whereas maintenance infusion rates and recovery times remain unaltered.[12] At clinical dosages, the effect of the association of propofol and remifentanil on hemodynamic parameters remain modest while the synergistic interaction on the respiratory drive is major and may result in severe respiratory depression. Bouillon *et al.*[13] reported that the interaction between propofol and remifentanil is synergistic for loss of response to shaking and shouting and for loss of response to laryngoscopy, as a remifentanil concentration of 4 μg/ml reduces the propofol concentration by approximately two-thirds. Further increases in remifentanil only modestly reduce the propofol concentration required to ablate the response to either stimulus. On bispectral index monitoring and electroencephalographic approximate entropy, the interaction is additive, but in the clinical range remifentanil has little effect on these measures. Other studies specifically investigating the interaction between propofol and remifentanil with regard to clinical endpoints found similar results.[14,15] Drug interaction studies have characterized the synergy between remifentanil and propofol over a wide range of predicted effect-site concentrations. From these data, drug interaction models have been developed that relate predicted remifentanil and propofol effect-site concentrations to patient conditions that are of interest to an anaesthesiologist, such as the probability of loss and return to responsiveness.[16]

ANAESTHESIA FOR CARDIAC SURGERY

Many patients undergoing cardiac surgery cannot have hemodynamic instability precipitated by the noxious stimuli in the precardiopulmonary bypass period. Particularly, tachycardia which is strongly linked to the degree of sympathetic stimulation, and is a risk factor for production of perioperative myocardial ischaemia/infarction, especially in patients with coronary artery disease and those with a hypertrophic left ventricle. Concomitant rises in blood pressure increase the left ventricular wall stress and may also cause decompensation of an already failing heart. Therefore, attenuation of neurohumoral responses to surgical stress has always been the main focus of cardiac anaesthesia.[17] Cardiac anaesthesia consisting of high-dose opioids analgesia with fentanyl or sufentanil, supplemented by a relatively low concentration of an inhalation or intravenous anaesthetic agent are frequently used to achieve intraoperative hemodynamic stability and to minimize sympathetic responses to surgical stimuli. However, because of their pharmacokinetic characteristics both of these opioids may accumulate in the body, causing delayed recovery, respiratory depression, and the need for prolonged ventilatory support.[18] As a consequence, this practice has been questioned and efforts to facilitate a rapid recovery from anaesthesia were attempted. Aims of the so-called fast track cardiac anaesthesia include early tracheal extubation and decreased length of ICU and hospital stay with subsequent cost reduction. Any intervention that reduces postoperative complications and, therefore, total hospital length of stay should be considered an integral component of fast track cardiac anaesthesia. Many authors demonstrated that a reduction in the dosage of opioid administration is a key component of fast track cardiac anaesthesia. Immediate onset and offset of the analgesic effect of remifentanil makes it a perfect agent to instantly control painful stimuli during surgery and, therefore, it is frequently used in cardiac surgery to facilitate fast-track protocols.[19] We now summarize all the large (more than 50 patients) randomized controlled trials (RCTs) ever published in cardiac anaesthesia and comparing an anaesthesiological plan with remifentanil to an anaesthesiological plan without remifentanil. A PubMed search was performed entering the term "remifentanil AND anaesthesia " and "remifentanil AND cardiac surgery". The search was completed by searching the "related links" for each of the trials reported herein and by citation snowballing.

Lehmann *et al.*[20] compared sufentanil–midazolam versus remifentanil–propofol for CABG surgery and found that both anaesthesia regimens provided stable hemodynamics and adequate anaesthesia (measured with bispectral index monitoring). In a study by Gerlach and coworkers,[21] remifentanil was compared to sufentanil, showing a reduced time on mechanical ventilation after remifentanil use. Similarly, Lison *et al.*[18] compared remifentanil versus sufentanil in a randomized fashion and reported a faster recovery profile, lower time to extubation and better protection against intraoperative stimuli. Guggenberger *et al.*[22] performed a RCT comparing propofol/remifentanil or propofol/sufentanil in CABG surgery, demonstrating that intraoperative use of high-dose remifentanil may be associated with better recovery of pulmonary function and shorter postoperative hospital length of stay than sufentanil.

