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Australia and New Zealand Horizon Scanning Network

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AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Mini-cardiopulmonary bypass system

May 2008



**Australian
Safety
and Efficacy
Register of New
Interventional
Procedures -
Surgical**



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College of Surgeons**

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PRIORITISING SUMMARY

REGISTER ID

S000076

NAME OF TECHNOLOGY

MINI-CARDIOPULMONARY BYPASS SYSTEM

PURPOSE AND TARGET GROUP

**PATIENTS UNDERGOING CARDIAC SURGERY WHICH
REQUIRES CARDIOPULMONARY BYPASS**

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | |
|---|--|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication
or modification of technique |
| <input checked="" type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|---|-------------|-----|
| <input type="checkbox"/> Yes | ARTG number | N/A |
| <input checked="" type="checkbox"/> No | | |
| <input type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Finland		✓	
France		✓	
Germany		✓	
Italy		✓	
Japan		✓	
Netherlands		✓	
Singapore		✓	
Switzerland		✓	
United Kingdom		✓	
United States		✓	

IMPACT SUMMARY

Several manufacturers provide a minimally invasive cardiopulmonary bypass system (mini-CPB) with the aim of reducing the deleterious effects of conventional

cardiopulmonary bypass (CPB). The technology is available in specialist medical centres as an alternative to conventional CPB during cardiac surgery.

BACKGROUND

CPB is a form of extracorporeal circulation that maintains blood and oxygen circulation during surgical procedures in which the heart must be arrested or stopped for a period of time. It provides a stationary, bloodless operating field and the ability to easily expose all of the major coronary arteries. Components of CPB, which are connected by a series of tubes, include a venous cannula to remove oxygen deprived blood from the body into a venous reservoir, an oxygenator to remove carbon dioxide and deliver oxygen, a heat exchanger to control blood temperature, a pump to maintain and control blood flow, suction to remove blood from the operative field, and an arterial cannula to return the oxygenated blood to the body via a cardiotomy reservoir (blood storage area).

The use of CPB is mandatory during many cardiac surgical procedures, including coronary artery bypass grafting (CABG) and aortic and mitral valve procedures. CABG surgery is performed in selected patients with significant narrowing and blockage of the coronary arteries due to the build up of fatty plaque (coronary artery disease). The surgery uses veins from the leg or arteries from another part of the body to re-route blood around narrowed and blocked coronary arteries to maintain sufficient blood flow to the heart muscle (Parment et al 2004). Another procedure which typically uses CPB is valve replacement, which is performed in patients with a leaky or partially blocked valve. During such cardiac surgery, CPB oxygenates and recirculates blood that has been diverted from the heart and lungs to allow the surgeon to operate on a non-beating heart (Shann et al 2006).

Conventional CPB has recognised complications. CPB initiates a systemic inflammatory response largely caused by the blood contact with foreign surfaces with subsequent complement activation, pro-inflammatory cytokine secretion and leukocyte activation (Fromes et al 2002). This inflammatory response can lead to cellular damage and potentially to bleeding disorders, respiratory failure, renal dysfunction, neurocognitive decline, multiple organ failure, and death (Bical et al 2006). The heart itself undergoes a local inflammatory reaction due to the ischemia (restricted blood flow) and reperfusion cycle of CPB, and the systemic inflammatory response may exacerbate any heart muscle damage (Fromes et al 2002).

A number of alternatives to conventional CPB have emerged in an attempt to avoid or reduce the systemic inflammatory response. Off-pump (beating heart) coronary artery bypass grafting (OPCAB) avoids the use of CPB by using snares and special instruments on the beating heart to stabilise the artery being bypassed (Parment et al 2004). However, technical problems with OPCAB can include difficulty suturing the graft due to movement of the heart, blood in the surgical field, haemodynamic instability resulting from manipulation of the heart, and myocardial ischaemia (Kamiya et al 2006). In addition, CPB is still required for many complicated cardiac procedures (Valtonen et al 2007). Modifications have also been made to the CPB procedure to reduce the systemic

inflammatory response, including changes to the materials from which the CPB circuit and oxygenator are composed, refinement of the pump and blood circuit, and alterations in priming volume and anticoagulation management (Ranucci & Isgro 2007).

