

OPCAB

The Secrets of the Beating Heart

S Moodley

Moderator: R Naidoo



**UNIVERSITY OF
KWAZULU-NATAL**

**INYUVESI
YAKWAZULU-NATALI**

**School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care**

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INTRODUCTION

Off-Pump Coronary Artery Bypass (OPCAB) has been shown interest over the past 20 years, in an attempt to avoid the complications associated with Cardio-Pulmonary Bypass. Initially, OPCAB was thought to be superior to CABG with CPB, but currently, it has been shown to offer equivalent outcomes in experienced hands. It is the technique of choice in many large high-volume centres, and is definitely a procedure which every anaesthetist should be knowledgeable about.

HISTORY OF OPCAB

OPCAB was the only option prior to the widespread use of CPB in the 1960's. The improvement in CPB (better circuits and pumps, and oxygenators improved from bubble to membrane) made CABG with CPB the preferable and more reproducible technique. During the 1980's, OPCAB made a come-back for the purpose of avoiding the issues with CPB, aortic clamping, cardioplegia arrest and haemodilution, as well as to facilitate cardiac surgery in centres with limited resources.

Of recent, the avoidance of CPB is primarily due to attempts to avoid the complications of CPB in high-risk patients. CPB has been associated with many adverse outcomes in the past, including neurological deficits (stroke, post-operative neurocognitive dysfunction, coma), renal dysfunction, and Systemic Inflammatory Response Syndrome (SIRS).⁽¹⁾ SIRS is characterised by generalised inflammation after a morbid event (e.g. trauma, inflammation and surgery).

The contact of blood to non-physiological surfaces in Cardio-Pulmonary Bypass circuits, together with ischaemia of the myocardium, reperfusion and hypothermia lead to cytokine release.⁽¹⁾ A few trials have used S100 b as a marker for brain injury, and have shown a correlation with increased levels and the amount of microemboli exiting the pump (but they have failed to show decreased neurocognitive function declines after 1 week when compared to OPCAB).⁽¹⁾ As a result of surgical technique improvement and the development of cardiac stabilising retractors, OPCAB has become an established procedure.

TECHNIQUES OF CORONARY ARTERY REVASCULARIZATION

The principle of coronary artery revascularization is to graft all vessels with flow-reducing lesions on the anterior, lateral and/or inferior surface of the heart.

Risk stratification systems used by surgeons include STS score (USA) and the EURO score (Europe and South Africa).

With CPB

- Conventional CABG (CPB and ischaemic cardioplegic arrest)
- CABG with CPB (beating heart or bypass assisted)

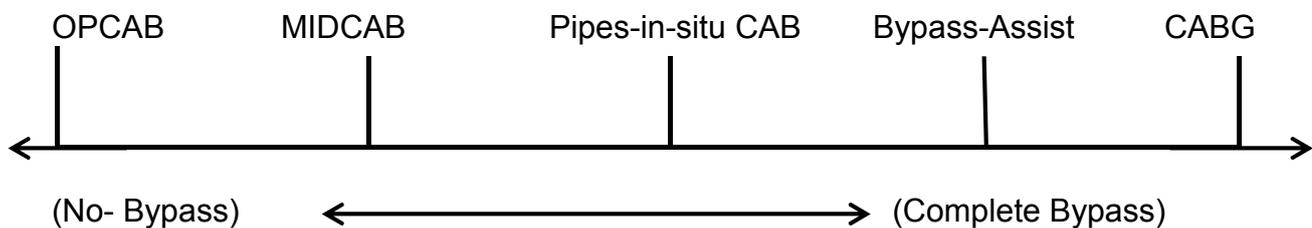
Without CPB

- OPCAB
- MIDCAB
- Robotic assisted MIDCAB
- Robotic assisted TECAB (total endoscopic)

Minimally Invasive Direct Coronary Artery Bypass (MIDCAB): Minimally Invasive Direct - Access Coronary Artery Bypass

- With this technique, the left Internal Mammary Artery (LIMA) is anastomosed to the Left Anterior Descending Coronary Artery (LAD) via a small anterior thoracotomy incision. ⁽²⁾ This technique is not favoured to its limitation of only single vessel surgery. Patients are required to be carefully selected and to have favourable coronary anatomy. ⁽³⁾ Also, this technique can be demanding and may lead to sub-optimal results. ⁽²⁾ and pain post-thoracotomy was found to be more painful than post-sternotomy. ⁽⁴⁾

