Kyriakos Anastasiadis
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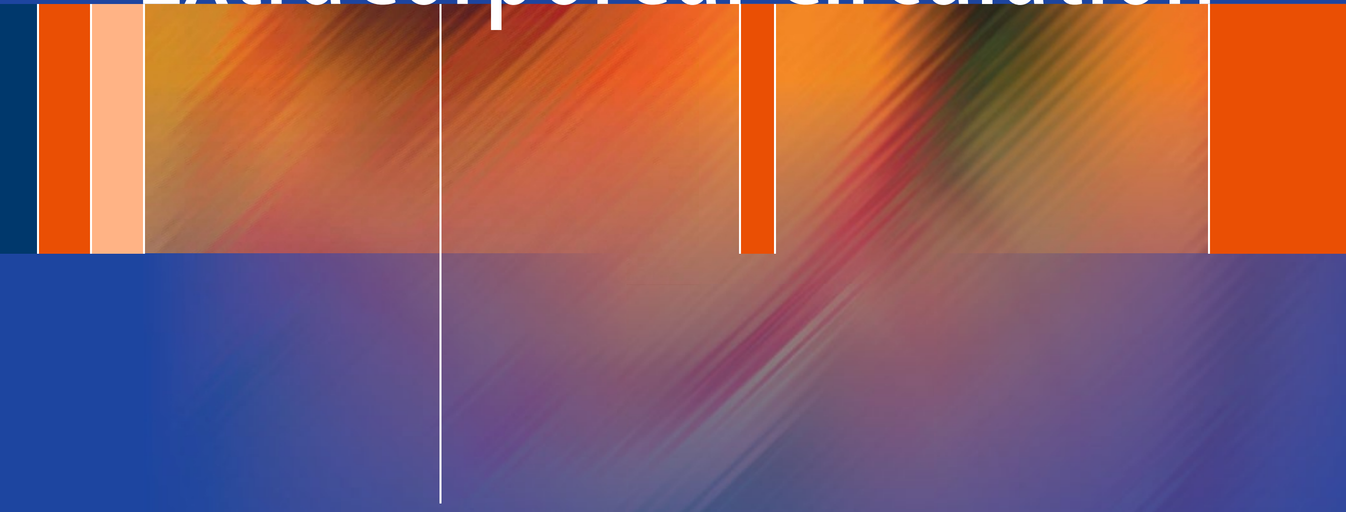
Principles of Miniaturized ExtraCorporeal Circulation



From Science and Technology to Clinical Practice

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Do not go where the path may lead,
go instead where there is no path
and leave a trail.

Ralf Emerson

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Foreword I

It is a great pleasure for me to write a foreword for a book that concisely addresses a new concept for extracorporeal circulation (ECC). Regardless how we name it – miniaturized, minimized or mini ECC – the principle of less traumatic ECC was successfully translated into clinical practice in the recent 10 years. Perfusion at a constant volume with less blood damage, less haemodilution, reduced postoperative inflammatory response and a lower requirement for intra- and postoperative blood transfusion has been achieved in both adult and paediatric cardiac surgery.

Numerous more or less sufficiently powered studies showed beneficial effects in terms of reduction of myocardial and neurological damage, the number of transfused patients and less inflammatory response. Despite promising results the concept of miniaturized extracorporeal circulation gained only limited worldwide acceptance among cardiac surgeons. Why? As a matter of fact the clinical impact of this novel approach has not been sufficiently addressed, at least in adults, in multicenter randomized controlled trials which would allow a conclusive statement on the clinical benefit. Without sufficient evidence the miniaturized perfusion technique remains a useful and reliable tool only for those who have consequently translated this approach into their own surgical techniques and into perioperative patient management.

One company, MAQUET Cardiopulmonary AG, was the first that caught the concept of minimized ECC and introduced the minimal extracorporeal circulation system (MECC) in 2002 as a closed, compact and fully-coated set of disposables. MECC works with or without a bubble trap or an arterial filter and thus priming volume is as low as 500 mL. Three other companies now offer different miniaturized systems: Medtronic's Resting Heart system, Sorin's Synergy Mini-Bypass and ECC.O systems and Terumo's ROCSafe™ system.

The development of miniaturized ECC systems has not only brought this technology into the operation theatres but also set the path for the consequent development and propagation of mini systems, e.g. MAQUET's CARDIOHELP system at intensive care units, combat grounds and for patient transport with ongoing extracorporeal life support. This development represents a successful continuation of the philosophy of minimizing systemic injury induced by extracorporeal perfusion.

This book was compiled by surgeons and perfusionists who were pioneers in the field of miniaturized ECC. I am quite confident that this book is a valuable source of information for all those who believe in minimal surgery and also for novices who would like to receive information before they start in the theatre. I wish to thank all my coauthors, my colleagues and, last but not least, my family for their patience to work on this project.

Regensburg, Germany Alois Philipp, ECCP

Foreword II

The foreword by Alois Philipp is an excellent summary of minimally invasive ECC described in this book. MECC is the logical union of ECMO (which began as modified CPB) and full classical CPB (which began as a means to treat massive pulmonary embolism, the ideal ECMO indication). The early success of ECMO was because we eliminated the blood gas interface used for CPB at the time (hence ‘membrane oxygenation’). As ECMO progressed the patients got more complex and support runs got longer (now as long as 2 months), but the inflammatory response that occurs in an hour with CPB does not occur with ECMO. Meanwhile, the inflammatory response to long bypass runs decreased as membrane oxygenators replaced direct gas interface devices during CPB. This prompted us to look for the differences between ECMO and CPB.

It is now clear that air exposure and extreme negative pressure (causing cavitation) are the factors accounting for the difference. The major source of air/blood exposure in CPB is in the reservoir and the cardiotomy suction. Negative pressure (over −600 mmHg) regularly occurs with cardiotomy suction and causes haemolysis. MECC eliminates air exposure, the open venous reservoir and cardiotomy suction; it is essentially ECMO to support cardiac operations. The inflammatory response is minimal, and the incidence of haemolysis and organ failure is much less than conventional CPB. All these factors are well discussed in this book.

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Robert H. Bartlett, MD, PhD

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Preface

Minimal ExtraCorporeal Circulation (MECC) systems are used for more than one decade in clinical practice. However, most of the cardiac surgeons and perfusionists do not really know much about them. Despite the excellent clinical results from their use, which are widely dispersed into the literature, and the recent meta-analyses, which show prognostic superiority as well as reduced postoperative morbidity of MECC compared to conventional cardiopulmonary bypass, their penetration in contemporary practice remains low. The main reasons for this oxymoron are the reluctance of the perfusionists to adopt this new technology and the lack of teamwork performance in most cardiac surgical teams. However, MECC requires a learning curve and a more active intraoperative involvement of both the perfusionist and the anaesthesiologist compared to heart surgery with the use of conventional cardiopulmonary bypass. On the other hand, the novel modular systems purge concerns regarding lack of safety when using them. We strongly believe that every cardiac surgical team should at least be familiar with this technology. Moreover, we think it is time to incorporate MECC into scientific guidelines for cardiac surgery.

The aim of this comprehensive textbook is to concisely present the rationale, the principles, the tips, tricks and pitfalls for the use of MECC. This could be the first step towards initiating a training scheme for any cardiac surgical team, and the topics covered in the ten chapters of the book have been thoroughly selected to serve this purpose. We have to sincerely thank the contributors of the book, Bob Bartlett, Alois Philipp, Apostolos Deliopoulos, Adrian Bauer and Frans Waanders who are pioneers in the field. We wish that the readers will find the book useful.

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1 Introduction

The development of the heart–lung machine by John Gibbon at the University of Minnesota revolutionised cardiac surgery. The so-called ever after cardiopulmonary bypass (CPB) or extracorporeal circulation (ECC) was first utilised in 1953 to repair a large atrial septal defect in an 18-year-old woman (Fig. 1.1) [1]. Multiple improvements in CPB technology established the use of ECC with aortic cross-clamping and cardioplegic arrest of the heart as the gold standard technique in cardiac surgery. Regarding epicardial surgery, such as the coronary artery bypass grafting (CABG) procedures, CPB provides optimal conditions (a bloodless field and an arrested heart) for complete and accurate myocardial revascularisation, while in intracardiac procedures, such as valve surgery or repair of structural defects, CPB is considered mandatory. Experience accumulated for almost 6 decades through a huge number of cardiac procedures performed under ECC worldwide has contributed to improved results, despite the increasing percentage of elderly and high-risk patients [2], and established a high level of quality of modern heart surgery over the years.

In the current era, ECC use is universally considered safe, and mortality rates from cardiac surgery are consistently low [3, 4] in large series of patients. This resulted mainly from technological advances in CPB equipment as well as from continuous improvement in surgical technique used in the fields of myocardial protection, anaesthesia and management of postoperative complications. Moreover, numerous technical modifications have been implemented in CPB circuit design through the pioneering and collaborative efforts

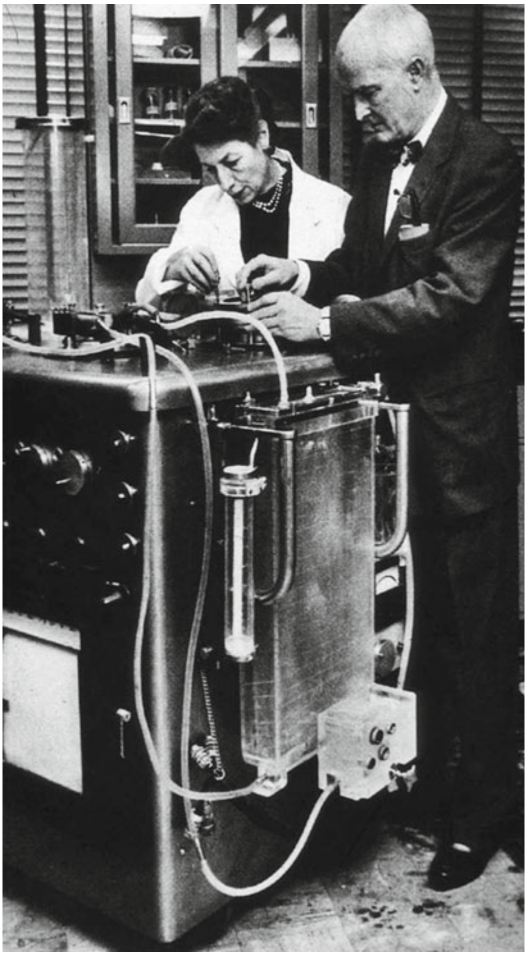

Fig. 1.1 Dr. Gibbon with his wife with the first heart–lung machine

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of physiologists, chemists, physicists, engineers and physicians, who were all motivated by the idea of sustaining life by diverting the native circulation through synthetic surfaces in order to correct treatable lesions of the heart, lungs or other vital organs [5].

However, despite all this progress, the major drawback of ECC is a potential systemic adverse effect through triggering of an inflammatory response syndrome, known as SIRS [6]. Contact of blood with artificial surfaces during CPB provokes a pathophysiological response similar to that of post-traumatic shock, the so-called post-perfusion syndrome, that may lead into SIRS, adult respiratory distress syndrome, sepsis and ultimately to multiorgan failure [7, 8]. In detail, surface-dependent (contact of blood with non-endothelial surfaces and air) and surface-independent factors (hypothermia, ischemia-reperfusion, endotoxemia and surgical trauma itself) are thought to induce a complex inflammatory response by activation of different cellular and humoral components of the immune system [9]. Complement activation triggered by contact of blood with foreign material is addressed as an important initiator of this inflammatory cascade [10], which then induces a variety of postoperative complications responsible for the observed postoperative morbidity and mortality [11]. It appears that the magnitude of the inflammatory response to CPB adversely influences clinical outcomes [12]. Hence, the overall morbidity associated with cardiac surgery is relatively high, with over a third of CABG procedures reporting complications [13].

Various strategies have been developed in order to control SIRS after cardiac surgery. They aim to attenuate the deleterious effects of the systemic inflammatory response while preserving the ability of the patient to mount an appropriate defence to the physiological trespasses of the perioperative period. Modulation of the stress response, rather than simple inhibition, is likely to confer substantial benefit [14]. Various attempts have been made for achieving this objective, including pharmacological strategies and modification of surgical techniques and equipment [9, 15].

