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**Research Article**

# LET'S TALK ABOUT ULTRA FAST TRACK IN OFF PUMP CORONARY ARTERY BYPASS GRAFTING: IS THERE ANY PLACE FOR DESFLURANE AND REMIFENTANIL?

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**A B S T R A C T**

Nowadays, patients undergoing Off-pump Coronary Artery Bypass Grafting (OPCAB) and Minimally Invasive Direct Coronary Artery Bypass (MIDCAB) could be extubated in the operating room (OR) immediately after surgery reducing peri-operative morbidity and costs. This management is defined as "Ultra-Fast-Track"(UTF). The combination of desflurane and remifentanil may be an excellent option for UTF because of their pharmacokinetics properties. Moreover, both drugs provides cardio-protection against ischaemia/reperfusion by Ischemic-Preconditioning (I-Pre) and Ischemic-Post-conditioning (I-Post) mechanisms by activation of Protein Kinase-C (PKC), generation of reactive oxygen species (ROS), uncoupling effects of mitochondrial ATP-sensitive potassium channels ($K^+_{ATP}$), and over-expression of Pim-1 kinase among others, preserving mitochondrial integrity after ischemia/reperfusion via an anti-apoptotic effect and reducing the perioperative levels of necrosis myocardial markers after cardiac surgery.
This review article tries to summarize the cardio-protective mechanisms of desflurane and remifentanil and the advantage of UTF-OPCAB and UTF-MIDCAB in term of reduction of morbility, UCI -length of stay (UCI-LoS) and costs. We also mention the potential benefits of the use of desflurane/remifentanil combination for UTF-OPCAB and MIDCAB due to its pharmacokinetics (Pk) and important cardioprotection properties.



## INTRODUCTION

Early extubation after cardiac surgery, particularly after Off-pump Coronary Artery Bypass Grafting (OPCAB) and Minimally Invasive Direct Coronary Artery Bypass (MIDCAB) has become the goal of many cardiovascular teams as a way to achieve reduction of perioperative morbidity and costs. Fast Track or Ultra-Fast Track (UFT) management are possible when specific surgical modifications and new anaesthetics techniques are combined.

This review article tries to summarize the cardio-protective mechanisms of desflurane and remifentanil and the advantage of UTF-OPCAB and UTF-MIDCAB in term of reduction of morbility, UCI -length of stay (UCI-LoS) and costs. We also mention the potential benefits of the use of desflurane/remifentanil combination for UTF-OPCAB and MIDCAB due to its pharmacokinetics (Pk) and important cardioprotection properties.

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With the development of new anaesthetic techniques and surgical procedures, the "Fast Track" management has increased its use in cardiovascular surgery to reduce perioperative morbidity and costs. This management refers to an extubation 1–6 hours after surgery in order to get shorter length of stay in Intensive Care Unit (ICU-LoS) and allowing early mobilization of patients (1,2). Previous studies have mentioned some factors as possible contraindications for "Fast-Track" extubation, such as obesity, females, excessive bleeding, inotropic support, use of intra-aortic balloon counterpulsation (IABC), hypothermia, prolonged extracorporeal circulation, and prolonged surgery time (3,4). Nowadays, some of these conditions have been considered relative contraindications. Furthermore, patients undergoing Off-pump Coronary Artery Bypass Grafting (OPCAB) could be extubated much earlier, in the operating room (OR) immediately after surgery without major complications. This anaesthetic technique is defined as "Ultra-Fast-Track"(UFT) (5-8). UFT was originally designed for low-risk patients. However, today this technique has become the goal of many cardiovascular teams even in high-risk patients undergoing cardiac surgery (9).

Many publications have described a direct relationship between UFT extubation and reduction in the use of sedatives and analgesic agents as well as a reduction of intravenous fluids, inotropic agents, vasopressors, and anti-arrhythmic in the ICU (1,10).

The UFT management has sparked controversy in some anaesthesiology and ICU departments because its still infrequently practiced in the field of myocardial revascularization surgery. However, some authors report that immediate extubation in the OR just after cardiac surgery is possible and safe, describing many benefits in comparison with later extubation (5,6,7).