Howie *et al.*[23] conducted a RCT published in 2001, in which remifentanil versus fentanyl, combined with isoflurane/propofol, were evaluated in 304

patients undergoing CABG. The remifentanil-based anaesthesia (consisting of a bolus followed by a continuous infusion) resulted in significantly less response to surgical stimulation and less need for anaesthetic interventions compared to the fentanyl regimen (consisting of an initial bolus, and followed by subsequent boluses only to treat hemodynamic responses). The study also found no differences between the groups in time until extubation, discharge from the surgical ICU, ST segment and other electrocardiogram changes, catecholamine levels, or cardiac enzymes. These data were confirmed by Cheng and coworkers,[24] thus indicating that remifentanil is safe and as effective as fentanyl when used as the opioid component of a balanced anaesthetic technique for fast-track cardiac anaesthesia. In 2002, Myles and colleagues[25] enrolled 77 cardiac surgical patients in a RCT that compared remifentanil (0.83 μg/kg/min) with fentanyl (12 μg/kg and 24 μg/kg). Both remifentanil and fentanyl (12 μg/kg) were associated with a reduced time to tracheal extubation than was fentanyl (24 μg/kg). Remifentanil was also associated with a marked reduction in urinary cortisol excretion. Möllhoff *et al.*[26] published a RCT comparing high-dose remifentanil continuous infusion with intermittent bolus fentanyl regimen in combination with propofol for CABG. Responses to maximal sternal spread, sternal skin incision and sternotomy were lower with remifentanil, but on the other hand more drug-related adverse events were reported and median time to extubation was longer. A comparison of bolus remifentanil (5 μg/kg) versus bolus fentanyl (20 μg/kg) for induction of anaesthesia and tracheal intubation in patients with cardiac disease was published by Joo *et al.*[27] Heart rate, mean arterial pressure, systemic vascular resistance, and cardiac output were similar between the two groups during induction of anaesthesia and tracheal intubation. The incidence of adverse events such as bradycardia, hypotension, and ischaemia was also similar. Maddali *et al.*[28] investigated the time of extubation after CABG in a randomized study. After induction of general anaesthesia, patients received a continuous infusion of propofol accompanied by: continuous fentanyl infusion (group 1), fentanyl bolus doses intraoperatively and diclofenac postoperatively (group 2), continuous infusion of remifentanil perioperatively and fentanyl as an immediate postoperative bolus followed by a continuous fentanyl infusion. Extubation time was shorter in group 2 compared to group 3; a possible explanation could be the high dosage of fentanyl administered in group 3 in addition to remifentanil.

Engoren *et al.*[29] conducted a RCT comparing fentanyl, sufentanil and remifentanil in patients undergoing cardiac surgery, concluding that the shorter acting opioids, sufentanil and remifentanil, produced equally rapid extubation and similar time to ICU discharge and time to hospital discharge to fentanyl, indicating that any of these opioids can be recommended for fast-track cardiac anaesthesia. Ahonen *et al.*[30] compared remifentanil and alfentanil for use with propofol in patients undergoing minimally invasive CABG and found that times to awakening and tracheal extubation were shorter in patients receiving remifentanil, and interpatient variations in times to awakening and tracheal extubation were smaller.

Intrathecal morphine and thoracic epidural anaesthesia have been investigated in a number of studies, some of them including a remifentanil-combined analgesia, as a mean to facilitate the fast-tracking process. Bowler *et al.*[31] published a RCT where remifentanil combined with intrathecal morphine in patients undergoing CABG surgery was found to provide earlier tracheal extubation, decreased level of sedation, excellent analgesia and improved spirometry in the early postoperative period, compared to a fentanyl-based anaesthesia. Lena and coworkers[32] found a shorter time to extubation after general anaesthesia with remifentanil combined with intrathecal morphine, while Latham *et al.*[33] and Zarate *et al.*[34] were unable to show the superiority to sufentanil. A retrospective study by Djaiani *et al.*[35] compared remifentanil and epidural analgesia with fentanyl, showing no significant difference in terms of extubation and ICU and hospital stay. However, in these studies the combination of general and regional anaesthesia for the surgical interventions may have confounded the results.

High-dose remifentanil (1–5 μg/kg/min), commonly used for cardiac surgery, was associated with muscle rigidity, hypotension, bradycardia, and reduced cardiac output. Steinlechner *et al.*[17] studied the optimal lower remifentanil dose able to suppress hemodynamic responses to stressful stimuli (i.e. intubation, skin incision, and sternotomy) and accompanied by few adverse events. They found that remifentanil at 0.3 and 0.4 μg/kg/min in combination with a target controlled infusion of propofol in the pre-bypass period is well tolerated. It appears to mitigate potentially hazardous hemodynamic responses from stressful stimuli equally well as higher doses when compared with data from the literature. Bauer *et al.*[36] applied remifentanil dose

constant at 0.3 μg/kg/min and used higher target propofol plasma concentration; these dosages completely blunted the release of epinephrine and cortisol during surgery and guaranteed stable hemodynamics. Howie *et al.*[37] compared three remifentanil dose-finding regimens for coronary artery surgery. They found that after lorazepam premedication, remifentanil infusion (2–4 μg/kg/min) supplemented intermittently with low inspired concentrations of isoflurane provided an effective anaesthetic regimen.