Off-Pump Coronary Artery Bypass Grafting (OPCAB): The second technique allows for the grafting of multiple vessels, without CPB. A standard median sternotomy approach is used, allowing for access to all coronary vessels. This technique has led to an improvement in graft patency as opposed to MIDCAB. ⁽⁵⁾



OPCAB AND ITS ISSUES INTRA-OP

As the surgeon, issues regarding obtaining adequate exposure of the surgical site and ensuring maximum myocardial protection, whilst doing so, are faced. The anaesthetist is faced with issues regarding the consequences of the surgeon manipulating the myocardium and the chambers. Surgical manipulation of the heart can result in episodes of myocardial ischemia, alterations of haemodynamics, and episodes of cardiac pump decline.

Haemodynamic Changes during OPCAB

Manipulation of the beating heart during OPCAB may lead to a variety of changes in pressures within the chambers and vessels. These changes are a result of either compression or suctioning, and largely depend on the site of anastomosis. Surgery on the LAD is easily accessible through a median sternotomy. However, with regards to vessels in the lateral and posterior wall of the heart, it requires lifting and tilting of heart out of the pericardial cavity.

Upon tilting of heart in a vertical position, the ventricles are now situated above the atria. Blood is required to now flow upwards, into the ventricle. This results in pressures within the atria increasing, (much more to corresponding ventricle pressure increase). Therefore, end-diastolic pressures are required to be maintained at higher than normal levels in order to compensate⁽²⁾.

Another cause of haemodynamic instability in OPCAB is the use of stabilization devices which minimise motion in the area of anastomosis. Its position can affect cardiac output tremendously. The anterior and lateral walls have a larger contribution to stroke volume, in comparison to the septal and posterior-inferior walls; hence the greatest haemodynamic disturbances are seen during circumflex artery anastomosis as lateral wall exposure is required.



Medtronic Starfish® 2

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Evolution

Heart Positioner

Tissue Stabilizer

Heart Positioner

Also, distortion of the mitral and tricuspid valves secondary to the vertical positioning of the heart, can lead to significant mitral and tricuspid regurgitation. Surgical technique specifically, and the choice thereof, can also influence the haemodynamic changes seen in OPCAB. Two techniques have been identified. The first involves the displacement of heart and “heart-rocking” by a tissue suction stabilizer device, which results in compression of the right ventricle between the pericardium and the left ventricle. On TOE, what may be seen is the bulging of the inter-atrial septum, with the left ventricle showing no dilatation, and a small part of the compressed right atrium with right outflow obstruction⁽²⁾.

Circulation and coronary blood flow can be improved by Trendelenburg position; however, this leads to increased RV and LV preload, and an increased heart rate.

The second technique involves heart enucleation by aspiration of the apex with a suction device, or lifting of the pericardium using stitches. There is a short-lasting decrease in cardiac output only when the heart is manoeuvred for pericardial stitch insertion.

In summary, haemodynamic changes and their extent depend largely on the site of anastomosis. Good communication between the surgeon and anaesthetist is mandatory in order to ensure minimal haemodynamic changes and efficient pressure adjustments.

Myocardial Ischaemia

Episodes of ischaemia are manifested by ST-elevation when the coronary artery is clamped in order to allow for an optimal surgical field. New RWMA are also seen on echo during these episodes. The degree of ischaemia largely depends on which artery is being anastomosed and the extent of stenosis. Occluding highly collateralised vessels produces less ischaemia than occluding “terminal” vessels. Also, occlusion of vessels with a higher degree of stenosis produces less ischaemia, compared to vessels with a lesser degree of stenosis. Hence, recommendations include beginning with the anastomoses of vessels which are highly stenosed.

Dysrhythmias

Dysrhythmias are commonly seen during OPCAB with manipulation of the heart and vessel occlusion. RCA occlusion, especially if it is not highly stenosed, can result in severe arrhythmias (e.g. complete AV block) secondary to decreased blood flow to the AV node artery.