The off-pump coronary artery bypass technique (OPCAB), which was introduced worldwide in the late 1980s, represents the initial attempt to decrease the CPB-induced inflammatory response. Myocardial revascularisation is performed on a beating-heart without CPB [15, 16]. Forced by the industry, there was an overwhelming enthusiasm for OPCAB technique in the mid-1990s, though medium- and long-term results compared to the gold standard conventional CPB with cardioplegic arrest were lacking [17]. Moreover, the need to reduce operative costs, especially in developing countries, promoted OPCAB procedures [18]. OPCAB gained popularity arguing that the deleterious aspects of CPB could be avoided so as to maintain the functional integrity of major organ systems and gradually became a well-accepted and safe technique to perform myocardial revascularisation. This was based in short-term and midterm angiographic follow-up studies of off-pump constructed grafts which showed comparable results to the conventional technique [19]. Moreover, multiple clinical studies suggested that OPCAB was beneficial in reducing stroke rate, time on mechanical ventilation, need for reoperation, postoperative bleeding, wound infection, renal failure, postoperative length of stay [20], postoperative atrial fibrillation and inotropic requirement [21]. These encouraging early results demonstrated by observational studies were not confirmed in subsequent meta-analyses of randomised controlled trials, which found no statistically significant reductions in short-term morbidity and mortality [22]. Recently, ROOBY study, the largest randomised, controlled, single-blinded trial to evaluate CABG with and without CPB, showed no difference between the two procedures in the rate of postoperative complications. At one-year follow-up, patients who underwent OPCAB had a significantly higher rate of the composite endpoint of morbidity and mortality while they had significantly less complete (fewer grafts done than planned) and less durable (decreased patency at one year) revascularisation [23]. These results tempered the enthusiasm from the technique and raised a strong criticism about its superiority over CABG with CPB. Nevertheless, despite a high level of experience, OPCAB is controversially discussed mainly due to a less than optimal control in the operative field, which may result in incomplete, difficult or even unsatisfactory procedures [24]. Technical difficulties and limitations predominantly due to haemodynamic instability may result in inefficacious coronary anastomoses with a lower graft patency [25], in the possibility of incomplete revascularisation [19, 26, 27], and a higher rate of early reoperation [28]. Due to these drawbacks, the vast majority of myocardial revascularisation procedures worldwide (from 60 to 85 %) are still performed with the use of CPB [17, 29].

The limitations of off-pump technique are related mainly to haemodynamic instability occurring as a consequence of cardiac displacement. This problem has stimulated the development of novel devices that provide temporary circulatory support with fewer adverse affects than conventional pump-oxygenator circuits [30]. In an attempt to attenuate the pathologic effects of CPB, miniaturized or mini-extracorporeal circulation (MECC) systems have been developed to allow the ease of on-pump surgery while tempering the disadvantages (Fig. 1.2) [31]. There is an opinion that the MECC systems may be considered as a simplification of traditional CPB and may, therefore, represent an attractive alternative between on-pump and off-pump CABG by significantly attenuating morbidity related to conventional CPB while permitting technical surgical conditions more favourable compared to the off-pump technique. The authors believe that MECC system represents a totally new philosophy in applying cardiac surgery and the system itself should be considered more as an extracorporeal cardiac assist device with a centrifugal blood pump, an oxygenator and a closed loop of short tubing rather than a modification of the traditional CPB circuit.

Technology supporting the implementation of CPB has advanced beyond recognition since its introduction. However, throughout the 1990s, pump-oxygenator circuits and cardioplegia techniques plateaued [32]. The principle of MECC was developed and successfully introduced in clinical practice by Alois Philipp and colleagues at the University Hospital of Regensburg and was initially conceived to assist circulation in beating-heart procedures [33]. Later on, its application was extended to CABG with cardioplegic cardiac arrest [34]. Miniaturized ECC systems integrate all the advances emerged through clinical research towards minimising the side effects from CPB use. The basic idea is to ensure adequate perfusion by a closed, less aggressive and more biocompatible pump-oxygenator circuit. Thus, the beneficial effects of these systems are derived from the implementation of all advances into one technology. This refers to the use of closed rather than open venous reservoirs, heparinized tubing and oxygenators, minimising prime volume, use of a centrifugal pump, elimination of cardiotomy suction and traditional venous reservoir (Fig. 1.3). Mini-CPB significantly reduces the foreign surface area-blood contact, thus attenuating the

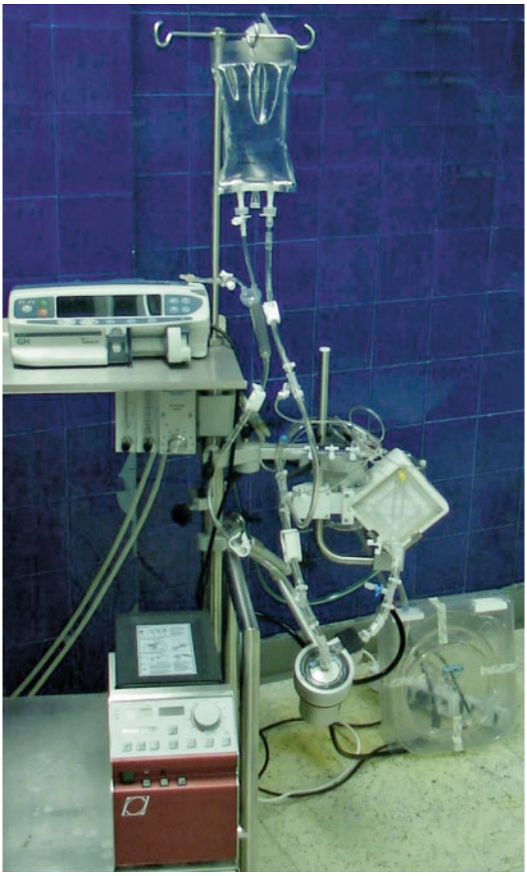

Fig. 1.2 The miniaturized extracorporeal circulation system – MECC (MAQUET Cardiopulmonary AG)

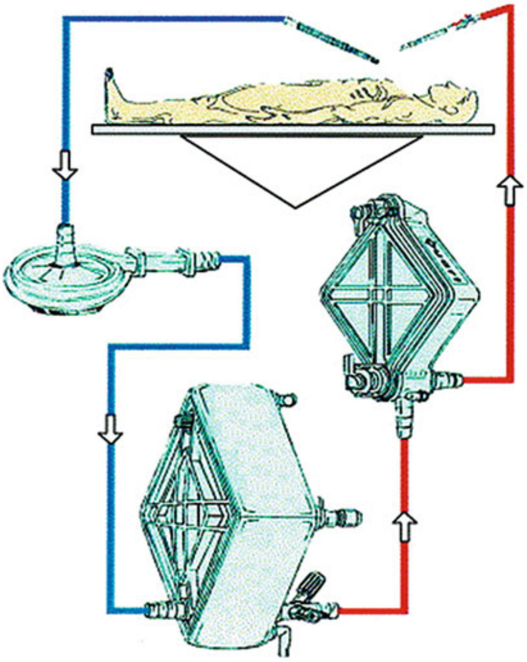

Fig. 1.3 Classic schematic drawing of MECC system; note the simplicity of the circuit

systemic inflammatory response syndrome [35]. The system eliminates blood–air contact by avoiding a venous reservoir and by means of suction blood separation, minimizes haemodilution and mechanical blood trauma which result in less systemic blood activation, shed blood loss, need for colloid–crystalloid infusion and need for blood transfusion [36, 37].

The idea of MECC systems has initiated important new efforts within science and industry to improve the biocompatibility of CPB systems and minimize their side effects, offering better global end-organ protection. To achieve this goal, such a system should include a blood pump with optimal biocompatibility, especially low thrombogenicity, reduced haemolysis and activation of leukocytes as well as mediators; all components should be minimized to reduce the priming volume required and thus haemodilution, leading to fewer blood transfusions; it should provide access to all coronary regions as well as to intracardiac structures; temperature management of the different forms of normothermia or hypothermia depending on the need should be possible; use of modern concepts of myocardial protection, like blood cardioplegia, must be easy to integrate; for open-heart surgery, safe de-airing procedures must be possible; and it should support modern concepts of fast-track anaesthesia. Conventional extracorporeal circulation (CECC) systems can meet these criteria only in part [17].

MECC has adopted all modern technology and integrated the results from research in its structures. The basic rationale for miniaturization of ECC is to reduce foreign surfaces as well as priming volume and therefore to limit SIRS and alterations in perioperative haemostasis [38]. Coating techniques stand as an important step towards higher haemocompatibility of blood-contacting surfaces in the artificial devices used for ECC. Thus, heparin-bonded devices demonstrate lessened humoral and cellular activation, better platelet protection and more favourable postoperative lung function. Employment of these devices results in reduced blood loss and improved clinical outcome that translates into shortened hospital stay, reduced mediastinal bleeding and cerebral complications [8]. Use of such heparinized circuits in the MECC systems results in the ultimate use of less heparin; ACT, when using the MECC circuit, has to be over 300 s while in the CECC systems this has to be about 50 % more. This policy is followed by a low-dose administration of protamine, based on a heparin–protamine titration method, and this restores blood coagulation, but not the platelet responses to thrombin during heparin neutralisation; an overdose of protamine activates platelets and may predispose patients to excessive bleeding after cardiac surgery [39]. MECC systems have reduced tubing length, hence, they offer low prime volume requirements compared to the standard prime volume of the open CPB circuits integrated in CECC systems; this results in reduced haemodilution and, ultimately, less blood loss during the procedure, fewer blood transfusions and earlier patient recovery [40]. Furthermore, use of centrifugal pumps instead of roller pumps in the circuit reduces platelet aggregation and results in lower susceptibility to postoperative thrombotic complications [41]. Integration to the ECC circuit of both a centrifugal pump and heparin coating improves further CPB biocompatibility

[42]. Avoidance of cardiotomy suction not only reduces the recirculation of debris and lipids from the shed mediastinal blood but also reduces haemolysis [43], restores haemostasis and attenuates postoperative bleeding [44]. Moreover, the combination of tubing coating and avoidance of shed blood recirculation has been shown to maintain physiological coagulation levels and markedly reduce red blood cell trauma in ECC procedures [45].

Numerous clinical studies have shown that MECC does not reduce mortality but exerts a considerable beneficial effect on postoperative morbidity compared to conventional CPB. Reported benefits include reduced haemodilution, mediastinal bleeding, need for blood transfusion, improved myocardial protection, reduced length of intensive care unit stay and better renal, inflammatory and neurological function [46–49]. However, a recent meta-analysis of the reported randomised trials including 24 studies with a total of 2,770 patients concluded that use of MECC in coronary and valve surgery resulted in improved short-term outcome as reflected by reduced mortality and morbidity compared with conventional ECC [50]. Use of MECC was associated with a significant decrease in mortality, in the risk of postoperative myocardial infarction and neurologic events; it was also associated with reduced SIRS, haemodilution, need for red blood cell transfusion, better myocardial protection, reduced incidence of low cardiac output syndrome, need for inotropic support, higher peak creatinine level, reduced occurrence of postoperative atrial fibrillation, duration of mechanical ventilation and intensive care unit stay [50].

Comparing MECC with OPCAB, there is a quite good simulation of their results using MECC [51, 52]. However, off-pump can be applied only in epicardial heart surgery. As the majority of open-heart procedures mandate use of CPB, MECC offers a new way of practising cardiac surgery and not only operating on diseased coronaries. Interestingly, the total amount of valve, multivalve and redo procedures is still increasing.

Introduction of mini-CPB circuits allows for a comparison of perfusion outcomes between different centres. Indeed, these circuits have a comparable fluid dynamic characteristic and surface area. All of them have a haemocompatible coating, and the technique avoids return of the pleuropericardial aspirations into the systemic circulation. As a consequence, results are very comparable to those obtained by beating-heart surgery [53]. In recent years, many companies have released into the market a series of CPB devices, inclusive of a centrifugal pump, an oxygenator, circuit and accessories that have been defined as mini-CPB or minimally invasive CPB or in a similar fashion [54].

In principle the MECC system is characterised by reduced postoperative bleeding and improved blood cell preservation. However, blood trauma still remains a severe drawback of currently available MECC systems. Miniaturized CPB systems in open-heart surgery appear to limit inflammatory response but a small bioreactive free perfusion circuit is still to be found [55]. Moreover, due to the fact that during a MECC procedure there can be limited decompression of the heart during aortic cross-clamping and the use of suckers or vents is only possible by means of a cell-saving device, thus removing the plasma, concern was raised about the benefits of these systems. In order to overcome this drawback, we advocate use of a pulmonary artery vent integrated to the venous bubble trap of the circuit which alleviates the heart. Moreover, use of a soft cell reservoir, which may store intermittently some blood from the patient in case of volume overload, ultimately decompresses the heart and offers a bloodless field for accurate suturing of the coronaries or the prosthetic valves. Limited venting possibilities, air leaks and difficult volume management in the presence of massive bleeding make surgery using a MECC system more cumbersome. New developments in MECC systems realised these shortcomings. Air filters, vents and even cardiotomy suckers have been added to the system in order to facilitate open-heart surgery and valve replacement procedures.