In a remifentanil-based anaesthetic regimen, because of the rapid decline of its plasma concentrations, the risk of insufficient postoperative pain control is usually prevented by various techniques, including prolongation of remifentanil infusion with a lower dose, additional epidural analgesia, patient-controlled analgesia, nurse-controlled analgesia or boluses of piritramide.[18,20]

Some authors inquired the overall costs of treatment in the case of fast-track cardiac anaesthesia with remifentanil and it was found that, despite the larger acquisition costs, total hospital costs are not increased.[25,29]

Other studies were not included in this review either because small or published in non-cardiac surgery settings. Overall, remifentanil was safe, associated with signs of deep intra-operative analgesia and anaesthesia such as lower blood pressures and heart rates. On the whole, recovery was faster and times to obeying a command, to extubation, to initiation of spontaneous ventilation and to adequate ventilation seemed to be shorter in remifentanil-treated patients than in other opioid-treated patients.[10]

CARDIAC PERCUTANEOUS AND DIAGNOSTIC PROCEDURES

Advances in interventional cardiology and minimally invasive techniques facilitate a growing number of procedures to be performed outside the operating room environment and offer new challenges for anaesthesiologists. In addition to general anaesthesia, sedation is often performed and presents several advantages: enhances patient cooperation, simplifies the procedure and reduces operating time.[32] Remifentanil shows ideal properties of sedative agents and is becoming as popular as propofol or midazolam in many contexts. Besides continuous infusion, also patient-controlled analgesia and target-controlled infusion as infusion techniques for remifentanil allow many advantages.[38] According to Covello *et al.*,[5] remifentanil and local anaesthesia can be safely used in transcatheter aortic valve implantation, when transfemoral or trans-subclavian approaches are employed. Recently, Ussia *et al.*[39] reported a successful case of percutaneous transcatheter mitral valve repair using conscious sedation with remifentanil (0.08 μg/kg/min) and local anaesthesia in a patient with severe contraindication to general anaesthesia. Remifentanil is often used in combination with propofol or midazolam also for elective cardioversion in atrial fibrillation. In addition, in the case of radio frequency treatment of atrial flutter, Lena *et al.*[40] compared a TCI propofol infusion with a basal infusion plus patient-controlled analgesia of remifentanil finding that both techniques were adequate for the procedure. Moreover, in their view, remifentanil targets controlled infusion or a combination of remifentanil and propofol could further improve pain control.

Transesophageal echocardiography is a relatively less invasive diagnostic procedure, which can cause pain and emotional distress, therefore topical oropharyngeal anaesthesia and mild benzodiazepine sedation are used in the majority of cases. Despite this treatment many patients find the examination uncomfortable and recovery be prolonged. Renna *et al.*[41] assessed the efficacy and safety of an alternative sedation protocol based on remifentanil combined with a very low-dose of midazolam (0.5 mg) and found a significantly reduced median time-to-discharge, with almost all patients ready to "street discharge" within 5 min of removal of the probe. Overall ease and quality of the procedure were significantly better and no effects on respiratory drive were registered. Moreover, the ultra-short action and rapid elimination of remifentanil offer the possibility to treat any side-effect by stopping the infusion.[41]

INTENSIVE CARE UNIT

The vast majority of patients admitted to ICUs receive both analgesic (opioid) and sedative agents to control pain, relieve agitation and anxiety, aid compliance with mechanical ventilation, and hence overall, to help maintain comfort. When administered over several days, the pharmacodynamic effects of conventional opioids such as fentanyl and morphine become unpredictable and are often prolonged as a result of redistribution and accumulation. This may increase the risk of suppressed respiratory drive and potentially delay weaning and extend the duration of mechanical ventilation.[42] Therefore, the rapid offset of the analgesic effect of

remifentanil has generated considerable interest in its use to shorten the duration of mechanical ventilation.