ANAESTHETIC TECHNIQUE/IMPLICATIONS

OPCAB poses a great challenge to anaesthetists due to its haemodynamic and ischaemic issues. More involvement of the anaesthetist is required, in comparison to CPB, where responsibility is shared with the perfusionist. The anaesthetist is required to be alert and proactive in maintaining adequate haemodynamics and preventing ischaemia. The surgical procedure should be observed carefully, and good communication between surgeon and anaesthetist is mandatory.

Pre-operative

A complete history from the patient and a full physical examination is mandatory. Special attention should be paid to the class of angina and effort tolerance of the patient, as this indicates the allowable level of fluctuations of the haemodynamics intraoperatively. Good communication between surgeon and anaesthetist is essential in order to allow for the charting of the anaesthetic plan. Adequate medication, pre-operatively, may be prescribed in order to avoid tachycardia, which should be avoided in order to not affect the oxygen supply-demand balance. Clopidogrel should be stopped at least 1 week before surgery.

Intra-operative

Monitors

Standard monitors including pulse oximetry, central venous pressure monitoring, invasive arterial blood pressure monitoring, core and peripheral temperatures and urine output measurement should be mandatory, as in any other cardiac surgery. A 5-lead ECG can also be used, but results may be influenced by the changing position of the heart during surgical manipulation.

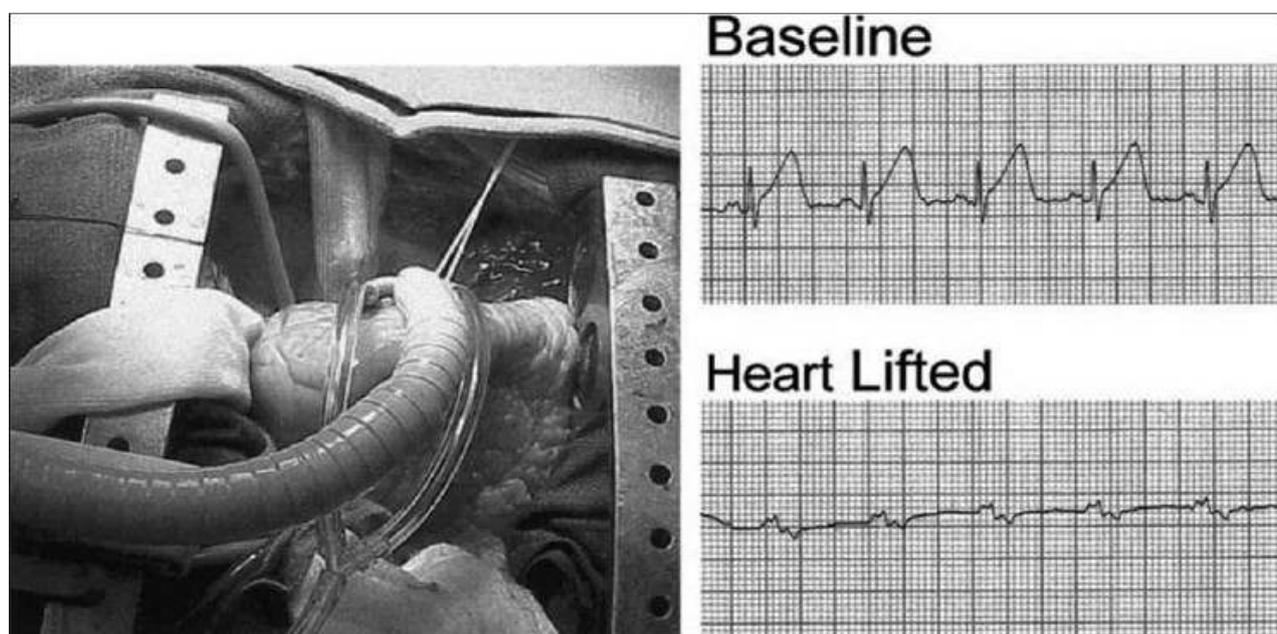


Figure 1: A reduction in ECG voltages with "Heart tilting")⁽⁶⁾

The TOE provides detailed information about left and right ventricular function, regional wall motion, the function of the heart valves, and the overall performance of the heart. A complete TOE examination can be done at the beginning of the surgery to establish a baseline.⁽⁶⁾ TOE allows for the evaluation of the effectiveness of manoeuvres such as Trendelenburg position or pleural incision in the management of hypotension.⁽⁶⁾ TOE may facilitate the detection of worsening cardiac function as evidenced by the weakening of the contraction of the myocardium, the dilation of the ventricles, or increasing mitral/tricuspid regurgitation during the occlusion of the coronary arteries⁽⁶⁾. New segmental wall motion abnormalities are excellent indicators of intraoperative ischemia of the myocardium.⁽⁷⁾ The quality of images of TOE during coronary artery bypass construction may be affected by the use of posterior swabs, changes in heart positions, and air in the pericardial cavity.