This book consolidates current evidence and assesses whether MECC is a viable alternative to conventional CPB. It describes the pathophysiology of CPB, the contemporary available equipment, the perfusion principles, the optimum anaesthesiologic management and the surgical considerations during MECC procedures. It also analyses the results of different studies that evaluate surgery with MECC compared to CECC and to OPCAB, the application of MECC in valve surgery, its use in other cardiac as well as noncardiac pathologies and the future perspectives of this technology. It is widely accepted that there is a relatively slow adoption of this new technology into routine clinical practice. The low penetration of MECC in contemporary practice means that few surgical centres have accumulated sufficient experience to share it with the scientific community. This book intends to expand the adoption of the new and promising technology of mini-CPB systems in heart surgery. It aims to provide an up-to-date and comprehensive overview providing practical advice on how to use MECC systems for those who are new to the field as well as tips, pitfalls, research and clinical evidence and latest developments. It also offers a systematic review of all published studies with a variety of commercially available MECC systems. This book will enable physicians to gain a better understanding of these new systems as well as to understand the rationale for their use in cardiac surgery. MECC requires a multidisciplinary approach for applying it safely and for obtaining the best results from it, and this book will serve as an essential reference guide for all health care professionals working in the cardiac surgical operating room, in particular cardiothoracic surgeons, anaesthesiologists and perfusionists.

Having already very good results from the contemporary way of performing cardiac surgery, further improved patient outcomes are going to take a concerted team effort to achieve, from the point of less traumatic surgical technique, improved biocompatibility and shear resistance of circuits, monitoring and minimizing of ischemia to organs, minimal cross-clamping trauma, optimised blood management and combinatorial drug strategies. Surrogate endpoints for major organ dysfunction will play an important role to make sense of multiple interventions by the cardiac surgical team and to monitor continuous improvement to patient outcomes [56]. Applied MECC systems as the preferable way to practise heart surgery may serve this purpose and may have important implications to the healthcare system.

The question brought up lately in the literature whether MECC is an evolution or revolution in cardiac surgery [30] has to be eventually answered. We hope the reader will find the answer himself in the data presented in this book.

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Pathophysiology of Cardiopulmonary Bypass

2

Cardiopulmonary bypass (CPB) has been established for the last 60 years from the time it was introduced into the clinical practice back in 1953 [1] as the gold standard technique for performing cardiac surgery. Especially in coronary artery bypass grafting (CABG), CPB creates an ideal setting for complete revascularization because all coronary anastomoses are performed in the presence of a bloodless surgical field. However, it is associated with significant morbidity, related to pulmonary, renal, neurological and gastrointestinal disorders. The underlying mechanisms are multifactorial, including surgical trauma, haemodynamic disturbance and blood contact with the foreign surfaces of the CPB system [2–5]. It is recorded that only about 65 % of conventional CABG procedures reported no complications, and the morbidity of CABG is largely attributed to the use of CPB [6]. This is mainly due to the fact that use of CPB is associated with a systemic inflammatory response. It is already 30 years now when Kirklin et al. reported that the exposure of blood to a large foreign surface such as the extracorporeal circulation (ECC) activates the complement system [7]. The contact activation of blood cells with artificial surfaces and air, the operative trauma itself, ischaemia-reperfusion injury, haemodilution and endotoxemia caused by intestinal hypoperfusion are the predominant triggers of complement activation, alteration of the cytokine steady state, alteration of coagulation and fibrinolysis, activation of immune-competent cells and endothelial damage [8]. This leads clinically to a postperfusion syndrome characterised by fever and fluid accumulation in the interstitium [9]. This so-called systemic inflammatory response syndrome (SIRS) is similar to sepsis [3, 6, 10, 11]. Patients who experience severe SIRS often require longer duration of ventilatory support, have increased postoperative bleeding and demonstrate increased capillary permeability leading to fluid shifts and multiorgan failure mainly involving the lungs, the kidneys and the central nervous system. The SIRS is complex and can be partly attributed to the nonendothelial lining of the pump tubing, the damaging effect of shed pericardial blood, the cardiotomy reservoir and the blood–air interfaces. It is also incited by the wide fluctuations in temperature and ischaemia-reperfusion injury. Complement activation, neutrophil activation with degranulation and proteolytic enzyme release, oxygen-derived free radical production, endotoxin as well as cytokine release, nitric oxide, endothelin and platelet-activating factor production result in a sustained and amplified SIRS (Fig. 2.1). The clinical manifestation of this inflammatory response varies, while it can be sometimes fatal [13–19].

The SIRS which is also called “the capillary leakage syndrome” as well as “the reperfusion injury of the lungs and the heart” are entities reflecting the possible clinical impact of an unphysiological activation of the immune system. An activation of the immune system is observed during any operative procedure as a physiological response to the surgical trauma [20]. Hence, SIRS is not an exclusively side-effect

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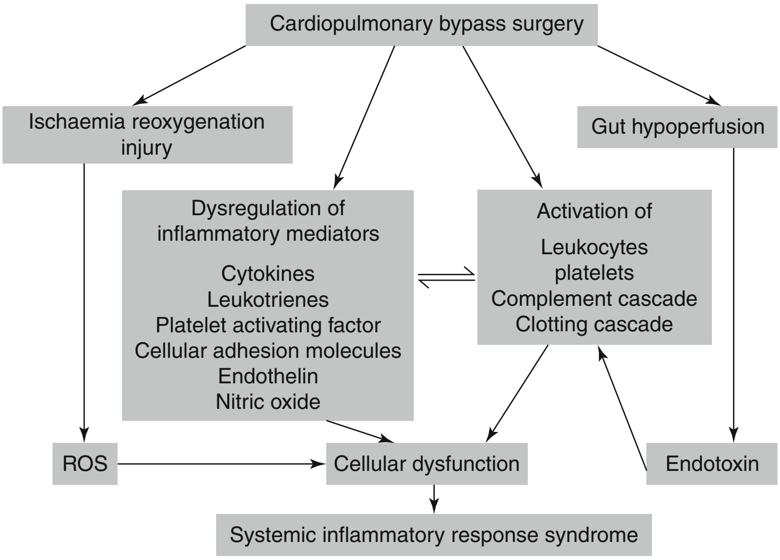


Fig. 2.1 Activation of systemic inflammatory response triggered by CPB. *ROS* reactive oxygen species (From Melley et al. [12])

of CPB use but this machine remains a major factor in SIRS apparition. Generally, the pathophysiology of SIRS is not completely known; it results in vascular injury and tissue damage by leukocyte-endothelial interactions mediated by cytokines and adhesion molecules. The complex process of SIRS involves several protein families including proinflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor α, adhesion molecules (i.e. sVCAM-1) and chemokines (i.e. PMN elastase); another cytokine (interleukin-10) might have regulatory effects during the inflammatory process [15, 21–25]. The activation of neutrophils, resulting in the excessive release of elastase and oxygen free radicals, has been shown to play a significant role in systemic inflammatory responses caused by CPB [26, 27]. Moreover, although the development of pulmonary injury associated with CPB is complicated, recent studies suggest that release of protease enzymes and oxygen radicals from activated neutrophils is a final common pathway, resulting in the endothelial injury of the pulmonary microcirculation [28]. One of the most important mechanisms in the initial phase of SIRS and acute lung injury is priming, activation and sequestration of polymorphonuclear neutrophils (PMN). As has been already discussed, SIRS with CPB is most likely caused by contact between blood and the artificial surfaces of the perfusion circuit. This insult makes PMN prime, and when a second insult such as endotoxemia occurs, PMN will adhere to activated endothelium and release various cytotoxic contents, such as neutrophil elastase. Neutrophil elastase is an extremely cytotoxic protease, which degrades connective tissue components along with fibrinogen, coagulation factors, antithrombin III and complement [29]. It has been shown that 5–10 % of circulating leukocytes become adsorbed to circuit surfaces during CPB. The great majority of these are neutrophils, which are significantly activated. Adsorbed leukocytes constantly encounter the systemic circulation, possibly stimulating systemic activation of coagulation and inflammation [30].

The endothelial cell plays a pivotal role in the regulation of vascular homeostasis. Structural and functional damage to the pulmonary vascular endothelium has been demonstrated after CPB use. This is thought to lead to a cascade of events resulting in increased pulmonary vascular resistance and platelet and neutrophil activation and sequestration [31, 32]. Endothelial-derived nitric oxide (NO) produces vasodilation and inhibits platelet aggregation and leukocyte activation. Impaired production of NO may account for the increased pulmonary vascular resistance (PVR) encountered when using ECC and the efficacy of inhaled NO therapy for pulmonary hypertension and reperfusion injury [33, 34].

The bypass machine induces inflammation through contact between granulocytes and the foreign materials in the circuit. Therefore, the materials and methods used for extracorporeal circulation are important determinants of the degree to which neutrophils and chemical mediators are activated. Use of heparin-coated circuits could attenuate the intensity of the inflammatory reaction with respect to cytokine release and neutrophil activation [35, 36]. Gourlay et al. demonstrated that neutrophil activation increases proportional to the artificial surface area but in inverse proportion to the haematocrit. The cardiotomy suction reservoir reinforces the inflammatory response not only by its additional artificial surface but also by introduction of a blood–air interface [37].

The severity of postoperative SIRS and the possibilities of developing acute lung injury (ALI) or multiple organ failure, or both, may be related to precedent or subsequent insults such as endotoxemia, hypoxia and ischaemia-reperfusion injury that would not cause clinically significant results individually. Among those insults, endotoxemia is particularly important, because it is the strongest trigger for the development of ALI and its mortality and morbidity remain very high [38]. Activated PMN, monocytes and macrophages produce IL-8; neutrophil elastase released from PMN further induces IL-8 expression. Elevation of plasma IL-8 level may be related to cardiac and pulmonary dysfunction [39]. Hence, for the prevention or treatment of SIRS and ALI from CPB, several distinct strategies were used to protect against injury related to PMN. Leukocyte depletion using a leukocyte filter or circuits with copolymer surfaces contributed to some improvements in experimental and clinical studies. Although they may be useful, it is probably difficult to improve the clinical course if other insults are added to ECC. This is because a large percentage of PMN have already strongly adhered to the endothelium, have accumulated in pulmonary tissue and have released elastase by the time a diagnosis of ALI is made [40–42].

The bypass-induced inflammatory response is characterized also by the activation of the coagulation, fibrinolytic, kallikrein and complement cascades [7, 43]. The complement system, which is one of the major pathways of inflammation, is activated during open heart surgery with CPB in a multifactorial way. Activation takes place predominantly through the alternative pathway and results in the generation of the anaphylatoxins C3a and C5a and formation of the membrane attack complex (C5b-9). The half-life of C5a in the circulation is extremely short and instead sC5b-9 is often used as a more reliable but indirect measure of C5a activation. Circulating levels of PMN elastase provide a measure of degranulation of neutrophils. Both C5a and IL-8 are important triggering mechanisms for activation of neutrophils in the inflammatory response. Degranulation induces tissue damage during CPB. The causes of cytokine release as well as complement activation are multifactorial. Other factors than the exposure to artificial surfaces such as surgical trauma and tissue ischaemia may possibly be more powerful stimuli [7, 44–46]. Moreover, tissue injury itself caused by surgical incision contributes to complement activation in patients who are operated for heart problems off-pump [47].

The dysfunction of organ systems in the postoperative period have been linked to SIRS and may be exacerbated by coagulation derangement [48, 49]. When vascular injury occurs and blood interferes with tissue factor, haemostatic action occurs in the following order: fibrin network formation occurs through the coagulation pathway, fibrin is removed by fibrinolysis, and fibrinolysis is then suppressed [50, 51]. Physiologic activation of blood coagulation is mediated almost exclusively via the tissue factor pathway, and t-PA is the major physiologic activator of fibrinolysis. However, ECC is not a physiologic condition and blood is exposed to nonbiological surfaces. Under these circumstances, contact activation also plays an important role for activation of both coagulation and fibrinolysis [52]. Activation of blood protease systems increases the risk of bleeding, along with the thrombotic and inflammatory complications associated with bypass use [53].

