A NON RANDOMISED TRIAL OF 'ON BYPASS' Vs 'OFF BYPASS' CORONARY ARTERY REVASCULARISATION

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SUMMARY

BACKGROUND: Several groups have reported a decreased postoperative morbidity and length of hospital stay in 'off pump' coronary artery bypass grafting (CABG). We report on our initial 'off by-pass' CABG series and these compare with the unselected consecutive patients operated upon the same time period in our institution.

METHODS: We retrospectively collected data of 100 consecutive patients who underwent CABG with cardiopulmonary bypass (Group A = 55 patients) or without cardiopulmonary bypass (Group B = 45 patients) during a 4-months period. In the patients in Group A normothermic cardiopulmonary bypass was used with intermittent aortic cross-clamping and ventricular fibrillation. In Group B a CTS Access System (Cardiothoracic Systems, Cupertino, Ca, USA) was used to allow adequate exposure and stabilisation of the coronary arteries. Mean age of the patients in group A was 55 years while 63 years in Group B. Four patients in Group B had experienced a cerebral vascular accident in the 12 months preceding the heart operation and 3 patients had asymptomatic severe bilateral carotid artery disease. The average number of grafts was 3±1 in Group A vs. 2.5±0.8 in Group B in which branches of the Circumflex artery were revascularised in 21 patients (42%). In 50% of the patients in Group A and in 5% in Group B at least two arterial grafts were used.

RESULTS: There was no hospital death. Post operative myocardial infarctions or ischemic ECG changes were not recorded in either of the two groups. Mean intubation time and ICU stay were similar in Group A and in Group B. Mean hospital stay was 5 days in Group A while it was 5.7 days in the 'off by-pass' group. The incidence of post-operative atrial fibrillation was 5.4% in Group A while 15% in Group B.

CONCLUSION: Our initial experience failed to show an advantage in the early post-operative period in the patients operated 'off by-pass' compared to the ones 'on by-pass'. The 'non randomised' allocation of patients with more non cardiac co-morbid conditions towards the 'off by-pass' treatment group may explain these early findings. Further studies and randomised trials are needed before OPCAB used as routine procedure.

BACKGROUND

There has been renewed interest in off bypass surgery, as the problems associated with the cardiopulmonary bypass become better known OPCAB is not a new technique. Kolessov in the Former Soviet Union first performed it. Other in the west tried the technique but due to high risk of poor anastomosis and technical difficulties abandoned the technique. Developments of myocardial stabilisers and recent advances in detection of immunological consequences of CBP have resulted in renewed interest in the technique. There has been a lot of debate about the need for and ability to perform multi vessel graft in the beating heart. Mostly this technique has been used to perform single vessel graft. We set out to demonstrate that multiple grafts can be performed on the beating heart without adverse out come. It was also our intention to identify possible limitations of the technique.

METHODOLOGY

Retrospective study of 100 consecutive patients over the period of four months who underwent CABG with cardiopulmonary bypass (Group A = 55 patients) or without cardiopulmonary bypass (OPCAB)
Anesthesia and Intraoperative Monitoring:
After instituting invasive monitoring General Anaesthetic was induced with etomidate in both groups of patients. In addition fentanyl (20-30 mg/kg) was administered. Muscle relaxation was achieved using Pancuronium. Anesthesia was maintained with an inhalation agents (Isoflurane) and continuos infusion of Fentanyl (100mg/h). Routine hemodynamic, electrocardiographic, and arterial blood gas monitoring were routinely performed during the procedures, a cardiopulmonary bypass machine and a perfusionist were available at all times. In both group of patients bypass conduits ere harvested before administering Heparin. Arterial blood gases ere monitored in both groups and FiO2 was adjusted to achieve a PaO2 of 11 to 13 kPa.

Intraoperative Haemodynamic Management and Myocardial Protection
In-inpatients undergoing on bypass surgery cardiopulmonary bypass were instituted via an aortic and right atrial appendage canula. In the off bypass group before lifting the heart for distal anastomosis it was aimed to keep a pressure of 120-140 mm of Hg. After lifting of the heart the target blood pressure was 80-110 mm of Hg. During aortic anastomosis target pressure was < 90 mm of Hg. Esmolol GTN and boluses of Aramine and infusion of adrenaline were used to maintain these haemodynamic parameters.