Central venous pressure (CVP) can be used as proxy measures of changes in jugular bulb oxygen saturation (SjO₂).⁽⁶⁾ The desaturation of SjO₂ is used as a predictor of possible cognitive dysfunction post-operatively, due to the global cerebral oxygen balance being affected.⁽⁶⁾ However, it is important to note that routine SjO₂ monitoring is invasive and expensive. A CVP measurement of ≥ 8 mmHg, SvO₂ $\leq 70\%$, and PaCO₂ ≥ 40 mmHg are associated with jugular bulb desaturation (SjO₂ $\leq 50\%$) during OPCAB surgery. ⁽⁶⁾ The CVP can also supplement the ECG with rhythm diagnosis e.g. absent 'a' wave in atrial fibrillation and cannon 'a' waves in junctional rhythm. (8)

PAC use is also controversial in OPCAB. Mixed venous oxygen saturation can be measured if the PAC has an incorporated oximetry and can assist in providing information about oxygen delivery and tissue oxygen extraction and consumption. The BIS monitor has also been suggested to assist in hypoperfusion of the cerebrum during OPCAB. ACT is most commonly used for coagulation monitoring. However, there is no standardized ACT target value for OPCAB: an ACT value of approximately 300sec is accepted by +/- 80% of US/Canadian surgeons and +/- 60% of European surgeons.⁽⁹⁾ During awake OPCAB, there seems to be less pro-coagulant activity than in OPCAB with GA.⁽¹⁰⁾

Anaesthesia Options

The main objective is to maintain haemodynamic stability, to maximise cardiac protection, to maintain stability of cardiac rhythm, and to promote early ambulation together with optimal intra- and post-operative analgesia.⁽¹¹⁾

The aims for fast-track anaesthesia are:

- Extubation between 0=6hrs post-op
- Decreased length of stay in ICU/hospital
- Improved outcome
- Subsequent reduction in health care cost.....⁽¹²⁾

In OPCAB, the following approaches can be considered:

1. General Anaesthesia with the use of opioids and inhalational agents or Total Intravenous Anaesthesia (TIVA)
2. Combined General Anaesthesia with controlled ventilation and neural blockade using high Thoracic Epidural Analgesia (TEA) or Intrathecal Morphine (ITM)
3. Awake Regional Anaesthesia with spontaneous ventilation using TEA alone

With regards to General Anaesthesia alone, the use of volatile agents offers the advantages of pharmacological ischaemic preconditioning. Propofol has shown to not have cardio-protective effects.⁽¹³⁾ With regards to muscle relaxants, the use of long-acting agents may be associated with delayed recovery and hence, delayed tracheal Extubation. In order to facilitate fast-track surgery, rocuronium and cisatracurium are recommended.⁽¹⁴⁾

High doses of long-acting opioids should be avoided as use may lead to prolonged respiratory depression mandating ventilator support, hypotension resulting in myocardial ischaemia and infarction, and delayed bowel movement post-op. Remifentanil, Fentanyl and Sufentanil provide excellent haemodynamic stability and allow for rapid Extubation, making them suitable for fast-track anaesthesia. Intra- and post-operative use of opioids can be reduced by using Dexmedetomidine during OPCAB surgery. Its use leads to improved haemodynamic stability, as well as antiemetic effects.