Invariably, a larger proportion of patients who undergo elective or emergency cardiac surgery has high-risk factors. Safer procedures and advances in anaesthetic/surgical techniques for cardiovascular surgery have situated UFT management as an alternative, not just for young patients with low risk but also for elderly patients with high risk (11). UTF protocols could reduce ICU-LoS and Hospital length of stay (Hosp-LoS) with lower costs (7).

When comparing conventional vs. Fast Track protocols, there is still some controversy about how high-risk patients should be managed to reduce postoperative complications and mortality (12). Nonetheless, it is important to keep considering that conventional intensive care management after heart surgery includes prolonged pulmonary ventilation and different levels of sedation leading to a delay in beginning active movement, and therefore delaying the recovery (10,13).Of course, there are some predictive factors that would make necessary prolonged postoperative mechanical ventilation(MV), and we should recognize them (14). However, most of the time, there are not practical benefits of prolonging MV in patients after CABG or OPCAB with low and moderate cardiovascular risk(2,15). We think that Off-pump management with normothermia, and the use of tranexamic acid following original doses recommended by Harrow *et al*. (16) with a meticulous surgical technique (17,18) strongly contributed to reduce postoperative bleeding without important increment of ischemic coronary, stroke, and thromboembolic events (19).We agree with Scott B.H *et al*. 2005 who found that prolongation of Hosp-LoS is in fact, a function of bleeding with needing of transfusions (13).

For UTF-OPCAB anaesthetic management, we think the following aspects are paramount: A proper selection of drugs to use during the perioperative management, the maintenance of normothermia (20,21); keeping hemodynamic stability by proper fluid intravenous administration, vasopressor drugs, and Trendelenburg position in addition to early detection of any cardiac issue by Trans-oesophageal-echocardiography (TEE) monitoring. Finally, the cornerstone of UTF is to provide an excellent level of multimodal perioperative analgesia including regional analgesia with local anesthesia (LA) which has a strong recommendation and high-quality evidence for Off-pump Minimally Invasive Direct Coronary Artery Bypass (MIDCAB) , and OPCAB according to American Pain Society Guidelines (22).

Despite the fact of reliability of intraoperative TEE monitoring of left ventricular segmental wall motion during OPCAB surgery has been questioned, TEE is still an excellent, integral, minimally invasive, and convenient means (23). However, the greatest utility of TEE during the intraoperative time comes after the reperfusion (24). It is well established that detection of persistent cardiac regional wall motion abnormalities (RWMA) are associated with postoperative cardiac RWMA, higher cardiac enzyme levels, and more clinical problems. Such persistent RWMA after revascularization could lead the surgeon to re-evaluate the patency of the coronary bypass graft helping to reduce the rate of PO angina pectoris or MI (23).

***Remifentanil: An opiod with cardio-protection effects which maybe useful in UFT***

Conventional anaesthetic techniques incorporate high doses of opioids such as fentanil, alfentanil and sufentanil to reduce intraoperative oxidative stress and sympathetic-adrenergic stimulation (25). Conventional management is associated particularly with more than three to six hours of MV, a higher requirement of endovenous fluids or vasopressors, and more than 24 hrs of ICU-LoS. Prolonged time to extubate patients often is deleterious to early recovery, delays hospital discharge, and could be associated with poor outcome according to many medical publications (26).

The use of remifentanil (a very short acting opioid-esterase metabolism depending, non-hepatic/renal depending excretion way) with a very rapid context-sensitive half-life time has shifted the traditional intermediate acting opioids and permits to handle the intraoperative time for UTF management allowing profound analgesia during surgery time without prolongation of respiratory depression, providing reduction of oxidative stress and giving a very fast awakenings. Remifentanil is very titrable and has similar hemodynamic stability profile than intermediate opioids; of course, if it is used with the recommended doses (0.15-0.3 μg/Kg/min) (27, 28). Although remifentanil has an excellent pharmacokinetic (Pk) profile for UTF, there is some controversy regarding the use of remifentanil due to the possible appearance of early opioid-induced hyperalgesia (remifentanil opioid analgesic effect entirely stops acting in about 15 minutes), and many anaesthesiologists are still discouraged to use it. In order to avoid any hyperalgesic events, it is essential to establish from the beginning, a multimodal analgesic plan, even considering the low-dose use of NMDA-receptor blocker, such as ketamine (26, 29-33).