SURGICAL TECHNIQUE

Sternotomy and Harvesting of Conduits:
In both groups of patients preoperative angiogram was used to identify target vessels. LIMA was harvested and if required a saphenous vein was harvested. Anticoagulation was achieved as described latter. LIMA was sprayed with dilute papaverin solution after placing it on a surgical swab. It was then gently moved out of the operating field.

Heparin and Protamine Management:
In the on pump group Heparin 300 IU/kg was administered to achieve a target activated clotting time (ACT) of 480 seconds or above before commencement of CPB. The ACT was monitored during the bypass period (every 15 minutes) and an additional 100 IU/kg of heparin was administered to maintain target ACT. On the other hand in the off pump group, heparin 100 IU/kg was administered near the completion of IMA harvesting. The target ACT in this group was of 250 to 350 seconds. At the end of the procedure Protamine was used to reverse the effect of heparin and return the ACT to preoperative levels in both groups.

PROCEDURE

In the on bypass group a standard circuit was used: a Bard tubing set, which included a 40mm arterial filter, a Stockert roller pump (Sorin Biomedica, Midhurst, UK), and a hollow-fiber membrane oxygenator (Monolyth; Sorin Biomedica, Midhurst, UK). The extracorporrial circuit was primed with 1,000 ml Hartmann's solution, 500 ml Gelofusine, 0.5g/kg Mannitol, 7ml 10% calcium gluconate, and 60 mg heparin. CPB was commenced after ascending aortic and two stage single venous cannulation in the right atrial appendage with non-pulsatile pump flow to achieve a cardiac index of 2.4lm/m2 was used. Vasoconstrictors were used to achieve a mean pressure of above 60mm of Hg. Myocardial protection was achieved by Ventricular Fibrillation technique. In addition moderate hypothermia was used. On completing all distal anastomosis, the aortic cross-clamp was remove and the proximal anastomosis performed with partial ascending aortic clamping.

In the off bypass group after opening the pericardium the heart was gently lifted by placing adequate number of surgical swabs behind the heart. The heart was gently rotated gradually to assess all of the target vessels that had been identified on the angiogram. If the haemodynamic status deteriorated at any stage pressure on the heart was eased as an initial step. Once haemodynamic status improved the maneuver was continued. Once the target vessels had been identified the target coronary artery was occluded, proximal and distal to proposed arteriotomy site, by widely placing double-looped 5-0 Prolene (Ethicon, Somerville, NJ) sutures taking care to exclude any major branches proximal to the stenosis, these sutures were snugged and arteriotomy was made after stabilising the beating heart with Mechanical stabilization was achieved by a modified cardiac stabiliser (Cardiothoracic Systems, Cupertino, CA). Visualization of the anastomotic area was aided with
carbon dioxide mist blower.
The distal anastomosis was performed using a continuous 6-0 Prolene (Ethicon, Somerville, NJ) suture. After completion of the anastomosis, the target vessel snuggers were released and hemostasis achieved. In cases where free grafts were used, proximal anastomosis to the aorta was made on a punch aortotomy after applying a side clap to the ascending aorta. To aid myocardial perfusion, the proximal anastomosis was made before the next distal anastomosis. The LIMA to LAD anastomosis was performed last of all.

Heparin was reversed in all of the patients. Sternotomy was closed in a routine fashion after inserting drainage tubes. All patients were shifted to intensive care unit with mechanical ventilatory support.

INTENSIVE CARE UNIT MANAGEMENT
At the end of surgery, patients were transferred to the intensive care unit (ICU). The lungs were ventilated with 60% oxygen using volume-controlled ventilation and a tidal volume of 10ml/kg with 5 cm H2O of PEEP. Adjustments in FiO2 and respiratory rate were made according to routine blood gas analysis, in order to maintain PaO2 between 11kPa and 13kPa, and PaCO2 between 4kPa and 4.5kPa. Forced air warming was used, until a stable nasopharyngeal temperature of 37°C had been reached. When fully warmed, and if there was no further significant blood loss, and hemodynamics were stable, patients were weaned off the ventilator and extubated. Postoperative pain control was achieved with intravenous doses of propofol (50mg/kg) and morphine (2mg) as needed.

FOLLOW UP CARE
After discharge patients were followed up in the outpatients clinic. Follow up beyond six weeks was through the general practitioner of the patients with a low threshold for referral back to the cardiac surgical ward rather than then the outpatients department.