General Anaesthesia with high Thoracic Epidural Analgesia provides better analgesia, improved pulmonary outcome, a decrease in peri-operative morbidity and mortality, a decrease in Extubation time, and a shorter hospital stay, as compared to General Anaesthesia alone.⁽⁶⁾ High TEA decreases the risk of haemodynamic instability, decreases the oxygen demand of the myocardium, improves renal function, improves the perfusion of the coronary and mammary arteries by providing thoracic sympatholysis, and attenuates neuro-hormonal response.⁽⁶⁾

The insertion of TEA 1 day before surgery or up to 1 hour before heparin is administered, may reduce the likelihood of haematoma formation, however, minimum safe-time waiting period between epidural catheter insertion and heparinisation has not yet been proven.⁽¹⁵⁾ The patient requires a thorough assessment of his/her coagulation status, and surgery should be postponed in the event of a wet tap.⁽⁶⁾ Timing of catheter removal must be coordinated with anticoagulation therapy and the patient MUST be monitored up to 12hrs after catheter removal.

Intra-thecal Morphine requires the use of low doses of morphine, which does not provide adequate analgesia, hence, this technique requires the use of intravenous opioid infusions as well (e.g. Remifentanil and Fentanyl). The effectiveness of this technique and the optimal morphine dose required to provide adequate analgesia with minimal respiratory depression still needs to be investigated. Awake OPCAB with combined TEA + femoral block⁽¹⁶⁾, or TEA + spinal anaesthesia⁽¹⁷⁾, or TEA alone with local anaesthetic infiltration to facilitate the harvesting of the vessel graft is a promising modality. It is definitely feasible but should be performed by a highly experienced, specialized health care team in selected patients. It is definitely a modality that requires further studies in order to determine its role in cardiac anaesthesia.

Temperature Control

Temperature management in OPCAB patients can be challenging due to the lack of heat exchangers provided by Cardio-Pulmonary Bypass Also the exposure of the open thorax and the extremities increase the rate of heat loss. Fluid warming and air-warming blankets are useful tools in maintaining temperature haemostasis.⁽¹⁸⁾

Haemodynamic Maintenance

The haemodynamic changes that occur during heart manipulation can be reduced by:

- Trendelenburg position (to 20° head-down), which increases the preload and improves the cardiac output
- Inotropes and/or vasopressors
- Cautious fluid management
- α-adrenergic agonists- useful when peripheral resistance is low resulting in low a Mean Arterial Pressure (MAP)

If hypotension persists, myocardial ischaemia should be investigated by observing ST segments and by looking out for new Regional Wall Motion Abnormalities (RWMA) by TOE.

It is important to note that patients with left ventricular dysfunction can be expected to not tolerate hypotensive episodes; hence efforts must be made to prevent haemodynamic instability as far as possible. These patients may warrant placement of an intra-aortic balloon pump, which manages hypotension by counterpulsation. “Pre- and perioperative IABC therapy offers efficient hemodynamic support during high-risk OPCAB surgery, lowers the risk of hemodynamic instability, is safe and shortens both ICU and hospital length of stay significantly, and is a cost-effective therapy.”⁽¹⁹⁾ If hypotension persists and is unresponsive, or malignant arrhythmias or new RWMA develop, conversion to Cardio-Pulmonary Bypass should occur.

On the other side of the spectrum, high systolic pressures can predispose to aortic dissection during the anastomosis of proximal grafts. Volatiles, intravenous anaesthetic agents and intravenous nitroglycerine are options for reducing blood pressure in these circumstances. In the earlier decades, induced- bradycardia was practised in order to allow for a more optimal surgical environment. However, the development of stabilizing devices has negated this practice.

Myocardial Ischaemia Management

The temporary occlusion of the target coronary vessel to ensure a bloodless surgical field can result in ischaemic injury. A Mean Arterial Pressure of >70mmHg allows for adequate perfusion. Careful fluid loading, Trendelenburg positioning, and inotrope and/or vasopressor use are useful options to consider. The heart rate should be maintained between 70 and 80 bpm. Tachycardia needs to be avoided in order to prevent increased oxygen consumption which will inadvertently affect coronary oxygen supply-demand balance. It can be treated with Esmolol or Diltiazem.

Dysrhythmias can occur during manipulation and positioning of the heart, and need to be watched out for. Antiarrhythmic prophylaxis may also be considered, with Lidocaine and Magnesium both being options. The prophylactic use of β-Blockers decreases the incidence of Atrial Fibrillation post-op. A shunt can be inserted into the coronary artery by the surgeon in order to maintain perfusion to the myocardium, preventing left ventricular function deterioration, and stabilizing of haemodynamics.