As we are aware of the advantages and disadvantages of remifentanil, UFT-OPCAB protocols must include the use of LA: wound infiltration by surgeons or placement of a multi-perforated catheter into the intercostal or paravertebral space for MIDCAB to use postoperative bupivacaine or ropivacaine infusion (for 36-48 hrs PO). When OPCAB is performed by medial sternotomy approach (no by left thoracotomy), is appropriate to use regional analgesia by parasternals infiltration with LA or leave wound multi-perforated catheters for post-operative infusion of bupivacaine or ropivacaine. Adding to regional analgesia, an "around the clock" prescription of NSAIDs(parecoxib or dexketoprofen), paracetamol and Morphine SOS/rescue by PCA represent an effective method of PO pain management that convey to a decrease of complications as consequence of the use of high doses of intermediate opioids and sedatives in the postoperative period (26,34).

Moreover, remifentanil has a crucial non-Pk property: Remifentanil provides cardioprotection against ischemia-reperfusion by Ischemic-Preconditioning (I-Pre) and Ischemic-Postconditioning (I-Post) mechanisms via κ and δ opioid

receptors and activation of Protein Kinase-C (PKC), generation of reactive oxygen species (ROS), uncoupling effects of mitochondrial ATP-sensitive potassium channels ($K^+_{ATP}$), activation of tyrosine kinase and phosphatidyl-inositol-3-kinase(PI3-K), glycogen synthase kinase 3β (GSK3β), mitochondrial permeability transition pore (MPTP) among others, reducing the perioperative levels of necrosis myocardial markers after cardiac surgery (Troponin-I, CK-MB, ischemic-modified-albumin, and fatty-acids/cardio-protein-complex)(35-40). Additionally, remifentanil also provides antiarrhythmic effects (41) that could counteract any potential or hypothetic increase of heart rate because of using of desflurane (dose depending effect) in comparison with sevoflurane (42).

***Desflurane: Pharmacologically suitable for UFT with very good cardio-protection properties***

On the other hand, desflurane is a volatile anaesthetic agent that has a very low blood-oil/gas partition coefficient and low solubility, so that it is very titrable due to an ultra-rapid uptake (starts to act very fast), very rapid output and excretion without any important metabolism. These Pk properties situate desflurane as an excellent option to combine with remifentanil for UTF management. Moreover, as other volatile agents, desflurane also provides cardioprotection effects against ischaemia reperfusion injury (IRI) (43) even better than sevoflurane (44). This volatile anaesthetic and its property to induce I-Post have been studied in detail, confirming the role of reactive oxygen species generation (ROS), the activation of the cellular signaling pathways, and the actions on mitochondrial $K^+_{ATP}$-channels, along actions documented in humans. The main receptor involved in cardio-protection includes a receptor coupled to G-proteins. These G-protein activate different intracellular effectors in the cell membrane or cytosol. These effectors can modulate the intracellular second messengers, such as 3′-5′-cyclic adenosine monophosphate (cAMP), inositol triphosphate (IP3), calcium and diacylglycerols. Moreover, the contribution of beta-adrenergic receptors (via protein-kinase-A and calcium/calmodulin-dependent protein kinase modulation) in desflurane-induced I-Post was demonstrated by Lange *et al*. (45), who showed that co-administration of esmolol with desflurane during the initial reperfusion blocked desflurane-induced I-Post. Other studies also suggest that desflurane I-Pre is mediated by activation and nuclear translocation of STAT3 (nuclear transcription factor signal transducer and activator of transcription 3) and Pim-1 kinase. Pim-1K reduces infarct size in cardiomyocytes and is regulated by STAT3. Desflurane reduced cytosolic content and enhanced the nuclear content of phospho-STAT$Ser^{727}$, and after 48h of ischemia, desflurane enhanced Pim-1 activity (46).

Several studies provided evidence of the profound cardioprotective properties of Pim-1 kinase either in vivo or in vitro. Over-expression of Pim-1 kinase has been shown to reduce myocardial infarct size and to preserve mitochondrial integrity after ischaemia/reperfusion via an anti-apoptotic effect (47-50). Also, it has been demonstrated to influence the role of the JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription 3) pathway in the intracellular signaling cascade of late desflurane-induced I-Pre. The JAK/STAT pathway is a well-known mediator of late ischaemic preconditioning (51-52).