Many clinical trials compared remifentanil to other opioids or sedative agents. A recent meta-analysis by Tan *et al.*[42] examined the benefits of using remifentanil as a sedative agent in critically ill patients. Eleven RCTs comparing remifentanil with another opioid or hypnotic agent in 1067 critically ill adult patients were identified. Remifentanil was associated with a reduction in the time to tracheal extubation after cessation of sedation. Remifentanil was, however, not associated with a significant reduction in mortality, duration of mechanical ventilation, length of ICU stay, and risk of agitation when compared to an alternative sedative or analgesic agent. Despite these evidences, given the pharmacokinetic properties of remifentanil, a potential benefit over the conventional sedative agents should be most apparent in patients with organ failure and therefore should be recommended in this subgroup of patients. Casey *et al.*[43] conducted a RCT to evaluate the role of remifentanil in alleviating pain due to chest drain removal in post-cardiac surgical patients. In fact, multiple methods have been tried unsuccessfully, including non-steroidal anti-inflammatory drugs, opioids, halogenated gases, entonox, local anaesthesia and nonpharmacological methods. They found that a bolus of remifentanil 0.5 μg/kg provides effective and safe analgesia for chest drain removal and may have broader application for similar short and painful procedures. Surprisingly, Payen *et al.*[44] published a large observational study of sedation and analgesia practices in several ICUs in France, and found that among patients receiving opioids, only 10% received remifentanil. Concerns could be linked to the costs of this opioid. However, an economic analysis was performed on a prospective, open-label study of 80 postoperative cardiac surgery patients randomized to remifentanil and propofol versus midazolam and fentanyl for ICU sedation of 12–72 h. The collected economic variables included the cost of drugs, personnel, and adverse events, based on 2003 data. Despite higher costs of study drugs in the remifentanil/propofol group, the total cost of care was not significantly different between the two examined populations. The study shows that these drugs can have economic benefits, given their clinical effects such as less time in the ICU and under mechanical ventilation.[45]

CONCLUSIONS

The unique pharmacokinetic profile of remifentanil justifies its frequent use in many contexts. Drug-related adverse effects seem to be comparable with other opioids even in critically ill patients, thanks to its plasmatic metabolism. In cardiac surgery, many RCTs have shown, that the potential benefits of the use of remifentanil not only include a profound protection against intraoperative stressful stimuli, but also rapid postoperative recovery, early weaning from mechanical ventilation and extubation. However, different anaesthetic regimens and a wide range of remifentanil dosage are administered and, as a consequence, it is difficult to evaluate the effective advantages of its use. The rapid advances in minimally invasive procedures will probably highlight the importance of remifentanil in sedation for interventions even in critical patients. Similarly in ICU, the use of remifentanyl iwll increase, as its properties have been well established.

REFERENCES

1. Panzer O, Moitra V, Sladen RN. Pharmacology of sedative-analgesic agents: Dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. Crit Care Clin 2009;25:451-69.
2. Elliott P, O'Hare R, Bill KM, Phillips AS, Gibson FM, Mirakhur RK. Severe cardiovascular depression with remifentanil. Anesth Analg 2000;91:58-61.
3. DeSouza G, Lewis MC, TerRiet MF. Severe bradycardia after remifentanil. Anesthesiology 1997;87:1019-20.
4. Lehmann A, Boldt J, Zeitler C, Thaler E, Werling C. Total intravenous anesthesia with remifentanil and propofol for implantation of cardioverter-defibrillators in patients with severely reduced left ventricular function. J Cardiothorac Vasc Anesth 1999;13:15-9.
5. Covello RD, Ruggeri L, Landoni G, Guarracino F, Bignami E, Gonfalini M, *et al*. Transcatheter implantation of an aortic valve: Anesthesiological management. Minerva Anestesiol 2010;76:100-8.
6. Wong GT, Huang Z, Ji S, Irwin MG. Remifentanil Reduces the Release of Biochemical Markers of Myocardial Damage After Coronary Artery Bypass Surgery: A Randomized Trial. J Cardiothorac Vasc Anesth 2010;24:790-6.
7. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal. Clin Pharmacokinet 1995;29:80-94.
8. Vankova ME, Weinger MB, Chen DY, Bronson JB, Motis V, Koob GF. Role of central mu, delta-1, and kappa-1 opioid receptors in opioid-induced muscle rigidity in the rat. Anesthesiology 1996;85:574-83.
9. Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. Anesthesiology 1997;87:1070-4.
10. Komatsu R, Turan AM, Orhan-Sungur M, McGuire J, Radke OC, Apfel CC. Remifentanil for general anaesthesia: A systematic review. Anaesthesia 2007;62:1266-80.
11. Lang E, Kapila A, Shlugman D, Hoke JF, Sebel PS, Glass PS. Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 1996;85:721-8.
12. Servin FS. Remifentanil: An update. Curr Opin Anaesthesiol 2003;16:367-72.
13. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, *et al*. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology 2004;100:1353-72.
14. Röpcke H, Könen-Bergmann M, Cuhls M, Bouillon T, Hoeft A. Propofol