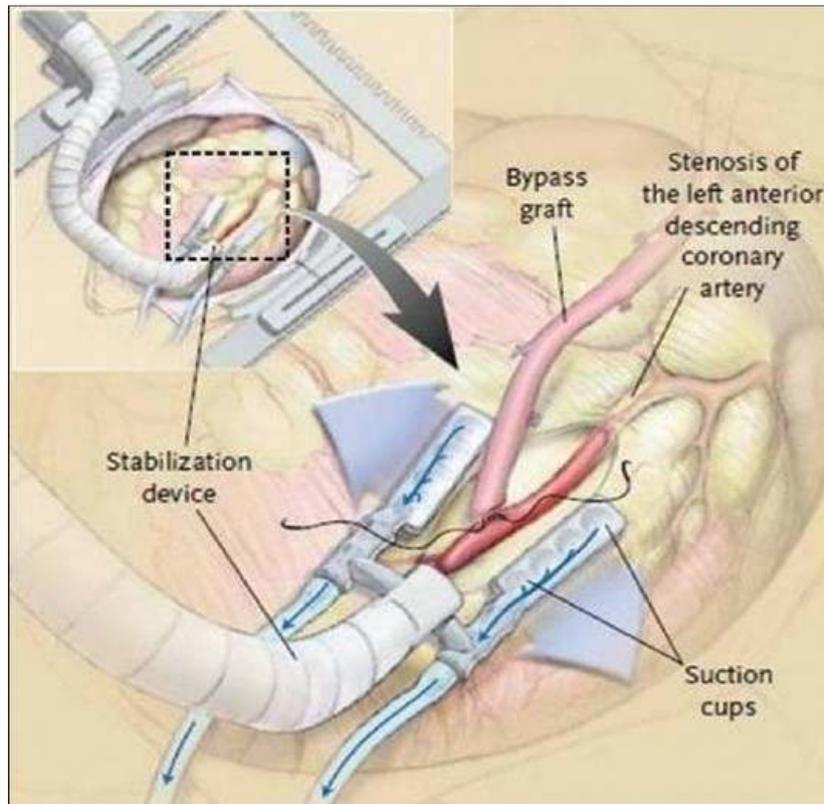


Figure 2: Coronary artery bypass graft and stabilization device⁽⁶⁾

Another option is ischaemic preconditioning, which refers to the brief ischemic insults to the myocardium administered by the surgeon, resulting in the myocardium being “trained” to rapidly adapt, hence decreases the rate of cell death during subsequent ischaemic periods. Ischaemic precondition enhances the performance of the myocardium and suppresses arrhythmias. It is elicited by short periods of occlusion of the coronary vessels by the surgeon.

Reperfusion

Upon reperfusion, ischaemic changes seen on the ECG tend to disappear. Post-revascularisation, T-wave inversion and new Region Wall Motion Abnormalities are frequently seen. It becomes significant when the new severe RWMA persist. This has significant prognostic value for post-operative complications and adverse outcomes.⁽⁶⁾ Electrolytes must be closely monitored, especially potassium and magnesium levels, in order to avoid arrhythmias secondary to perfusion. Correct Protamine dosage must be calculated and administered. Graft patency, thereafter, can be assessed by angiography or U/S Doppler.

Post-operative

Extubation and ICU

Early Extubation should be targeted unless contra-indicated. Immediate Extubation (Ultra-Fasttrack Anaesthesia) requires a fully reversed, normothermic, normovolaemic, stable, pain-free, alert patient at the end of surgery

OPCAB vs. CPB- THE CONTROVERSIES, AND ATTEMPTS TO CLEAR THEM UP

The use of CPB with aortic cross-clamping and cardioplegic arrest was the gold standard for patients requiring myocardial revascularisation for more than 30 years. However, the current era is of evidence-based medicine, in order to avoid the complications of CPB, OPCAB has become a recognised procedure. The issues with CPB include SIRS (Systemic Inflammatory Response Syndrome), fibrinolysis, coagulopathies, excessive clotting factor consumption, platelet dysfunction, renal impairment and atrial fibrillation. Over the last decade, three large trials were carried out: ROOBY⁽²⁰⁾, CORONARY⁽²¹⁾, GOPCABE⁽²²⁾: all which provided significant information, yet all with their own flaws.