Recently, several manufacturers have developed small biocompatible extracorporeal circulation systems (mini-CPB systems) aimed at reducing the most hazardous aspects of conventional CPB, such as haemodilution and contact of blood with air and foreign surfaces. In contrast to standard CPB, there is no cardiotomy reservoir in the core circuit of the mini-CPB system. These mini-CPB systems incorporate the following features: a closed circuit, centrifugal pump, hollow-fibre oxygenator, biocompatible surfaces, reduced membrane surface area, separation of the pericardial shed blood suction and reduced priming volume (Ranucci & Isgro 2007; Valtonen et al 2007). The biocompatible treatment of the mini-CPB circuit and oxygenator with heparin, phosphorylcholine, or sulphate-sulphonate is designed to limit thrombin formation, platelet count reduction, and inflammatory reaction. Other important changes from conventional CPB are the introduction of a closed circuit which separates the surgical field suction blood, the reduction of the circuit size to reduce haemodilution, and the reduced fluid volume required for priming the system (Ranucci & Isgro 2007). A limitation to this new technology is that many mini-CPB systems have problems handling air trapped in the lines, and this limits their use mainly to isolated CABG procedures rather than valvular and other complex cardiac surgical operations.

Mini-CPB systems which have been developed and used in trials include the mini-extracorporeal circulation system (MECC) (Jostra AG, Hirrlingen, Germany), the Extra-Corporeal Circulation Optimized system (ECC.O) (Dideco Srl, Modena, Italy), the Synergy™ Mini-Bypass System (Cobe Cardiovascular, Inc., Arvada, CO, USA), the CorX (CardioVenton, Inc., Santa Clara, CA, USA), an early Medtronic device and the later Resting Heart® System (RHS) (Medtronic, Inc., Minneapolis, MN, USA). Some mini-CPB systems, such as the RHS, have an additional safety device to detect and eliminate air entering the circuit (Kamiya et al 2006).

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, 1.7% of people surveyed in the 2004-05 National Health Survey reported having manifestations of coronary artery disease, which corresponds to around 334,500 Australians affected. In 2003, there were an estimated 49,800 coronary artery disease events (sum of non-fatal hospitalisations for acute myocardial infarction and the number of coronary heart disease deaths in the population) among 40 to 90 year olds, with a fatality rate of 43% for these events. Coronary artery disease accounted for 164,226 hospitalisations in 2003-04, and was the largest single cause of death in Australia in 2004, accounting for 24,576 deaths (19% of all deaths and 51% of cardiovascular deaths) (AIHW 2006). The 2000-01 health expenditure in Australia for cardiovascular disease in general was \$5.5 billion, amounting to 10.9% of the total allocated health expenditure (AIHW 2005). A substantial number of coronary artery disease sufferers undergo CABG and similar procedures requiring CPB each year. In Australia in 2001-02, there were 16,252 CABG operations, with most of these (approximately 90%) requiring CPB

(AIHW 2004; Personal Correspondence 2008). For each patient undergoing CABG the average expenditure for hospital treatment in 1998-99 was \$17,596 per admission, with a long average length of stay in hospital (11.7 days) contributing to this high cost (AIHW 2002).

DIFFUSION

Trials have been published on the use of mini-CPB in a number of countries, including Finland, France, Germany, Italy, Japan, the Netherlands, Singapore, Switzerland and the United States. The United States Food and Drug Administration (FDA) have provided 510k clearance for a number of mini-CPB systems for use, including the MECC in 2002, the RHS in 2003 and the ECC.O in 2005. The CorX was approved in 2003, but has since been withdrawn from the market probably due to financial reasons (Wippermann et al 2005). The FDA also mentions other approved systems, such as the NovoSci Ready System® (NovoSci, The Woodlands, TX, USA) which was listed in 2004 (FDA 2008). No mini-CPB systems are listed in the Australian Register of Therapeutic Goods (ARTG).