This multifactorial process is responsible for postoperative complications such as haemolysis, postoperative bleeding and single or multiple organ dysfunction particularly in high-risk patients [8, 54, 55]. During ECC, blood–foreign surface reaction on the inner surface of the circuit activates the contact phase of coagulation. The contact phase of coagulation is composed of factors XII and XI, prekallikrein and high-molecular-weight kininogen. Factor XII, which is activated on the foreign surface first, leads to the activation of prekallikrein to kallikrein, which activates factor XII. The active form of factor XII (XIIa) activates factor XI, which then activates the humoral coagulation cascade [56–58]. CPB also induces an increased thrombin-mediated or plasmin-mediated consumption of haemostatic factors and has a direct activating effect on platelets [57, 59, 60]. Furthermore, it is responsible for a rapid, early decrease in platelet numbers due to haemodilution [61]. Activation of blood cells and the coagulation, fibrinolytic and complement systems increase with time on bypass [62].

To inhibit blood clotting during cardiopulmonary bypass, heparin is used. Heparin, a glycosaminoglycan, promotes the activation of antithrombin III, increasing the affinity of antithrombin III for thrombin and potentiating the thrombin inhibitory potency of antithrombin III by more than 1,000 times. However, even with standard heparinization and heparin-coated circuits, thrombin generation is inevitable in cardiac surgery on CPB [50, 55, 63]. The defect of the bypass is not a defect intrinsic to the platelet but is an extrinsic defect such as an in vivo lack of availability of platelet agonists. The near universal use of heparin is likely to contribute substantially to this defect via its inhibition of thrombin, the preeminent platelet activator [60].

It is suggested that the amount of circulating thrombin and the severity of coagulopathy associated with CPB are substantially decreased by the fact that blood from the operative field is not added to the perfusion circuit, which is obtained by using a closed system. Besides its effects on coagulation and haemolysis, the recirculation of aspirated blood contaminated by tissue contact also decreases mean arterial pressure as a result of prostacyclin and prostaglandin E2 release [64]. This was shown to be the case for platelet degradation by Edmunds et al. with postoperative platelet count and percent difference in platelet count correlating significantly with the length of the pump time [65]. Cardiotomy suction and open venous reservoirs have been demonstrated to contribute to the activation of the coagulofibrinolysis and inflammation systems resulting in a significant increase in thrombin generation, neutrophil and platelet activation [66]; however, the contribution of each component has not yet been comparatively examined [62, 67–70]. All these may result in postperfusion organ damage and postoperative bleeding. Coating the foreign surfaces with heparin has shown good results in clinical as well as in biochemical studies. A clarification of the diverse effects of heparin, foremost its proinflammatory properties and the risk of bleeding associated with its use, led to the concept of reduced systemic heparin dosage, which is possible in conjunction with heparin-coated circuits [63].

Haemodilution is a widely recognised and documented consequence of ECC and it is considered as the primary cause of impairment of homeostasis. It leads to decreased levels of coagulation and fibrinolytic proteins in terms of drop in coagulation and fibrinolytic proteins. Low haematocrit which is the clinical result of haemodilution from CPB use has been identified as a principal contributor to organ dysfunction and increases the risk of long-term morbidity and short-term mortality [71–77]. Haemodilution is unavoidable because of mixing of the crystalloid prime solution with the patient's blood. The on-pump nadir haematocrit value can widely change according to patient body mass index and pre-CPB haematocrit level, as well as circuit prime volume. Also, during CPB a lower haematocrit value is a potentially changeable risk factor [74, 78, 79]. Haemodilution from ECC also leads to the usual need of blood transfusion after cardiac surgery. A dose–response relationship was reported between the number of units of whole blood or packed red blood cells received and the prevalence of infection, which was believed to be related to transfusion-related immunosuppression [77, 80]. It has been shown that blood transfusion in cardiac surgery increases morbidity and mortality and it is associated with negative effects of health-related quality of life. The use of homologous blood products has been linked to increased frequency of organ dysfunction or failure, neurological dysfunction, wound infection and long-term morbidity and mortality, in addition to the risk of transfusion-related communicable diseases [81]. In general, blood transfusion is associated with increased resource utilisation and contributes to longer intubation time and ICU stay, in addition to greater postoperative morbidity and 30-day mortality rates [76, 82–88].

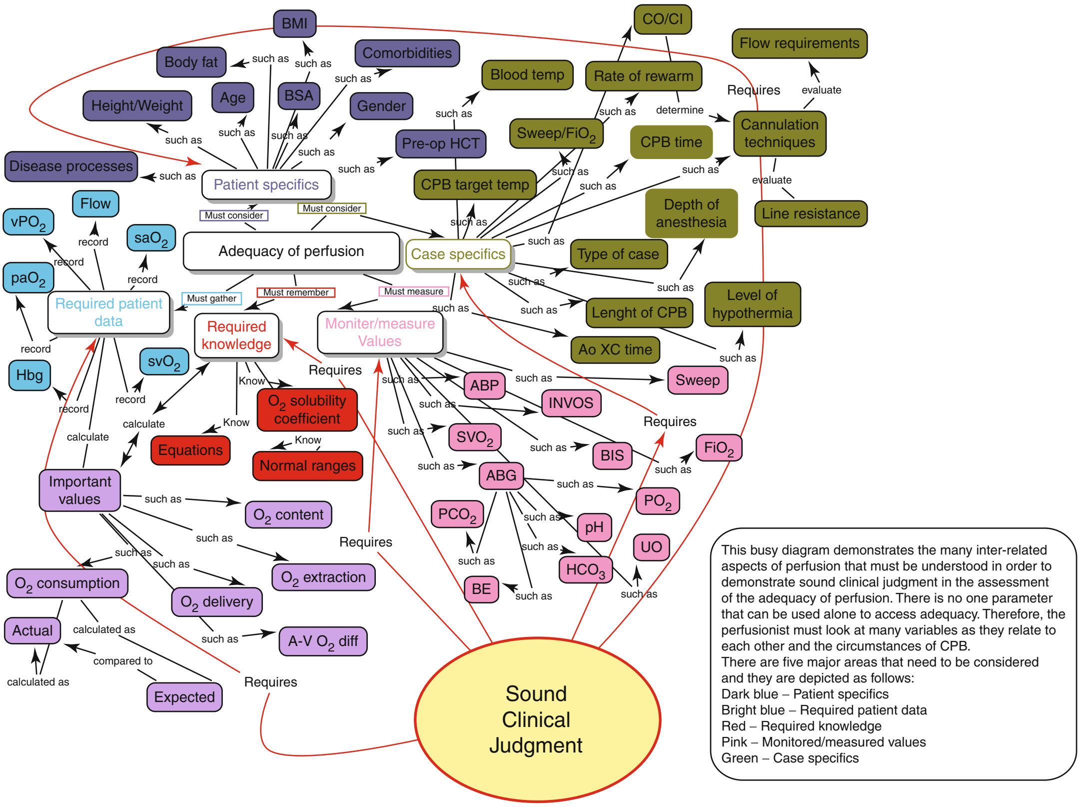
There is an ongoing discussion regarding the result from the pericardial shed blood use on SIRS. Svenmarker et al. compared cardiotomy suction with cell saver for salvage of pericardial blood with reference to proinflammatory cytokines and complement activation. They found that pericardial suction blood contained higher concentrations of proinflammatory cytokines, but no differences were found on terminal complement complex [89]. Joharchi et al. compared inflammatory parameters in elective CABG patients in whom suctioned blood was retained or retransfused at the end of the operation. Systemic levels of PMN and IL-6 were significantly increased in those patients with retransfusions. Clinically, the authors did not observe differences [90]. Retransfusion of pleuro-pericardial shed blood could obscure possible improvements in the biocompatibility of extracorporeal circuits and the overall effects of the material-independent blood activation (blood–air interface, cardiotomy suction, haemolysis, etc.) may finally blunt the total effect of biocompatible surfaces [68, 91–95]. Interestingly, haemolysis provoked by the addition of air in the cardiotomy suction system in an in vivo experiment showed a tenfold rise compared to controls [96]. Other detrimental effects of shed blood have been identified as induced by lipid micro-embolization, activated complement or cytokine release by pooled leukocytes [97, 98]. The cellular debris and lipid microparticulates which are contained in the blood suctioned by standard cardiotomy suction are associated with lipid microembolization in the brain [99, 100]. Likewise, the brain injury marker, S100b, has been also indicated to play a pivotal role in the deleterious effects of cardiotomy suction [99, 101]. Despite the weak evidence so far, avoidance of shed blood recirculation has been proposed to minimise these effects. The cardiotomy suction has been replaced in some institutions with alternatives, such as cell salvage, improving biocompatibility; however, the biggest drawback with the autotransfusion cell-saver device is that the plasma proteins, coagulation factors and platelets of the shed blood are discarded [102, 103].

Besides embolization of lipid microparticles, CPB carries the risk of air embolism, even though the number of gas bubbles developed into the circuit decreases over time [104]. The evolution of microbubbles into the system is unavoidable and can be observed in virtually all patients undergoing extracorporeal circulation [105]. They are formed along temperature gradients in the membrane oxygenator, as a consequence of drug administration into the extracorporeal circuit, and by adhesion of air on the inner surfaces of the tubing during priming [106]. There are numerous air bubble sources, including venous cannulation site, vent use, patient anomalies, administration of medication via the sample port into the venous line, blood sampling, active kinetic drainage using a centrifugal pump to drain the patient and manipulation of the heart during surgery while on bypass [107]. Additionally, suctioning blood into the circuit contributes to this phenomenon since the procedure mixes air with blood and forms bubbles, often in a foam-like matrix. These bubbles are large and consist of nitrogen. Hence, they are more stable and are associated with other blood products or aggregate material. The larger stability is due to the differences in solubility of nitrogen in blood compared to oxygen and carbon dioxide. Due to this, a larger risk to the patient is promoted when filtration techniques are inadequate [108, 109]. The overall clinical result from these air bubbles passing into the patient's blood circulation is microembolism in the capillary bed of all end-organs. Especially, organs with a high capillary density like the central nervous system are prone to consecutive dysfunction. Accordingly, microbubbles are considered a major cause for postoperative neurocognitive dysfunction including memory depression and impairment of attention and perception [110–112].

Kidney impairment commonly complicates cardiac surgery when acute kidney injury (AKI) compounds the effects of pre-existing disease [113]. AKI is mainly related to the adverse effects of CPB, which causes dramatic haemodynamic changes as well as activation of both innate and adaptive immune responses that can initiate or extend renal injury [114]. There are generally different mechanisms which have been described for the AKI including loss of pulsatile flow, diminished renal blood flow, hypothermia and a generalised inflammatory response [115, 116]. Besides several other factors, the kidneys' inefficient oxygen delivery system and high metabolic rate make them vulnerable to ischaemia-reperfusion injury [117]. The temporal pattern of the glomerular filtration rate (GFR) decline and creatinine rise depends on the specific operation performed being lowest in uncomplicated CABG procedures [118, 119]. The impact of the inflammatory response induced by ECC within the kidney is not completely understood. It is interesting that animal models of renal ischaemia-reperfusion injury have clearly demonstrated the pathologic role of interstitial inflammation and the elaboration of proinflammatory cytokines and reactive oxygen species in the production of tubular injury. This local inflammatory response in experimental models is identical to that seen on a more global scale during CPB [120–123].

In the setting of cardiac surgery, impaired renal function has been shown to be independently associated with higher short- and long-term mortality even after adjustment for multiple comorbid diseases [124, 125]. Consequences of AKI include an increase in mortality risk, which can exceed 60 % among patients requiring dialysis. Even when serum creatinine values remain within the normal range, modest increases from baseline values are associated with increased odds of death as well as longer hospital stay [126]. The postoperative incidence of AKI has been assessed using a variety of definitions. Although about 1–10 % of patients after CABG require dialysis postoperatively, up to 5–30 % patients after left ventricular assist device implantation or heart transplantation develop dialysis-dependent renal failure [127–131]. The mortality in patients who develop AKI is persistently high despite significant advances in supportive care. Mortality is also elevated in patients with mild renal dysfunction (creatinine > 1.5 mg/dl) [11, 132, 133]. In current clinical practice, AKI is typically diagnosed by measuring serum creatinine concentrations. Unfortunately, serum creatinine is very insensitive to even substantial declines in GFR. GFR measured by more accurate techniques may be reduced by up to 50 % before serum creatinine becomes elevated [134]. Moreover, several novel serum biomarkers have been evaluated to predict acute kidney failure in cardiac surgery such as IL-18, neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C. It seems that NGAL and cystatin C have excellent discriminatory and predictive performance in the prediction of AKI as early as at ICU arrival [135–137]. It has been suggested that urinary NGAL levels may serve as an early marker for ischaemic renal injury in patients after CPB.