The Randomised On/Off Bypass (ROOBY) trial included 2203 patients from the “Veteran Affairs Medical System”. It showed no significant difference with regards to major complications and mortality between OPCAB and CPB patients in the first 30 days (7% vs. 5.6%, P=0.19).⁽²⁰⁾ However, at 1 year, the OPCAB patients group showed an increased mortality, myocardial infarction and revascularisation (9.9% vs. 7.4%, P=0.04).⁽²⁰⁾ The CORONARY trial included 4752 patients from 79 centres in 19 countries. It reported no difference between OPCAB and CPB with regards to mortality, myocardial infarction, stroke, or new dialysis at 30 days.⁽²¹⁾ It did, however, show a decreased need for blood transfusion in the OPCAB group.⁽²¹⁾

The follow up after one year showed similar results when comparing OPCAB to CPB with the 30-day findings with regards to mortality, myocardial ischaemia, stroke and new dialysis. (12.1% vs. 13.3%, P=0.24).⁽²³⁾ Quality of life and neurocognitive outcomes were similar in both groups of patients. However, there was an increased incidence of repeat revascularisation after 1 year (1.4% vs. 0.8%, P=0.07).⁽²³⁾ GOPCABE assessed the likelihood of elderly patients benefitting from PCAB as opposed to CPB. 2539 patients, 75 years of age and older, were randomly assigned to both OPCAB and on-pump CABG.⁽²²⁾ As shown in the CORONARY trial, there was no increase in mortality, stroke and myocardial infarction at 30 days (7.8% vs. 8.2%, P=0.74) or at 1 year (13.1% vs. 14.0%, P=0.48).⁽²²⁾ The trial showed decreased transfusion requirements and increased repeat revascularisations in OPCAB.⁽²²⁾

Overall, outcomes were shown to be similar between OPCAB and CPB. The lack of experience with OPCAB by the surgeons may have influenced the negative 1-year outcomes in the ROOBY trial. Also, 3282 patients were excluded from the ROOBY trial due being “high risk”. The ROOBY trial patient group consisted of predominantly male patients, and patients who were younger and “healthier” than the average CABG-requiring population, however, observational studies have revealed that OPCAB is beneficial to women, as well as patients with severe co-existing illnesses.⁽²⁴⁾ Also, a recent meta-analysis of 59 randomised trials showed no difference between on-pump and off-pump surgery with regards to myocardial infarction and mortality⁽²⁵⁾, however, it is show a

reduction in stroke in off-pump surgery by 30%. All trials were small, and only two of the 59 trials had more than 500 participants and 35 trials had less than 100.⁽²⁴⁾

OPCAB was said to be beneficial to patients at risk, yet the CORONARY trial included high-risk patients, and the GOPCABE trial included elderly participants, and neither showed a benefit in off-pump surgery. Current evidence supports current guidelines that either approach is reasonable in majority of patients.⁽¹⁾

Both techniques are now widely used and should be in the armamentarium of every surgeon.

- The approach is tailored according to:
 - the patient (coronary lesions, co-morbidities)
 - the team (surgeon, anaesthetist, perfusionist, scrub nurses familiar with procedure, ICU staff)

CONCLUSION

OPCAB presents with its own unique challenges and risks, and excellent communication between surgeon and anaesthetist is mandatory during OPCAB surgery. Experienced personnel (anaesthetist and surgeon) are required in order reduce poor outcomes. The anaesthetist should be knowledgeable about the procedure and be vigilant with regards to treating the haemodynamic changes and ischaemic episodes that may develop.

Anaesthetic techniques which facilitate fast-track and ultra-fast-track anaesthesia are recommended. OPCAB has not been shown to be superior to CPB, but it is definitely warranted in specific patients. It is not an alternative to CABG, but a complimentary approach. More studies and investigations are definitely needed in order to ascertain its place in cardiac surgery.