DATA ANALYSIS
After collection of the relevant data SPSS was used for statistical analysis. Comparison of the two groups was performed by the nonparametric Wilcoxon rank sum test of independent groups. A p value of less then 0.05 was considered statistically significant, and the results are expressed as the mean ± standard deviation unless otherwise indicated.

RESULTS
Table 1 shows preoperative data of the two groups. Most of the patients in both groups were male, 84.4% and 90.9% and nearly equal number of them had suffered from MI pre operatively. On the other hand there were more Diabetics 8.9% Vs 5.5%; COPD 15.6% Vs 5.5%; Obese, 6.7% Vs 3.6% and CCS III symptom sufferers, 73.3% Vs 54.5%; in the off pump. Table 2 shows the total percentage of patients with CCS III symptoms Vs their ventricular function. Out of all the participants in the study 63% of the patients had CCS III symptoms and all of them had good or moderate ventricular function. This indicates that the severity of symptoms expressed, as CCS class does not correlate well with the ventricular function.

Table 1
ECHO / DOPPLER FINDINGS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>OFF PUMP (n 45)</th>
<th>ON PUMP (n 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>SEX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td>7</td>
<td>15.6%</td>
</tr>
<tr>
<td>MALE</td>
<td>38</td>
<td>84.4%</td>
</tr>
<tr>
<td>DIABETES</td>
<td>4</td>
<td>8.9%</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>6</td>
<td>13.3%</td>
</tr>
<tr>
<td>COAD</td>
<td>7</td>
<td>15.6%</td>
</tr>
<tr>
<td>MYOCARDIAL INFRACT</td>
<td>23</td>
<td>51.1%</td>
</tr>
<tr>
<td>OBESITY (BMI&gt;30)</td>
<td>3</td>
<td>6.7%</td>
</tr>
<tr>
<td>CCS III SYMPTOMS</td>
<td>33</td>
<td>73.3%</td>
</tr>
<tr>
<td>LV FUNCTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOOD</td>
<td>23</td>
<td>51.1%</td>
</tr>
<tr>
<td>MODERATE</td>
<td>15</td>
<td>33.3%</td>
</tr>
<tr>
<td>POOR</td>
<td>7</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

Table 2
CCS III SYMPTOMS

<table>
<thead>
<tr>
<th>LV FUNCTION</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>6%</td>
<td>53%</td>
</tr>
<tr>
<td>Moderate</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Poor</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 shows number of grafts that were performed in the two groups. 90.1% of the OPCAB group had multiple grafts. On average OPCAB group received 2.5±0.8 grafts while CPB coronary artery bypass group received 3±1 grafts.
Table 4 compares the postoperative outcome of the two groups. CPB group required ionotropic support more frequently than OPCAB group, but on the other hand OPCAB group had more frequent occurrence of atrial fibrillation 15% Vs 5.4%. Similarly readmission rate within six weeks of discharge was higher 11.1% Vs 10.9%. On further analysis of these results against the left ventricular function we discovered that in both groups all the complication occurred in-patients with good LV function. This probably indicates the higher liability of the good ventricle to suffer from acute myocardial injury intra-operatively in both groups of patients.

Out of all the patients in both groups, the patients who developed postoperative angina all belonged to the OPCAB group 4.4% Vs 0%. They were both female diabetics, hypertensive, obese, had CCS III symptoms and good left ventricular function. One of these patients had one graft while the other had 2 grafts. On analysing the records of the patients it was found that the distinctive characteristic of these patients when compared to a similar age, sex and number of grafts attached per patient was that they were both obese and one of them had diabetes mellitus. Although we were dealing with a small number of patients but our finding would indicate that obese and diabetic patients undergoing one or two grafts on the beating heart might be at increased risk of recurrence of symptoms.

**DISCUSSION**

**Consequences of CPB:**

Our understanding of immunological response to CPB seems to have increased the enthusiasm for OPCAB surgery. CPB once came to the rescue of the cardiac surgeons and made possible surgery that would otherwise not have been possible. As the patients population that is undergoing coronary artery surgery changes with more and more sicker patients undergoing surgery, factors previously regarded as minor are gaining importance.