Atrial fibrillation (AF) is the result of the dispersion of atrial refractoriness resulting in multiple re-entry wavelets in the atria [138]. Despite advancements in surgical technique, intensive care methods and pharmaceutical prophylaxis AF is common following cardiac surgery and can occur in over 30 % of patients who receive conventional ECC (CECC) [139]. Transfusion, blood loss and CPB have been identified as risk factors for AF and adverse outcomes such as early mortality [140]. The use of MECC circuits has been associated with reduction in the incidence of postoperative AF. Immer et al. demonstrated an 11 % incidence of postoperative AF in patients who received MECC compared to 39 % in CECC participants ($p < 0.001$) [141]. Wiesenack et al. also reported significantly lower rates of many postoperative complications, including AF as



This busy diagram demonstrates the many inter-related aspects of perfusion that must be understood in order to demonstrate sound clinical judgment in the assessment of the adequacy of perfusion. There is no one parameter that can be used alone to access adequacy. Therefore, the perfusionist must look at many variables as they relate to each other and the circumstances of CPB.
There are five major areas that need to be considered and they are depicted as follows:
Dark blue – Patient specifics
Bright blue – Required patient data
Red – Required knowledge
Pink – Monitored/measured values
Green – Case specifics

Fig. 2.2 Adequacy of perfusion diagram during CPB (Adapted from perfusioneducationonline.com)

well as myocardial infarction, low cardiac output, pneumonia, renal failure and cerebrovascular events [142]. Part of this improved early outcome with MECC could be due to a reduction in the incidence of SIRS and its complications. AF is thought to be triggered by the inflammation associated with the bypass system [115, 143, 144]. Koletsis et al. reported that the incidence of postoperative AF can be predicted by specific preoperative and perioperative parameters [145]. They showed that several factors contribute to the development of this arrhythmia such as intraoperative ischaemic injury, especially when combined with increased stress of the atrial wall. Factors like positive fluid balance and the amount of cardioplegia delivered represent, according to authors, excellent predictors of postoperative AF after conventional coronary artery surgery. The avoidance of the excessive haemodilution and the reduction in transfusion needs using MECC protect the patient from such a positive fluid balance. Moreover, the relative small volume of Calafiore cardioplegia used in MECC systems may further reduce the possibility of AF postoperatively.

In general, multiple physiological changes that occur during CPB render adequacy of perfusion a complex issue (Fig. 2.2); MECC aims to simplify this process.

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3

MECC Equipment

Components of a Miniaturized Extracorporeal Circuit

The search for a less aggressive and more biocompatible CPB circuit led to the development of miniaturized CPB, based on the idea of a closed oxygenator system which avoids contact of blood with air [1]. MECC integrates all the advances in CPB technology in one circuit specifically designed to minimise side effects from extracorporeal circulation. The essential components of a MECC circuit include (1) a blood pump, (2) a membrane oxygenator, (3) arterial and venous cannulae and (4) heparin-coated tubing to connect these devices. Blood–air interaction is avoided by eliminating the venous reservoir and cardiotomy suction. Thus, shed blood is completely separated from the systemic circulation [2].

Complementary to this basic equipment, additional components have been added to the circuit in an attempt to enhance safety and expand its application beyond coronary surgery to valve and other open-heart procedures [3]. These include (1) venous line air-handling devices to reduce the potential complications of venous air entrainment, (2) arterial line filters, (3) a cell-saver device, (4) a soft reservoir-collection bag and (5) venting to prevent distention of the left ventricle.

Blood Pump

In the clinical setting, minimized systems are characterised by kinetically assisted venous drainage through suction applied by a rotary blood pump. In rotary pumps the energy transfer to the fluid is due to velocity deflections within the impeller vanes. As a general concept, the characteristics of rotary pumps are best suited for large volume flows and low pressures.

Rotary pumps have three basic designs: radial (centrifugal), axial and diagonal. Axial pumps are increasingly utilised in ventricular assist devices due to their efficient pumping capability and small size. Centrifugal and diagonal pumps consist of a disposable housing which is coupled magnetically with an electric motor and are considered more suitable for routine CPB [4]. Centrifugal pumps are essentially vortex generators. They operate on the principle of moving fluid by creating a pressure gradient between the inlet and the outlet of the pump. This pressure gradient results from the creation of a vortex by the rotation of the pump head. The rotating motion creates an area of low pressure in the centre and an area of high pressure on the sides. The vortex can be created by spinning an impeller, which may consist of vanes or nested cones that impart motion to the blood by viscous shear (Fig. 3.1).

Centrifugal pumps are characterised as pressure pumps. Blood flow rate during pump function directly depends on the pressure gradient and is inversely proportional to the resistance produced at the outlet of the pump. Resistance is a function of two components: one is the CPB circuit (oxygenator, filter, tubing, arterial cannula), and the second is the systemic vascular resistance (SVR) of the patient. Therefore, centrifugal pump is considered afterload dependent.

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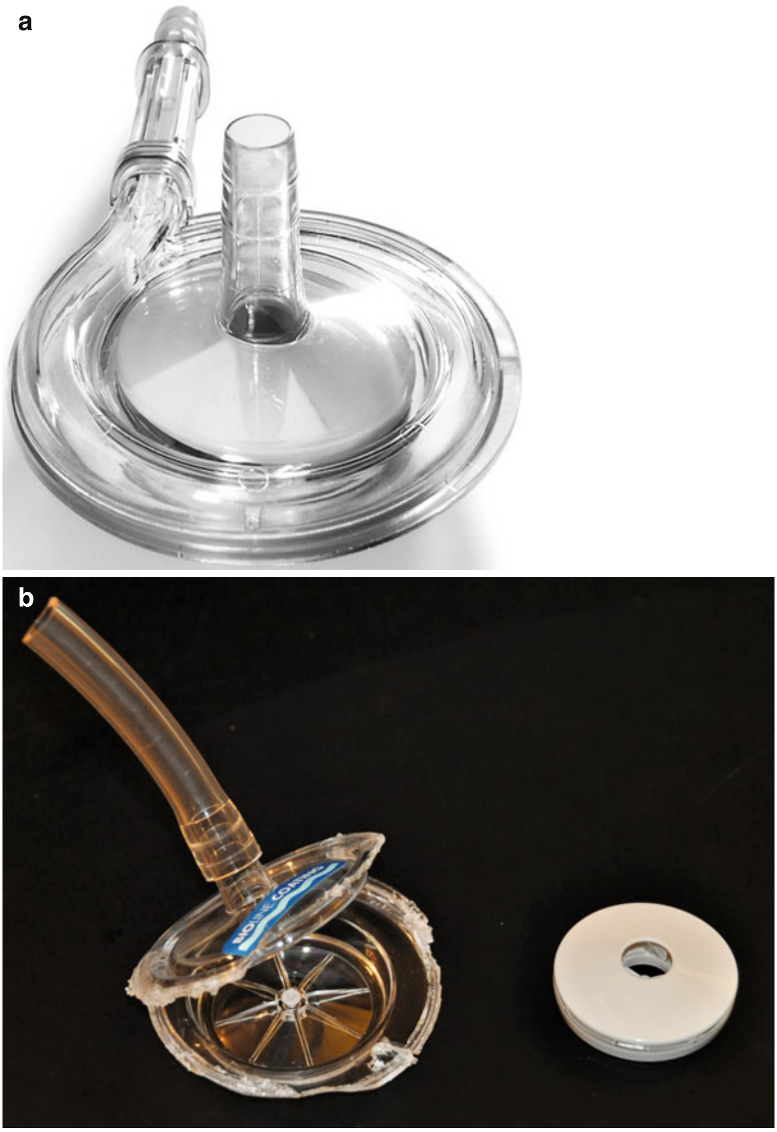

Fig. 3.1 Rotaflow centrifugal pump impeller (Courtesy of Maquet). Plastic cones or impeller (**b**) is mounted inside the conical plastic housing (**a**). The impeller is rotated by the motor outside and beneath the base of the plastic housing (magnetic coupling). The difference of the velocity of the narrow portion of the impeller cone at the top as compared with the wider basal portion of the cone creates a pressure differential which drives the blood through the pump

Unlike roller pumps, centrifugal pumps cannot generate excessive positive or negative pressures when the outlet tubing is occluded. Moreover, when the pressure in the patient is higher than the pressure generated by the pump, for example, when the pump is not running or the RPM is set too low, retrograde blood flow can occur which could cause air entrainment by the Venturi effect, most likely through cannulation sites [5, 6].

With centrifugal pumps, the risk for passing macroscopic air into the arterial line is reduced, while microair will still pass [7]. An inherent safety feature of centrifugal pumps is their inability to pump very large amounts of air. When air fills the pump chamber, the pump is not able to develop sufficient pressure to expel it against the back pressure of the extracorporeal circuit. The amount of microair that passes will depend on the design of a given centrifugal pump, but it may still be sufficient to cause neurologic injury. Table 3.1 gives an overview of the characteristics of commercially available centrifugal pumps used in MECC systems.

Table 3.1 Characteristics of commercially available centrifugal pumps

Model	Priming volume (ml)	Rated flow (l/min)	Rated pressure (mmHg)	Maximum speed (rpm)
Maquet Rotaflow	32	10	750	5,000
Medtronic Bio-Pump Plus	80	8	900	4,400
Sorin Revolution	57	8	800	3,500
Terumo Sarns	48	9.9	700	3,600

Data obtained from the manufacturer's instructions
rpm revolutions per minute

Flow meters are considered indispensable parts of centrifugal pumps. The in-line flow measurement allows accurate adjustment of pump speed in order to regulate flow in response to preload and afterload changes. Two types of measuring techniques are used: one works with an ultrasonic principle, the other with an electromagnetic principle.

With centrifugal pumps, damage to blood elements is attributed mainly on blood–material interaction and fluid dynamics. Shear stress and zones of stagnation and recirculation are associated with suboptimal flow which result in activation of red blood cells, white blood cells and platelets [8–10]. The damage is most prominent in a low-flow high-resistance setting. Generally, centrifugal pumps are considered less traumatic compared with the traditional roller pump. Several studies have shown advantages of centrifugal pumps in terms of haemolysis, platelet activation, proinflammatory cytokine release and complement activation [11, 12]. However, this does not correlate with any difference in clinical outcome [13, 14].

The only currently available diagonal pump is the DeltaStream (Medos Medizintechnik AG, Stolberg, Germany). This pump is designed for use not only in CPB procedures but also for longer duration of support, such as ECMO and ventricular assist [15]. The pump consists of a cylindrical electric motor integrated into the pump and an annular blood flow path that surrounds the motor for cooling purposes. The impeller is positioned between the pump inlet and the motor (Fig. 3.2). The motor cylinder and the impeller have a diameter of approximately 25 mm. The major advantages of this pump are its capability of generating pulsatile flow, small size and simple design [16]. A major drawback is that due to its diagonal design, the RPM necessary to achieve a certain flow against a given resistance will be higher than that of centrifugal pumps (7,000–7,500 vs. 3,000–3,500). This was associated with increased haemolysis [17].

Oxygenator

Microporous polypropylene membrane oxygenators are the predominant design used currently for various MECC systems worldwide (Fig. 3.3). There are two major types or configurations of the membrane material – hollow fibre designs and folded sheets with hollow fibres. The micropores making up the membrane material are less than 1 μm in diameter. The membrane is initially porous, before being exposed to proteins in plasma, which allows for a transient direct blood–gas interfacing at the initiation of CPB. After a short time, protein coating of the membrane and gas interface takes place, and no further direct blood and gas contact exists. Surface tension of the blood prevents gas leakage into the blood phase, which would create gaseous microemboli and denature the blood proteins [18]. The micropores provide conduits through the polypropylene membrane that give sufficient diffusion capability to the membrane for both oxygen and carbon dioxide exchange. After several hours of use, however, the functional capacity of micropore membrane oxygenators decreases because of evaporation and subsequent condensation of serum that leaks through the micropores, and therefore, the majority of these types of oxygenators must be changed after about 6 h.

In the hollow fibre design, blood flow is around the fibre bundle, while gas flows through the hollow fibres, which have a cylindrical shape. Blood flow through the fibre was abandoned due to high transmembrane pressure, the activation of platelets and the increased haemolysis [19]. Blood may flow either perpendicular to the fibre bundle (crosscurrent) or in the direction of the fibres. In the latter case, blood will flow in a countercurrent direction to the gas flow, which confers the advantage of optimised gas gradients during the dwell time. An important feature of membrane oxygenators is the reduction of streamlining, which is the flow of blood through an oxygenator without gas exchange. Streamlining is an example of an extracorporeal ventilation–perfusion mismatch that limits oxygenator performance.