BIBLIOGRAPHY

1. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology*. 2011;58(24):e123-e210.
2. Chassot PG, van der Linden P, Zaugg M, Mueller XM, Spahn DR. Off-pump coronary artery bypass surgery: physiology and anaesthetic management. *British journal of anaesthesia*. 2004;92(3):400-13.
3. Detter C, Reichenspurner H, Boehm D, Thalhammer M, Raptis P, Schutz A, et al., editors. Minimally invasive direct coronary artery bypass grafting (MIDCAB) and off-pump coronary artery bypass grafting (OPCAB): two techniques for beating heart surgery. *The heart surgery forum*; 2002.
4. Diegeler A, Walther T, Metz S, Falk V, Krakor R, Autschbach R, et al. Comparison of MIDCAP versus conventional CABG surgery regarding pain and quality of life. *The heart surgery forum*. 1999;2(4):290-5; discussion 5-6.
5. Calafiore AM, Vitolla G, Mazzei V, Teodori G, Di Giammarco G, Iovino T. The LAST operation: techniques and results before and after the stabilization era. *The Annals of thoracic surgery*. 1998;66(3):998-1001.
6. Hemmerling TM, Romano G, Terrasini N, Noiseux N. Anesthesia for off-pump coronary artery bypass surgery. *Annals of cardiac anaesthesia*. 2013;16(1):28.
7. Comunale ME, Body SC, Ley C, Koch C, Roach G, Mathew JP, et al. The concordance of intraoperative left ventricular wall-motion abnormalities and electrocardiographic ST segment changes: association with outcome after coronary revascularization. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. *Anesthesiology*. 1998;88(4):945-54.
8. Mehta Y, Malik M. Anaesthesia for off-pump coronary artery bypass grafting. *Oxford Textbook of Cardiothoracic Anaesthesia*. 2015:221.
9. Koster A. OPCAB: which kind of anticoagulation? *European Journal of Anaesthesiology*. 2007;24(S40):77-82.
10. Yachi T, Watanabe G, Tomita S. Activation of coagulation and fibrinolysis after off-pump coronary artery bypass grafting with or without endotracheal general anesthesia. *Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery*. 2010;5(6):444-9.
11. Hett DA. Anaesthesia for off-pump coronary artery surgery. *Continuing Education in Anaesthesia, Critical Care & Pain*. 2006;6(2):60-2.

12. Silbert BS, Myles PS. Is fast-track cardiac anesthesia now the global standard of care? *Anesthesia & Analgesia*. 2009;108(3):689-91.
13. Conzen PF, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. *ANESTHESIOLOGY-PHILADELPHIA THEN HAGERSTOWN-*. 2003;99(4):826-33.
14. Hemmerling TM, Russo G, Bracco D. Neuromuscular blockade in cardiac surgery: an update for clinicians. *Annals of cardiac anaesthesia*. 2008;11(2):80.
15. Hemmerling TM. Technical aspects of high thoracic epidural analgesia in cardiac surgery. *Techniques in Regional Anesthesia and Pain Management*. 2008;12(1):46-53.
16. Hemmerling TM, Noiseux N, Basile F, Noel M-F, Prieto I. Awake cardiac surgery using a novel anesthetic technique. *Canadian Journal of anaesthesia*. 2005;52(10):1088-92.
17. Lucchetti V, Moscariello C, Catapano D, Angelini G. Coronary artery bypass grafting in the awake patient: combined thoracic epidural and lumbar subarachnoid block. *European journal of cardio-thoracic surgery*. 2004;26(3):658-9.
18. Jeong S-M, Hahm K-D, Jeong Y-B, Yang H-S, Choi I-C. Warming of intravenous fluids prevents hypothermia during off-pump coronary artery bypass graft surgery. *Journal of cardiothoracic and vascular anaesthesia*. 2008;22(1):67-70.
19. Christenson JT, Licker M, Kalangos A. The Role of Intra-Aortic Counterpulsation in High-Risk OPCAB Surgery. *Journal of cardiac surgery*. 2003;18(4):286-94.
20. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, et al. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*. 2009;361(19):1827-37.
21. Lamy A, Devereaux P, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *New England Journal of Medicine*. 2012;366(16):1489-97.
22. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *New England Journal of Medicine*. 2013;368(13):1189-98.
23. Lamy A, Devereaux P, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *New England Journal of Medicine*. 2013;368(13):1179-88.
24. Alexander JH. Clinical-outcome trials in cardiac surgery--have we primed the pump? *The New England journal of medicine*. 2013;368(13):1247.
25. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: an updated meta-analysis and meta-regression of randomized trials. *European heart journal*. 2012;33(10):1257-67.