COMPARATORS

Different models/manufacturers of mini-CPB:

- MECC
- ECC.O
- RHS
- Synergy
- CorX (no longer manufactured)
- NovoSci Ready system
- Deltastream® (MEDOS Medizintechnik AG, Stolberg, Germany)
- Capiox® (Terumo Corporation, Tokyo, Japan).

Different surgical options:

- Conventional CPB
- OPCAB.

SAFETY AND EFFECTIVENESS ISSUES

At least nine randomised controlled trials (RCTs) were available for MECC, so the two with the largest patient numbers are discussed in this summary. An RCT by Remadi et al (2006) randomly assigned 400 patients undergoing CABG to either conventional CPB (n = 200) or MECC (n = 200), while the RCT by Mazzei et al (2007) compared an elective CABG procedure (isolated myocardial revascularisation via full median sternotomy) performed using either MECC (n = 150) or OPCAB (n = 150).

There was a limited number of RCTs for the other mini-CPB devices. In the RCT by Valtonen et al (2007), 40 patients undergoing elective coronary surgery (CABG) with

extracorporeal perfusion were randomly assigned to conventional CPB or ECC.O, while an RCT by Perthel et al (2007) randomly assigned 60 patients undergoing CABG to conventional CPB (n = 30) or ECC.O (n = 30). Kamiya et al (2006) randomly assigned 20 patients undergoing isolated CABG to conventional CPB (n = 10) or RHS (n = 10), and Huybreghts et al (2007) randomised 49 patients undergoing elective CABG to conventional CPB (n = 24) or Synergy (n = 25).

MECC

Remadi et al (2006) found that C-reactive protein levels (a measure of inflammatory response) were lower after MECC compared to conventional CPB at 24 hours ($p < 0.01$) and 48 hours ($p < 0.05$). Troponin-T levels (a measure of heart muscle damage) were also lower after MECC compared to conventional CPB in the first 24 hours ($p < 0.01$). The mean decrease in haematocrit during MECC was 2.1%. Although there was a significantly greater decrease in the conventional CPB group, the rate and level of statistical significance was not provided. The intraoperative transfusion rate was 6% in MECC and 25.8% in conventional CPB ($p < 0.001$), whereas the postoperative bleeding rate was not significantly different between the groups. The study found that at six hours post-operation the MECC group had lower blood creatinine ($p < 0.001$) and urea ($p < 0.01$) levels (measures of kidney function), and a smaller decrease in platelet levels ($p < 0.01$) compared to the conventional CPB group. There was no difference in leukocyte levels, and no difference between groups for any outcomes by day five post-operation (Remadi et al 2006).

Operative time and intensive care unit time were not significantly different between the two groups (Remadi et al 2006). There was no significant difference in 30-day mortality (three deaths in MECC (1.5%), five in conventional CPB (2.5%)). The causes of death were intestinal bleed (n = 1), sepsis (n = 1) and brain haemorrhage (n=1) in the MECC group, and low-cardiac output syndrome (n = 3), mesenteric ischaemia (n = 1) and respiratory failure (n = 1) in the conventional CPB group. The MECC group had lower rates of postoperative neurological complications ($p < 0.02$), renal failure ($p < 0.03$) and low cardiac output syndrome ($p < 0.001$) compared to conventional CPB. Five MECC and ten conventional CPB patients needed inotropic drugs (to alter the strength of heart muscle contractions) ($p < 0.03$), and one in conventional CPB needed intra-aortic balloon counter-pulsation to treat low cardiac output. Atrial fibrillation was the most frequent postoperative complication in both MECC (28%) and conventional CPB (34%) (Remadi et al 2006).