Various studies have shown inflammatory response to CPB. The inflammatory reaction involves plasma proteins and blood cells. Non blood variables such as biomaterial in contact with blood, the surface coating, temperature, aortic cross clamp time myocardial perfusion, activation of some proteins by the operation itself, steroids, antioxidants and use of protease inhibitors may modify the inflammatory response [1].

Various modifications of the CPB circuits have been tried to reduce inflammatory response. Heparin bonded circuits are claimed to attenuates terminal compliment complex formation. Other studies have shown reduced release of myeloperoxidase and lactoferrin by neutrophils in a heparin bonded circuit [2].

Patients undergoing CPB also suffer from endothelial cell insults including endothelial exposure to inflammatory mediators such as cytokines and endotoxins. All these insults cause endothelial cell activation, resulting in damaged tissue, impaired organ function and abnormal fibroproliferation response.

Endothelial activation promotes increased vascular tone by release of vasoconstrictors such as endothelin leucotrienes and angiotensin II. It also inhibits endothelial surface expression of heparin like substance, which normally potentiate action of antithrombin III, thereby preventing formation of fibrin. Release of prostaglandin I2 adenosine responsible maintenance of vasodilatation and prevention of platelets adhesion and aggregation are similarly inhibited. Thrombomodulin is also down regulated to enhance the procoagulant phenotype [3].
On the other hand release of tissue plasminogen activator lead to difficulty in clotting in some patients. on a local basis this process is protective but on a systemic basis as occurs in CBP, end organ damage occurs because of neutrophil adhesion throughout the entire vascular bed [4].

Despite recent advances in myocardial protective techniques, patients with impaired LV function who undergo conventional CABG are at increased risk of perioperative mortality compared to patients with normal LV function.

**COMMENT**

Surgery induces an inflammatory response in addition to Neuroendocrine response to stress, however patients undergoing OPCAB are spared the additional consequences of extracorporial circulation, temperature changes and cross clamping [7].

Preservation of septal movement is known to be better with OPCAB thus making it better suited for patients with impaired LV function. Our results indicate that patients with impaired LV function are better suited for this operation than patients with good LV function [6]. This might be due to preconditioning in previously ischemic myocardium possibly preventing an acute myocardial injury during stabalisation [5,8].

There is conflicting evidence regarding the need for complete revascularisation and the relationship of incomplete revascularisation to the recurrence of angina in OPCAB [12]. We note that the two patients in our study population who suffered from postoperative angina had undergone incomplete revascularisation. On the other hand it is claimed that intimal injury to the coronary vessels and poor anastomosis results in endothelial activation. Endothelial cell release of P Selectin results in leucocytes adhesion to endothelial cells. Subsequent neutrophil infiltration of perivascular tissue results in release of Oxygen derived free radicals, protease and elastase leading to non-specific cellular damage [3]. Various modifications to the surgical technique such as avoidance of the use of snuggers in order to avoid coronary artery intimal damage and thereby reducing the risk of acute thrombosis or later intimal hyperplaiia or angiogenesis, has not eliminated the problem.

Our study has shows a significantly higher incidence or AF in the OPCAB group. It is likely that in the presence of persevered LV function there is worse myocardial injury probably due to lack myocardial preconditioning that otherwise takes place in the presence of impaired LV function. Others have reported similar findings with regard to the incidence of atrial fibrillation [10].

**CONCLUSION**

We think that multi vessel disease in patients with moderate and poor ventricle can be treated by OPCAB with no increased risk of adverse out come. Arterial revascularisation of the coronary arteries without CPB is feasible, with results similar with those obtained with CPB and as others have suggested the two techniques are complementary and not antagonistic [11]. However patients with good ventricular function undergoing OPCAB surgery might be at increased risk of myocardial damage.

There is continued concern about the higher incidence of recurrence of symptoms after OPCAB when compared to conventional CABG. Routine use of angiogram to asses the quality of anastomosis is not helpful because majority of stenoses visualized at the early coronary angiography are not seen on later coronary angiography, which makes the interpretation of the angiogram unreliable as a tool for the decision as to redo-procedure in the early postoperative period [9,11].

Our initial experience failed to show an advantage in the early post-operative period in the patients operated off bypass compared to the ones on bypass. The non randomised allocation of patients with more non cardiac co-morbid conditions towards the off bypass treatment group may explain these early findings. Further studies and randomised trials are needed before OPCAB used as routine procedure.
REFERENCES