The majority of oxygenators consist of a module for gas exchange with an integrated heat exchanger. An external heater–cooler pumps temperature-controlled water into the heat exchanger,

Fig. 3.2 DeltaStream DP2 (**a**) and DP3 (**b**) diagonal pumps (Courtesy of Medos)

which is separated from the blood by a highly thermally conductive material. This is biologically inert, to reduce the risk of blood component activation. The external heater–cooler allows for precise control of temperature through thermostat-controlled heating and cooling elements within the console. Controlled cooling and rewarming of the patient are crucial to ensure an even distribution of temperature throughout the body and to prevent damage to blood components, proteins and tissues [20]. Adult devices range from 1.8 to 2.5 m^2 of surface area in a variety of configurations, and some are rated as high as 7–8 LPM of blood flow. Surface area of the more common oxygenators used in MECC systems is presented in Table 3.2.

Fig. 3.3 Quadrox-i membrane oxygenator (Courtesy of Maquet)

Cannulae

Standard commercially available heparinized cannulae are used for connecting the patient to the system. Ascending aorta is cannulated using an appropriate-sized arterial cannula. Special care must be taken in managing any active drainage perfusion system such as MECC during cannulation procedure. Hence, 'airtight' cannulation site is secured with two silk ties around the tourniquets and cannula in order to ensure fixation after placement of the cannula. A dual-stage venous cannula (32/40 Fr is usually adequate) is commonly used; two purse-string sutures and two snares for securing airproof sealing of the cannula are also of paramount importance. Arming the purse strings with Teflon pledgets depends on surgeon's preference and on the quality of the right atrial appendage tissue. The venous cannula is then also doubly enforced with two silk ties. Lines are connected with due diligence to avoid gaseous bubbles.

Accurate positioning of the venous cannula is of paramount importance so as to achieve the optimum drainage from venae cavae allowing minimum heart filling throughout the procedure. A three-stage cannula was introduced in an attempt to overcome the issue of poor venous drainage (Fig. 4.5) [21].

Tubing

A principle of MECC is to minimize blood–air contact and provide better biocompatibility by reducing tubing length and by complete heparin coating of a totally closed CPB circuit in order to lower the postoperative inflammatory response

Table 3.2 Surface area of commercially available oxygenators used in MECC systems

Model	Surface area (m^2)	Priming volume (ml)
Maquet Quadrox-i	1.8	215
Medtronic Affinity NT	2.5	270
Sorin Synergy	2	Integrated system
Terumo Capiox	1.5–1.8	270
ECC.O Dideco	1.1	Integrated system
Medos Hilite 7,000	1.9	275

Data obtained from the manufacturer's instructions

[22, 23]. The total length of the MECC circuit is <1 m, and tubing size is usually 3/8 in. for arterial and venous tubing.

Heparin-coated artificial surface was first used by Gott in an effort to mimic the natural endothelial surface [24]. The concept of coating the blood contact surface of bypass circuits with heparin was first explored to decrease the systemic need for heparin. Several methods of coating artificial surfaces with heparin have been developed. There are three broad categories: (i) ionic binding of heparin, (ii) covalent binding and grafting of heparin and (iii) endpoint attachment of heparin.

Ionic binding of heparin represents the best known method of coating artificial surfaces with heparin. It involves treatment of the artificial surface with tridodecylmethylammonium chloride and then adding heparin. The Duraflo heparin surface (Baxter, Irvine, CA) is an example of this type. A major drawback of ionically coated heparin surfaces is that the heparin molecule is able to leach out or off when in contact with the blood, mainly because large molecules such as albumin have ionic affinities for heparin. To improve the stability of heparin, methods of multiple covalent binding with a polyuric material were developed. Though becoming more stable, the desired coagulant property of the surface is inconsistent or absent. Endpoint attachment of heparin leaves its active pentasaccharide exposed to the blood in a predictable fashion which is the binding site for antithrombin on heparin. The Carmeda (Carmeda AB, Stockholm, Sweden) BioActive Surface is based on this process, as described by Larm. It is an imitation of the attachment of heparan sulphate on the endothelial cells [25].

The evidence that use of surface-heparinised equipment would avoid the need for full systemic heparinisation led to the introduction of heparin-coated CPB circuits in combination with reduced systemic heparin levels [26–29]. Heparin-coated circuits attenuate the inflammatory response to CPB and have been shown to preserve organ function during and after surgical intervention [30–32]. Currently available heparin-coated circuits have been reported to be associated with reduced expression of SIRS; this is the common end point of a variety of factors presented in Table 3.3; it should be recognised, though, that it is difficult to solely examine the effect of heparin coating on blood activation, because many other factors independent of ECC contribute to blood trauma [1].

Table 3.3 Factors associated with reduced SIRS with heparin-coated circuits

Reduced activation of neutrophils, monocytes and eosinophils [33]
Reduced activation of platelets [34]
Reduced activation of the complement system [35]
Limitation of cytokine release [36]
Reduced kallikrein/kinin complex activation [37]
Reduced stimulation of the coagulation system [38]
Suppression of tissue plasminogen activator (tPA) release [39]
Reduced plasmin–antiplasmin complex (PAP) levels [40]

The lower systemic heparin dose might subsequently lead to reduced bleeding and less need for blood transfusions [41–43]. In a large multicenter study of patients at higher risk, heparin-coated circuits were associated with a shorter intensive care unit and postoperative hospital stay and had a protective effect on lung and kidney function [44]. Another study has indicated that heparinized circuits reduce the cognitive dysfunction after CPB [45]. Recent data emerged from a large cohort study by Ovrum et al. indicate that the routine use of heparin-coated CPB circuits combined with reduced systemic heparinization is safe and has encouraging clinical results, with low rates of morbidity and mortality, as in OPCAB surgery. They reported few postoperative complications, limited need for banked blood transfusions and short periods of postoperative ventilatory support [46]. However, other studies showed controversial results, indicating no benefit when using heparin-coated circuits [47].

Newly invented synthetic materials have been developed recently in order to improve biocompatibility of the artificial circuit surfaces. Poly-2-methoxy-ethylacrylate (PMEA) is an alkoxyl polymer strain developed for use in CPB by polymerization of the monomer. Because the outer side of the PMEA molecule is chemically inert, its surface has little tendency to react with blood components [48]. ROCSafe (Terumo) circuit is completely covered with a PMEA coating to minimize the adsorption and denaturation of proteins and blood cells during extracorporeal circulation [49]. Circular dichroism spectroscopy revealed that low-platelet adhesion and spreading are closely related to the low degree of the denaturation of the protein adsorbed onto PMEA. Thus, activation of the clotting system should be prevented, and the inflammatory response attenuated [50]. Skrabal et al. failed to detect significant benefit with PMEA coating [51]. Other new developments of coating systems for CPB materials have shown promising results [52–54].

Bioline coating of the MECC system (Maquet) combines polypeptide and active heparin to simulate a natural endothelium. This coating method should ensure stable bonding of the heparin molecule and the immobilised polypeptide. Bioline-coated extracorporeal circuits are associated with platelet preservation, reduced activation of fibrinolysis and lower TNF-α levels indicative of a reduced inflammatory response. Unlike other methods of surface heparinisation, use of Bioline coating is associated with reduced PF4 release and reduced fibrinolysis during CPB [55]. Ranucci and colleagues recently performed a meta-analysis of 4,360 patients retrieved from 36 controlled randomised series, comparing biocompatible circuits with uncoated controls. Patients treated with biocompatible circuits had a lower rate of red cell transfusions and atrial fibrillation and shorter durations of stay in the intensive care unit [56].

Venous Bubble Trap

In keeping with the minimized concept, the first generation of MECC has not included specific de-airing features. Concerns over patient safety by using a MECC system without a safety feature to remove venous air have been raised [57, 58]. Under such circumstances, a potential risk for continuous microair embolisation exists during perfusion. This is of particular importance, when vacuum-based venous drainage is used in a closed-loop circuit concept [59, 60]. A study on the use of a customized MECC system was terminated prior to study completion due to venous air leakage [61]. The use of an air removal device at the venous side of the MECC system could avoid air entering this system and could increase patient safety. A venous bubble trap (VBT) was designed as an air removal device for air separation in the venous line of MECC systems (Fig. 3.4). Within the specified flow rate limits, the bubble trap separates macroscopic air

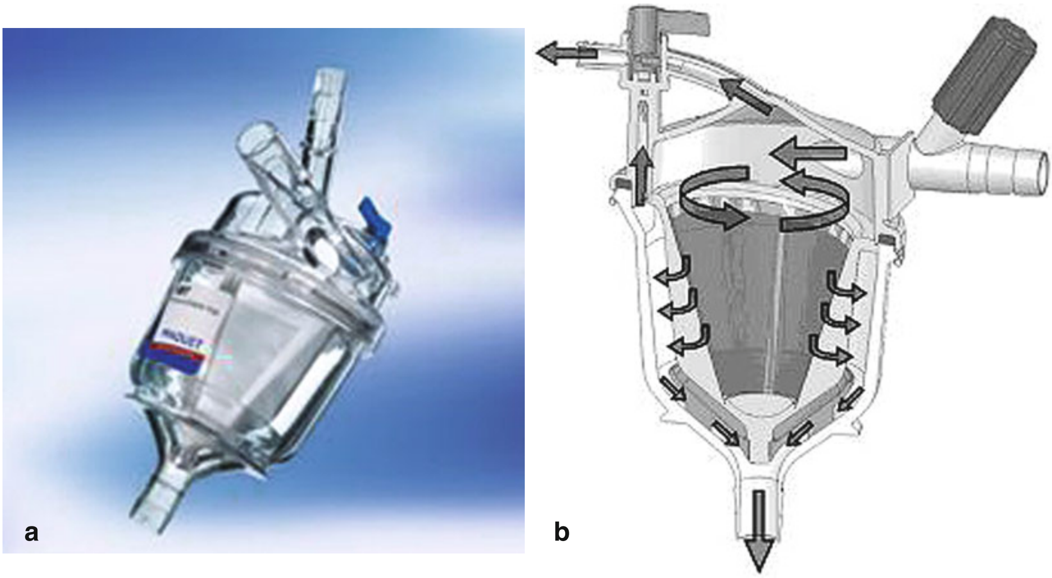

Fig. 3.4 Venous bubble trap. Outer (**a**) and inner (**b**) view. (Courtesy of Maquet)

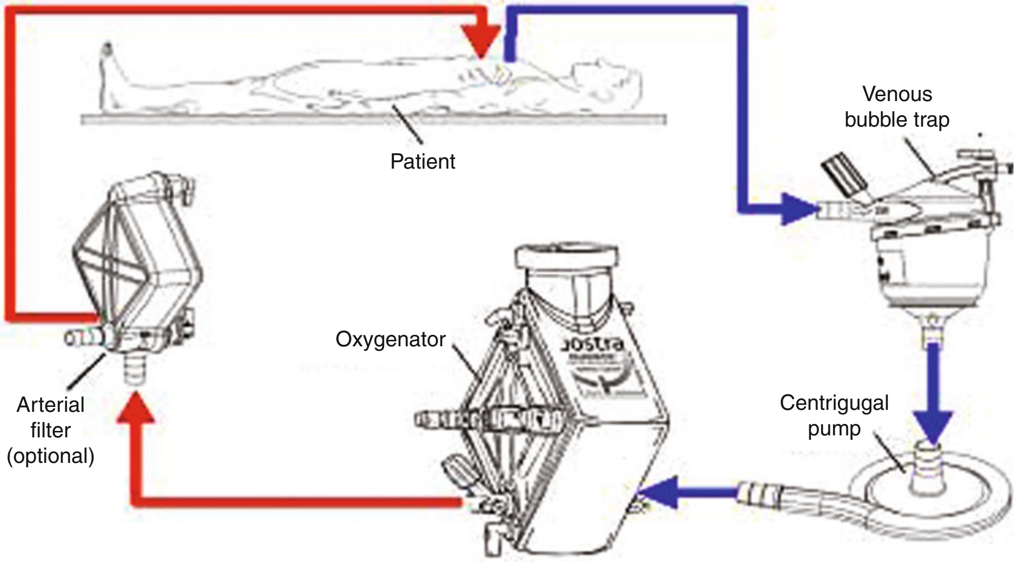

Fig. 3.5 Venous bubble trap incorporated into MECC system (Courtesy of Maquet)

bubbles from the venous line, eliminating them through the deaeration line and out of the extracorporeal circulation, and by doing so supports the perfusionist's obligation to exercise due caution.