The study by Mazzei et al (2007) found no significant difference between MECC and OPCAB in interleukin-6 (IL-6) levels (a marker of systemic inflammation) at six hours post-operation when IL-6 levels were at their peak ($p = 0.14$). In addition, the MECC and OPCAB patients had similar blood concentrations of peak creatine kinase (at 24 hours post-operation, $p = 0.28$) and S-100 protein (at end of surgery, $p = 0.058$), which are markers of heart muscle and brain injury respectively. The level of haemodilution in MECC patients was low, with the mean drop in haematocrit being comparable to that of the OPCAB patients ($p = 0.12$). The study authors contrasted this to conventional CPB

which is associated with a mean decrease in haematocrit of 15% as reported in the literature.

Operative time was slightly longer in the MECC group (287 ± 52 minutes in MECC versus 256 ± 63 minutes in OPCAB, $p = 0.027$) (Mazzei et al 2007). Six patients required emergency conversion to standard CPB, but the study did not report to which groups these patients belonged. Five MECC and two OPCAB patients required treatment for low cardiac output. There was no statistically significant difference between the two groups with respect to hospital mortality rates (two deaths in MECC (1.4%), three in OPCAB (2%), $p = 0.99$), length of intensive care unit and hospital stay, complication rates or need for allogenic transfusion. Postoperative complications (8 in MECC (5.3%) and 10 in OPCAB patients (6.7%), $p = 0.80$) included renal insufficiency, stroke, shock, sepsis and myocardial infarction. After one year, mortality rates (four deaths in MECC (2.7%), five in OPCAB (3.4%)) and rates of angina recurrence or perfusion defect were not significantly different between groups (Mazzei et al 2007).

ECC.O

When comparing inflammation and heart muscle damage in ECC.O and conventional CPB, Valtonen et al (2007) found that blood levels of troponin-T and creatine kinase-MB did not differ significantly between the two groups. The haemoglobin level was significantly higher during perfusion in the ECC.O group ($p = 0.0069$), while additional heparin doses ($p = 0.018$) and the total fluid balance ($p = 0.0036$) were lower compared to conventional CPB. Operative time, duration of intubation following surgery and length of intensive care unit stay and total hospital stay were not significantly different between the treatment groups. There were two acute myocardial infarcts in the conventional group and none in the ECC.O group, but this difference was not statistically significant (Valtonen et al 2007).

Perthel et al (2007) did not report measures of inflammation and heart muscle damage when comparing ECC.O to conventional CPB. The study found no difference in intra- or postoperative blood $p\text{CO}_2$, $p\text{O}_2$, base excess and HCO_3 concentration between the two patient groups, although intraoperative haemoglobin levels were higher in the ECC.O group 'after cardioplegia' ($p = 0.05$) and at the 'cross-clamp off' stage ($p < 0.05$). There was a significant difference in transfusion frequency, with 27% of ECC.O and 43% of conventional CPB patients receiving homologous blood transfusions ($p = 0.05$). In addition, the transfused volume was lower in ECC.O compared to conventional CPB ($0.53 \pm \text{SD}0.9$ versus 1.30 ± 1.93 units of blood, $p < 0.05$). Fresh frozen plasma was used in three conventional CPB patients and no ECC.O patients ($p < 0.001$). Postoperative bleeding was lower after ECC.O compared to conventional CPB ($p < 0.05$). There were no deaths in either study group (Perthel et al 2007).

RHS

The study by Kamiya et al (2006), which measured inflammation and heart muscle damage, found that at six hours post-operation, the increase in blood leukocyte count was slightly but not significantly lower in the RHS group compared to the conventional CPB group ($p = 0.10$). Blood C-reactive protein levels at 72 hours post-operation were

significantly lower in the RHS group than the conventional CPB group ($p = 0.045$). However, platelet count and levels of creatinine kinase and creatinine kinase-MB were not significantly different between the two groups. There was also no difference in the number of patients in each group requiring intraoperative blood transfusion (four RHS and five conventional CPB patients), and no difference in operative time, mean intubation time and length of stay in intensive care. One patient in the RHS group died on the fifth postoperative day due to cardiac arrest, and atrial fibrillation occurred in two RHS patients and three conventional CPB patients, with no significant difference between groups ($p = 0.61$). No other complications occurred in either treatment group (Kamiya et al 2006).