and remifentanil pharmacodynamic interaction during orthopedic surgical procedures as measured by effects on bispectral index. J Clin Anesth 2001;13:198-207.
15. Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J. Propofol reduces perioperative remifentanil requirements in a synergistic manner: Response surface modeling of perioperative remifentanil-propofol interactions. Anesthesiology 2003;99:347-59.
16. Johnson KB, Syroid ND, Gupta DK, Manyam SC, Egan TD, Huntington J, *et al*. An evaluation of remifentanil propofol response surfaces for loss of responsiveness, loss of response to surrogates of painful stimuli and laryngoscopy in patients undergoing elective surgery. Anesth Analg 2008;106:471-9.
17. Steinlechner B, Dworschak M, Birkenberg B, Lang T, Schiferer A, Moritz A, *et al*. Low-dose remifentanil to suppress haemodynamic responses to noxious stimuli in cardiac surgery: A dose-finding study. Br J Anaesth 2007;98:598-603.
18. Lison S, Schill M, Conzen P. Fast-track cardiac anesthesia: Efficacy and safety of remifentanil versus sufentanil. J Cardiothorac Vasc Anesth 2007;21:35-40.
19. Myles PS, McIlroy D. Fast-track cardiac anesthesia: Choice of anesthetic agents and techniques. Semin Cardiothorac Vasc Anesth 2005;9:5-16.
20. Lehmann A, Zeitler C, Thaler E, Isgro F, Boldt J. Comparison of two different anesthesia regimens in patients undergoing aortocoronary bypass grafting surgery: Sufentanil-midazolam versus remifentanil-propofol. J Cardiothorac Vasc Anesth 2000;14:416-20.
21. Gerlach K, Uhlig T, Hüppe M, Kraatz E, Saager L, Schmitz A, *et al*. Remifentanil-clonidine-propofol versus sufentanil-propofol anesthesia for coronary artery bypass surgery. J Cardiothorac Vasc Anesth 2002;16:703-8.
22. Guggenberger H, Schroeder TH, Vonthein R, Dieterich HJ, Shernan SK, Eltzschig HK. Remifentanil or sufentanil for coronary surgery: Comparison of postoperative respiratory impairment. Eur J Anaesthesiol 2006;23:832-40.
23. Howie MB, Cheng D, Newman MF, Pierce ET, Hogue C, Hillel Z, *et al*. A randomized double-blinded multicenter comparison of remifentanil versus fentanyl when combined with isoflurane/propofol for early extubation in coronary artery bypass graft surgery. Anesth Analg 2001;92:1084-93.
24. Cheng DC, Newman MF, Duke P, Wong DT, Finegan B, Howie M, *et al*. The efficacy and resource utilization of remifentanil and fentanyl in fast-track coronary artery bypass graft surgery: A prospective randomized, double-blinded controlled, multi-center trial. Anesth Analg 2001;92:1094-102.
25. Myles PS, Hunt JO, Fletcher H, Watts J, Bain D, Silvers A, Buckland MR. Remifentanil, fentanyl, and cardiac surgery: A double-blinded, randomized, controlled trial of costs and outcomes. Anesth Analg 2002;95:805-12.
26. Möllhoff T, Herregods L, Moerman A, Blake D, MacAdams C, Demeyere R, *et al*. Comparative efficacy and safety of remifentanil and fentanyl in 'fast track' coronary artery bypass graft surgery: A randomized, double-blind study. Br J Anaesth 2001;87:718-26.
27. Joo HS, Salasidis GC, Kataoka MT, Mazer CD, Naik VN, Chen RB, *et al*. Comparison of bolus remifentanil versus bolus fentanyl for induction of anesthesia and tracheal intubation in patients with cardiac disease. J Cardiothorac Vasc Anesth 2004;18:263-8.
28. Maddali MM, Kurian E, Fahr J. Extubation time, hemodynamic stability, and postoperative pain control in patients undergoing coronary artery bypass surgery: An evaluation of fentanyl, remifentanil, and nonsteroidal antiinflammatory drugs with propofol for perioperative and postoperative management. J Clin Anesth 2006;18:605-10.
29. Engoren M, Luther G, Fenn-Buderer N. A comparison of fentanyl, sufentanil, and remifentanil for fast-track cardiac anesthesia. Anesth Analg 2001;93:859-64.