The VBT effectively scavenges gaseous microemboli (GME) during uneventful procedures with the MECC circuit. Thus, the VBT strongly increases the safety of this closed-loop circuit concerning air handling. A MECC system with a VBT significantly reduces the volume of GME and strongly reduces the quantity of large emboli (>500 μm) [62]. A VBT can be interconnected in the venous line before the centrifugal pump. The aortic vent line ran through a drip chamber and is then connected to the VBT.

The MECC system is primed with 500 ml and increased to 650 ml, when the VBT is included into the system (Fig. 3.5). Air removal by the VBT is accomplished by a combination of two principles: centrifugal flow and bubble buoyancy. The 175 μm mesh screen separates air from blood and enables removal of trapped air from both sides of the screen through the evacuation port. This air-evacuation port can be connected to the autotransfusion system. The imparted rotational spin in the blood flow in the VBT increases separation and flotation of GME. Pulmonary artery vent is directly connected to the venous bubble trap maintaining a similar level of vacuum suction as in the whole closed system.

In clinical terms, Gerriets et al. showed that a complex and multifactorial problem as postoperative cognitive decline (3-month outcome) could be significantly improved by a bubble trap in a CPB circuit [63].

Arterial Filter

Arterial filters remain a proven safety feature in CPB systems worldwide. Their main purpose is to filter air instead of microparticles. However, with minisystems like MECC any air entrained needs to be removed prior to the pump, as the arterial filter offers only moderate defence against microbubbles. With a completely closed system that incorporates a system of active air removal, such as a venous bubble trap, and automated flow control as discussed above, the arterial filter is not compulsory, or at the minimum is on the wrong side of the pump. Moreover, the arterial filter requires a priming volume of approximately 180–200 ml, thus increasing total priming volume and haemodilution.

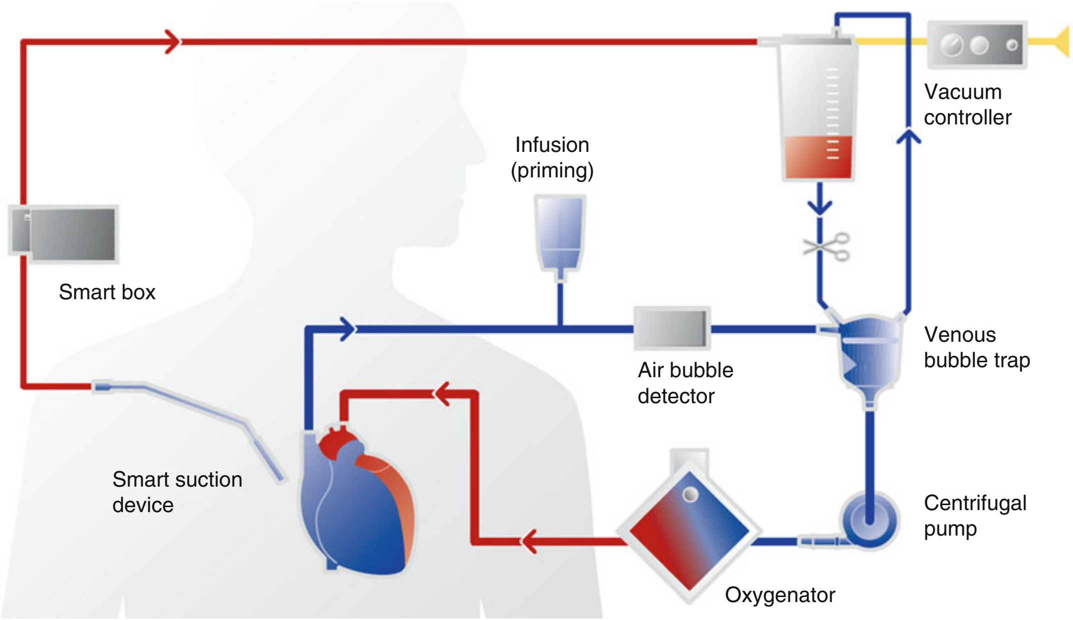

Fig. 3.6 MECC system configuration with incorporation of a SmartSuction and a venous bubble trap (Courtesy of Maquet)

Cell-Saver Device

During surgery with MECC intraoperative shed blood can be collected and processed with a standard cell-saver device. A recent technological advancement towards blood salvage during MECC is the development of an optoelectrical suction device (Cardiosmart AG, Muri, Switzerland) which could be integrated into the system. Aspiration of blood is controlled by an optoelectrical sensor at the tip of the suction cannula, and suction mechanism is started only when the tip of the suction cannula is in direct contact with the blood. The aspirated blood is directly retransfused into the venous line of the circuit, and therefore, no additional suction pump or reservoir is required [64]. However, since this setup renders the system as semi-closed and results in losing some of the qualities of the system, it is not preferred from many surgeons (Fig. 3.6).

Collection Bag: Soft Reservoir

In MECC systems a closed heparin-coated collection bag – commonly referred as soft reservoir – can additionally be filled leading to a reduced circulating blood volume thereby emptying the patient and lowering back bleeding. By installing a soft reservoir bag and connecting a vent circuit during CPB, the blood can be drained into the soft reservoir and be reserved. Therefore, it is possible to freely control both the size of the heart and the visual field of the target bypass area more effectively [65]. The soft or 'bag' reservoir is constructed of soft PVC with a 100–200 μm filtering screen. Typical reservoir capacity ranges between 200 ml and 3.0 L. Incoming venous air must be actively aspirated from the bag. When maintained properly air-free, bag reservoirs will not allow massive air embolism, because the soft bag simply collapses upon emptying, presenting nothing for the arterial pump to pass.

Also, use of a soft reservoir bag in a heparin-coated closed-loop CPB system allows the safe reduction of heparin dosage. This system therefore seems useful for distal aortic perfusion during aortic surgery [66].

Vent

Decompression of the heart during surgery with MECC is particularly important during coronary and valve procedures. A pulmonary artery vent

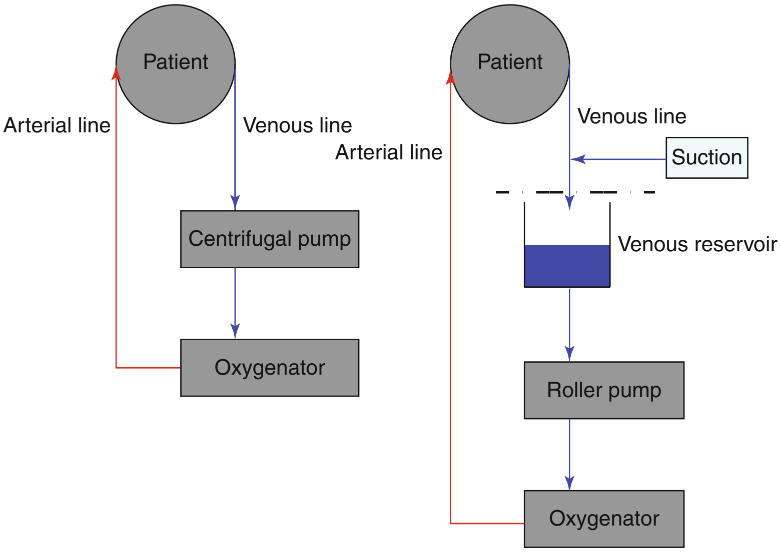

Fig. 3.7 Different configuration between a MECC and a CECC circuit. CECC becomes open at the level of the *dashed line*

can be used and inserted via the main pulmonary trunk distal to the pulmonary valve. It is directly connected to the venous bubble trap maintaining a similar level of vacuum suction as in the whole closed system.

An aortic root vent could also be added to the circuit connected to the venous bubble trap utilising a three-lumen catheter comprising of a small (i.e. 7 Fr) venting needle, a cardioplegia route and a line for root pressure monitoring. Optional sump suction directly through the aortotomy can be used when necessary. This vent may be used intermittently so as to alleviate a blood-filled left ventricle and limit coronary blood flow, creating a more comfortable surgical field. Special concern to avoid sucking air from the coronary arteries through the vent (which will be entrapped in the circuit) has to be undertaken. Continuous monitoring of the aortic root pressure is usually the threshold for venting. Aspirated blood could be directed to a cell-saving device.

Special Features of MECC Compared to Standard CPB

In a conventional ECC (CECC) circuit, deoxygenated blood is removed from the body by venous cannulae usually inserted into the right atrium. Any blood obscuring the operating field may also be cleared with cardiotomy suction or vents. Conventional circuit is described as 'open circuit' because blood from these three sources drains into a central hard-shell venous reservoir with fixed shape and volume where it can freely mix with air (Fig. 3.7). The blood subsequently passes through a membrane oxygenator to supply oxygen, a roller or centrifugal pump to provide an adequate arterial pressure and an arterial filter to remove air bubbles. A heat exchanger allows the temperature of the blood infused back into the body to be controlled. In most procedures, oxygenated blood is returned to the body via the aorta. Therefore, open systems are mainly characterised by direct blood–air contact in the reservoir and passive drainage of venous return. Conventional circuit uses 1/2-in. venous tubing and 3/8-in. arterial tubing size.

Large priming volumes are required in CECC that could result in significant haemodilution with low postoperative haemoglobin concentration and haematocrit level. Many authors have demonstrated the deleterious effects of severe haemodilution during CPB in terms of postoperative morbidity and mortality [67–69]. The hard-shell open venous reservoir is accused of being the foremost source of activated blood [70]. Consumption of coagulation factors is usually associated with excessive haemostatic activation and a continued decline in levels of coagulation factors and platelets after the initial reduction due to haemodilution [71]. Conventional CPB results in dramatic swings in the fibrinolytic system, including increased secretion of tPA during CPB, increased plasmin generation and fibrin degradation, all of which are associated with an increased risk of bleeding [40]. The basic rationale for miniaturization of ECC is to reduce foreign surfaces as well as priming volume and therefore increase biocompatibility and limit SIRS and alterations in perioperative haemostasis [72]. MECC systems differ from CECC in the following:

1. There is a centrifugal pump instead of a roller pump. Blood is actively drained from the right atrium.
2. There is no venous cardiotomy reservoir. The circuit is closed and blood–air contact is prevented.
3. When used without a collapsible reservoir, the system is equipped with various safety venous line air-handling devices that are able to detect and prevent air entering into the venous side.
4. Prime volume is low (approximately 500–1,000 ml in comparison to 1,500 ml in conventional circuits).
5. The circuit and the oxygenator are treated with a biocompatible coating (depending on the system, this could be a heparin coating, a phosphorylcholine coating, a multimolecular coating).
6. There is no cardiotomy suction. All shed blood from the operative field is removed by means of a cell-saver suction device.
7. Blood venting from the left-sided heart chambers may be simply gravity-assisted or pump-assisted. In this case, adequate safety devices are included to detect and eliminate air entering into the system from the active venting of the heart [73].

MECC has a radically reduced dimension of the tubing system. Together with lack of cardiotomy suction and venous reservoir, required priming volume is significantly decreased and consequently blood dilution effect. In addition, low-volume cardioplegic solution, a centrifugal pump instead of roller pumps and no blood suction on pump are applied. Hence, haemodilution, mechanical stress and blood activation triggered by contact with air and foreign surfaces are decreased by leaving out cardiotomy suction and reservoir [74]. This may partially be responsible for the observed reduction in the requirement of blood products.

In MECC system, anticoagulation is attained by administration of 150 IU/kg heparin to achieve an ACT of 300 s, corresponding to 50 % of the usually administered heparin dose. Ovrum et al. measured various coagulation and fibrinolysis parameters in patients undergoing CABG with full (ACT>480 s) and reduced (ACT>250 s) systemic heparinisation and concluded that CABG can be safely performed with reduced systemic heparinisation in combination with fully heparin-coated circuits [75].

Commercially Available MECC Circuits

Currently commercially available MECC systems include:

- MECC® System (Maquet)
- Resting Heart System (Medtronic)
- ECC.O (Sorin)
- Synergy (Sorin)
- ROCSafe Hybrid Perfusion System (Terumo)

The CORx MPC from CardioVention is no longer manufactured (Table 3.4).