Synergy

Huybregts et al (2007) quantified inflammatory response by measuring concentrations of leukocytes, IL-6, C-reactive protein and other organ injury markers. Postoperative C-reactive protein concentrations were similar in both groups. However, Synergy, when compared to conventional CPB, produced lower postoperative IL-6 levels ($p < 0.05$) and leukocyte counts ($p < 0.01$). Postoperative urine thromboxane B₂, an organ injury marker, was significantly lower in the Synergy group compared to the conventional CPB group ($p < 0.01$), as was postoperative urine N-acetyl-glucosaminidase (a measure of renal injury) ($p < 0.05$) and postoperative urine intestinal fatty acid binding protein (a measure of intestinal injury) ($p < 0.05$). Haematocrit levels measured during CPB were significantly higher in the Synergy group compared to conventional CPB ($p < 0.01$). The Synergy group lost fewer platelets during the operation ($p < 0.01$), required less blood products ($p < 0.04$) and had less postoperative blood loss ($p = 0.04$). There was no significant difference in operative time between the two treatment groups. In terms of complications, postoperative atrial fibrillation occurred in seven patients, with no significant difference between the two groups. Neither patient group experienced postoperative myocardial infarction, cerebrovascular or transitory cerebral ischaemic accident, acute renal injury, gastrointestinal complications or in-hospital death (Huybregts et al 2007).

COST IMPACT

Commercially available integrated mini-CPB systems require specific training, have a prolonged learning curve, require team work and are more expensive than conventional CPB (Ranucci and Isgro 2007). However, as yet, there are no studies comparing the cost-effectiveness of mini-CPB to conventional CPB or OPCAB.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Mini-CPB may provide an alternative for patients such as Jehovah's witnesses who refuse blood transfusions on religious grounds as it can preserve more haemoglobin than conventional CPB and reduce the need for transfusion (Vaislic et al 2003).

OTHER ISSUES

No other issues were identified from the retrieved material.

SUMMARY OF FINDINGS

A number of RCTs have been published on the safety and effectiveness of mini-CPB during CABG. The two included MECC studies, which assessed several hundred patients, found that inflammatory response and heart muscle damage as measured by surrogate endpoints were significantly lower in MECC compared to conventional CPB and were no different to OPCAB. One ECC.O study found no difference in inflammatory response and heart muscle damage compared to conventional CPB, while the RHS study found that only some inflammatory markers were lower in RHS compared to conventional CPB. The Synergy study found that inflammatory response and organ damage were significantly lower in Synergy compared to conventional CPB. These different results may indicate variations in performance between different mini-CPB systems, and more studies are required to determine if one type of system is superior to another.

Haemodilution during mini-CPB was comparable to OPCAB and was significantly lower than conventional CPB. Intraoperative and postoperative blood loss, as well as blood transfusion requirements, were also lower when mini-CPB was used instead of conventional CPB. Use of mini-CPB resulted in an operative time that was not significantly different to conventional CPB, but was slightly longer than OPCAB. From the included evidence, mini-CPB appears to be at least as safe as conventional CPB or OBCABG. Although there were differences in surrogate endpoints of inflammatory response and heart muscle damage between mini-CPB and conventional CPB, these generally did not translate into differences in complication rates after surgery, with only one included study reporting lower complication rates for mini-CPB compared to conventional CPB. The cost-effectiveness of this technology is yet to be assessed.

HEALTHPACT ACTION

Based on RCT evidence, mini-CPB appears to present a viable alternative to conventional CPB. The studies showed that mini-CPB can be used safely in patients undergoing CABG, and may produce favourable outcomes such as reduced systemic inflammatory response, organ damage and blood loss. Due to its potential, mini-cardiopulmonary bypass systems will be monitored for further developments.

NUMBER OF STUDIES INCLUDED

Total number of studies:	6
Level II intervention evidence	6

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SOURCES OF FURTHER INFORMATION

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SEARCH CRITERIA TO BE USED

Mini\$ AND cardiopulmonary bypass
Mini\$ AND extracorporeal circulation
MECC
ECC.O