The activation of the JAK/STAT cascade leads to nuclear translocation and transcription of genes for reported cardio-protective proteins such as cyclooxagenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (53,54,55). The majority of studies about cardio-protective effects of volatile agents has been done in patients undergoing CABG. There is not sufficient evidence that supports any advantages in terms of cardio-protection using volatile agents in patients undergoing valvular surgery without ischemic coronary disease (56, 57).

The safety of the ICU discharge over the the first postoperative 24 hs in patients undergoing CABG or OPCAB has been previously described (58). Many ICUs have reported that UFT has not been associated with an increased incidence of readmission to ICU or hospital readmission (2). Different authors mention that the age is not a limiting factor to use the UFT protocol in CABG (59), but its important to keep in mind that age >75 alongside female gender could be factors related to longer ICU-LoS and Hosp-LoS. However, bleeding requiring transfusion apparently is the stronger cause of failed extubation in OR and prolongation of Hospital-LoS.

The use of volatile agents (desflurane or sevoflurane) results in decreased morbidity and mortality in CABG due to their cardio-protective effects. The choice of an anaesthetic regimen based on the administration of these halogenated anaesthetics is associated with a better outcomes after CABG (60,61).

We think that the anaesthetic combination of desflurane plus remifentanil, (both with cardio-protection effects against ischemic reperfusion injury) (35,60) a meticulous intraoperative care with a very convenient surgical approach (OPCAB,MICAB) along with proper planned multimodal analgesia, nerve blocks, wound infiltration with LA and UTF management can contributed to better outcomes. Extubation in OR is especially achievable when OPCAB is used, as it decreases operating time and avoids important pathophysiological changes usually induced by CPB (9, 62, 63).

***Non-Touch Aortic Techniques and UFT***

It is very important to try to avoid proximal grafts anastomosis over ascending aorta in patients with an advanced calcified atheromatous disease because an aortic side-bite partial clamp can generate embolism responsible for the majority of PO neurological dysfunction. This topic is more important whether the surgery is done under CPB or Off-Pump. Moreover, OPCAB with non-touch aortic technique especially in elderly patients with advanced atherosclerotic disease (using combined grafts in "Y" LIMA/SV, LIMA/RA or with RIMA or gastro-epiploic artery bypass graft for very infero-posterior areas) places together the benefits of avoiding the deleterious effects of CPB and the reduction of cerebral embolism risk, leading to a decrease of neurological postoperative dysfunction incidence and stroke. (11).

***UFT could reduce cost but needs multidisciplinary consensus***

UFT is focused on providing a rapid postoperative period by extubation in the OR supported by a consensus on critical care (64) and earlier discharge from ICU; data that match with many studies (65,66).

A representative case-series study showed shorter ICU-LoS and Hosp-LoS when the Fast Track technique was applied.

They had a 53% reduction in ICU costs and a 25% saving in surgical expenses, unlike the traditional late extubation management. Total savings of about 13% in hospital costs were achieved (13).We agree with London, M *et al*. (59), who recognize that both "Fast-Track" and "Ultra- Fast-Track" management are not precise definitions, but in fact, these represents a change in methods that are now used in many surgical groups and cardiac and intensive care units. We also agree that its essential to have continuous communication between all members of the multidisciplinary team; it is really the key to success.

There is still some controversy about the consistent advantage of OPCAB vs. CABG under CPB as well as controversy about the efficacy and long-term outcome between both techniques (67-71).

UFT management is feasible to be used in low, moderate, and some selected high-risk cardiovascular surgical patients, and it produces excellent results regarding short-term morbidity and mortality in patients undergoing OPCAB or MICAB. This management allows very rapid recovery, a short ICU-LoS, and Hosp-LoS, offering the possibility of cost reduction; this fact could permit us to help a vast number of cardiac patients and is practical and realistic in a rural environment (72).

Finally, It is important to remember: the use of transfusion is significantly correlated with failure of UTF management, increased ICU-LoS, increases costs and it is strongly associated with prolongation of hospital length of stay.

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