30. Ahonen J, Olkkola KT, Verkkala K, Heikkinen L, Järvinen A, Salmenperä M. A comparison of remifentanil and alfentanil for use with propofol in patients undergoing minimally invasive coronary artery bypass surgery. Anesth Analg 2000;90:1269-74.
31. Bowler I, Djaiani G, Abel R, Pugh S, Dunne J, Hall J. A combination of intrathecal morphine and remifentanil anesthesia for fast-track cardiac anesthesia and surgery. J Cardiothorac Vasc Anesth 2002;16:709-14.
32. Lena P, Balarac N, Arnulf JJ, Bigeon JY, Tapia M, Bonnet F. Fast-track coronary artery bypass grafting surgery under general anesthesia with remifentanil and spinal analgesia with morphine and clonidine. J Cardiothorac Vasc Anesth 2005;19:49-53.
33. Latham P, Zarate E, White PF, Bossard R, Shi C, Morse LS, *et al*. Fast-track cardiac anesthesia: A comparison of remifentanil plus intrathecal morphine with sufentanil in a desflurane-based anesthetic. J Cardiothorac Vasc Anesth 2000;14:645-51.
34. Zarate E, Latham P, White PF, Bossard R, Morse L, Douning LK, *et al*. Fast-track cardiac anesthesia: Use of remifentanil combined with intrathecal morphine as an alternative to sufentanil during desflurane anesthesia. Anesth Analg 2000;91:283-7.
35. Djaiani GN, Ali M, Heinrich L, Bruce J, Carroll J, Karski J, *et al*. Ultra-fast-track anesthetic technique facilitates operating room extubation in patients undergoing off-pump coronary revascularization surgery. J Cardiothorac Vasc Anesth 2001;15:152-7.
36. Bauer M, Wilhelm W, Kraemer T, Kreuer S, Brandt A, Adams HA, *et al*. Impact of bispectral index monitoring on stress response and propofol consumption in patients undergoing coronary artery bypass surgery. Anesthesiology 2004;101:1096-104.
37. Howie MB, Michelsen LG, Hug CC Jr, Porembka DT, Jopling MW, Warren SM, *et al*. Comparison of three remifentanil dose-finding regimens for coronary artery surgery. J Cardiothorac Vasc Anesth 2003;17:51-9.
38. Borgeat A, Aguirre J. Sedation and regional anesthesia. Curr Opin Anaesthesiol 2009;22:678-82.
39. Ussia GP, Barbanti M, Tamburino C. Feasibility of percutaneous transcatheter mitral valve repair with the MitraClip system using conscious sedation. Catheter Cardiovasc Interv 2010;75:1137-40.
40. Lena P, Mariottini CJ, Balarac N, Arnulf JJ, Mihoubi A, Martin R. Remifentanil versus propofol for radio frequency treatment of atrial flutter. Can J Anaesth 2006;53:357-62.
41. Renna M, Chung R, Li W, Maguire C, Mullen MJ, Chambers J, *et al*. Remifentanil plus low-dose midazolam for outpatient sedation in transesophageal echocardiography. Int J Cardiol 2009;136:325-9.
42. Tan JA, Ho KM. Use of remifentanil as a sedative agent in critically ill adult patients: A meta-analysis. Anaesthesia 2009;64:1342-52.
43. Casey E, Lane A, Kuriakose D, McGeary S, Hayes N, Phelan D, *et al*. Bolus remifentanil for chest drain removal in ICU: A randomized double-blind comparison of three modes of analgesia in post-cardiac surgical patients. Intensive Care Med 2010;36:1380-5.
44. Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, *et al*. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: A prospective multicenter patient-based study. Anesthesiology 2007;106:687-95.
45. Muellejans B, Matthey T, Scholpp J, Schill M. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: A randomised, open-label, pharmacoeconomic trial. Crit Care 2006;10:R91.

Cite this article as: Ruggeri L, Landoni G, Guarracino F, Scolletta S, Bignami E, Zangrillo A. Remifentanil in critically ill cardiac patient. Ann Card Anaesth 2011;14:6-12.

Source of Support: Nil, **Conflict of Interest:** None declared.