MECC® System (Maquet)

The MECC® system (Maquet Cardiopulmonary AG, Hirrlingen, Germany) is a compact closed system, containing a Rotaflow centrifugal pump with a surface area of 0.019 m^2 and a Quadrox^D diffusion membrane oxygenator with a membrane surface area of 2.4 m^2 (Fig. 3.8). In contrast to conventional microporous membrane oxygenators, in which gas passes through pores in the wall of the capillaries, the tight membrane in the Quadrox^D prevents crossing of microbubbles from the gaseous to the liquid layer. This feature, originally designed to prevent plasma leakage in the long-term run, has been shown to be feasible also in the clinical setting of CABG

Table 3.4 Characteristics of commercially available MECC systems

	Pump	Oxygenator	Coating	Arterial filter/air-handling devices	Total prime volume (ml)
MECC® (Maquet)	Rotaflow Prime volume: 32 ml	Quadrox^{D} Prime volume: 250 ml Surface area: 2.4 m^2 Quadrox-i Prime volume: 215 ml Surface area: 1.8 m^2	Bioline	QUART arterial filter Prime volume: 180 ml Optional VBT Prime volume: 150 ml	500
RHS (Medtronic)	Bio-Pump Plus Prime volume: 80 ml	Affinity NT Prime volume: 270 ml Surface area: 2.5 m^2	Carmeda BioActive Surface	Affinity arterial filter Affinity VARD Prime volume: 212 ml	600
ECC.O (Sorin)	Revolution integrated in ECC.O unit Prime volume: 57 ml	Integrated in ECC.O unit Surface area: 1.1 m^2	Phosphorylcholine-coated (Ph.I.S.I.O.)	Air purge control (APC) Dideco arterial filter Prime volume: 100 ml	380
Synergy (Sorin)	Revolution integrated in Synergy unit Prime volume: 57 ml	Integrated in ECC.O unit Surface area: 2 m^2	Phosphorylcholine-coated (Ph.I.S.I.O.)	Air purge control (APC)	680
ROCSafe (Terumo)	Sarns Prime volume: 48 ml	CAPIOX® SX18X Surface area: 1.5–1.8 m^2	X Coating	AV6SV arterial filter ultrasound-controlled bubble detector (ABD), bubble trap (BT15) and an electronic venous line occluder (EVO)	800

surgery. Quadrox-i oxygenator has been introduced to the market recently. It includes an integrated filter and is suitable for use with volatile anaesthetic agents, such as isoflurane and sevoflurane. Via short tubing (usually less than 1 m tubing length), the venous line is directly connected to the centrifugal pump, which passes the oxygenator and, via the arterial line, returned to the patient.

All components are tip-to-tip Bioline coated. Bioline coating of the MECC® system combines polypeptide and active heparin to simulate a natural endothelium. This coating method should ensure stable bonding of the heparin molecule and the immobilised polypeptide. Bioline coating provides optimal biocompatibility of all components in contact with blood. It has been associated with platelet preservation, reduced activation of fibrinolysis and lower TNF-α levels indicative of a reduced inflammatory response.

To increase safety, a VBT can be interconnected in the venous line before the centrifugal pump. A QUART arterial filter could be installed in the arterial line to reduce microbubbles and particles. Total priming volume of the system required is approximately 500 ml (32 ml for Rotaflow pump, 250 ml for the Quadrox^{D} oxygenator or 215 ml for Quadrox-i, 180 ml for the arterial filter). VBT requires 150 ml of additional prime. The system can support flows ranging from 0.1 up to 7 L/min.

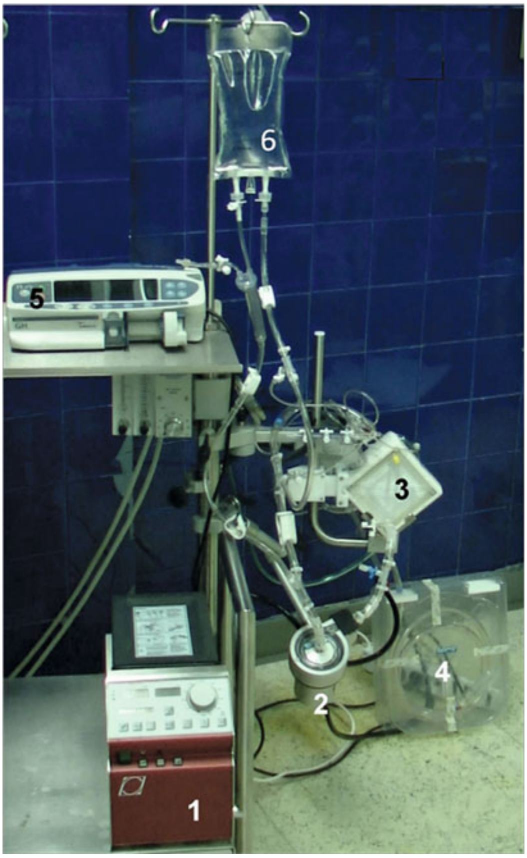

Fig. 3.8 MECC system developed by Maquet with its components as used by our department (*1* controller, *2* centrifugal pump, *3* oxygenator, *4* circuit, *5* cardioplegia infusion, *6* collection bag)

Resting Heart System (Medtronic)

The Medtronic Resting Heart System (RHS) is an integrated, low prime, semi-closed-loop CPB system, offering minimal air and blood interface and elimination of antifoam agents. The RHS consists of a preconnected tubing system, including a centrifugal pump (Bio-Pump Plus). The membrane oxygenator Affinity NT and a VBT with automatic air removal (AAR1000) are integrated into the system, as well as an arterial filter (Fig. 3.9). The priming volume of this circuit is 600 ml, and the membrane surface area for gas exchange is 2.5 m^2. Primary blood contact surfaces of this RHS are coated with Carmeda BioActive Surface throughout to provide thromboresistance and biocompatibility by mimicking critical characteristics of vascular endothelium. The RHS can offer blood flow from 1.0 to 6.0 L/min. A vent circuit is available in the RHS. The blood from this vent is reinjected into the pump inflow. The absence of cardiotomy reservoirs limits the artificial surface–blood contact that occurs secondary to aspiration of blood. Accordingly, an erythrocyte-scavenging device is necessary when using the RHS. In addition, this system has the technology to detect and remove small air bubbles in the circuit. If air is entrained from the right atrium, visual and audible alarms alert the surgical team to the condition so that it can be quickly remedied. Two pairs of ultrasonic fluid sensors in the venous air removal device detect air at the inlet of the device. When air enters the device through the venous return line, air bubbles are detected, and the device exerts evident visual and audible indications while removing the venous air. The air is automatically removed from the venous air removal device until its sensors detect no remaining air/blood mixture in the upper area of the device, and then it returns to normal setting [76].

Fig. 3.9 Medtronic Resting Heart System (Courtesy of Medtronic Inc.)

ECC.O (Sorin)

The ECC.O system (Sorin Group, Italy) is based on an integrated disposable that is a closed loop, kinetically assisted active drainage system including

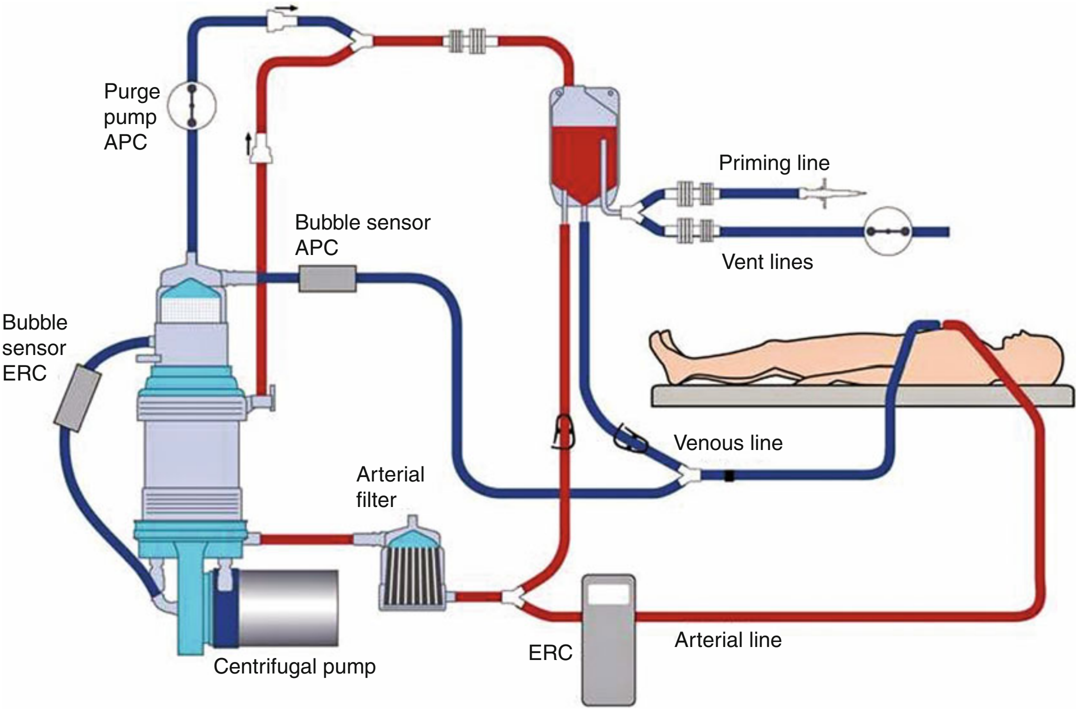

Fig. 3.10 ECC.O system (Courtesy of Sorin Group, Italy)

a venous bubble trap, centrifugal pump, heat exchanger and oxygenator, all integrated into a single device (Fig. 3.10). The system includes a hardware platform based on the Stöckert heart–lung machine and is intended for use with an autotransfusion system. Blood flows into the 3/8-in. inlet at the top of the bubble trap and through a 120 mm screen to aid in removing entrained air from the venous inlet line. The sudden reduction of blood velocity at the top of the bubble trap, combined with the tangential orientation and distance separating the inlet and outlet, allows venous air and microbubbles to rise easily to the top of the bubble trap. The bubble trap outlet is placed well below the inlet to also permit efficient microbubble separation even at high flow rates.

A tubing line connects the bubble trap outlet to the inlet of the Revolution centrifugal pump. The Revolution is an impeller-based design that permits a maximum pressure head generation and comparatively low flow rates. The pump possesses excellent air-handling characteristics, a low index of haemolysis and a low priming volume (57 ml). The large washout holes permit even flow with no stasis or areas of stagnating flow within the pump, and the reduced single pin-bearing design also results in a reduction in the level of heat generation more typical of previous centrifugal pump designs. The centrifugal pump pulls blood out of the venous side of the patient to the entry of the ECC.O stainless steel heat exchanger from the bottom to the top of the unit, where it then flows into the oxygenator bundle. The oxybundle consists of 1.1 m^2 of fibre in different compartments, specifically designed to promote maximal use of the fibre inside the bundle even at higher flow rates. The oxygenator is designed with a bottom to top to bottom flow path to maximise the air-handling characteristics as well. Oxygenated blood then leaves the ECC.O system back through a 3/8-in. arterial outlet line through a Dideco D733 40 μm arterial filter to the patient. It could provide up to 5.0–5.5 L/min. The system is provided in a 100 % phosphorylcholine-coated circuit (Ph.I.S.I.O.). Total priming volume required is 380 ml.

The ECC.O system also incorporates an integrated level of hardware to help manage micro- and

Fig. 3.11 Synergy integrated system (Courtesy of Sorin Group, Italy)

macroair. The air purge control (APC) is a dedicated automatic system for assisted removal of air from the bubble trap. Used in conjunction with a 3/8-in. bubble sensor on the venous inlet tubing line before the ECC.O bubble trap assists in removing entrained air with a dedicated roller purge pump. It aids in removal of air from the bubble trap without having to manage the purge roller pump manually. A second bubble sensor on the tubing line between the bubble trap outlet and the centrifugal pump inlet controls the electric remote clamp (ERC) that is placed on the arterial line. It can be utilized to automatically close the arterial line and prevent the device from depriming in case of massive air introduction. The ERC will close automatically also if retrograde flow is detected, preventing reverse flow through the system [77, 78].

Synergy (Sorin)

The Synergy mini-bypass system (Sorin Group, Italy) is an integrated disposable device that consists of a totally closed phosphorylcholine-coated system (Ph.I.S.I.O.), a hollow fibre oxygenator with a surface area of 2 m^2 together with integrated arterial filter, a centrifugal pump (Sorin Revolution) and venous bubble trap for managing venous air (Fig. 3.11). It utilises the same extra safety features of ECC.O system that is the APC system and the ERC that can effectively and automatically remove venous air via the purge line of the bubble trap. In the event that air travels through the bubble trap, ERC can be used to automatically clamp the arterial line, thus preventing air from entering the oxygenator and arterial line and permitting the perfusionist to resolve the air issue prior to opening the ERC and reinitiating bypass. The two systems are not dependent on each other and can be used independently in the bypass circuit, although the use of the APC and ERC together is recommended by the manufacturer [57].

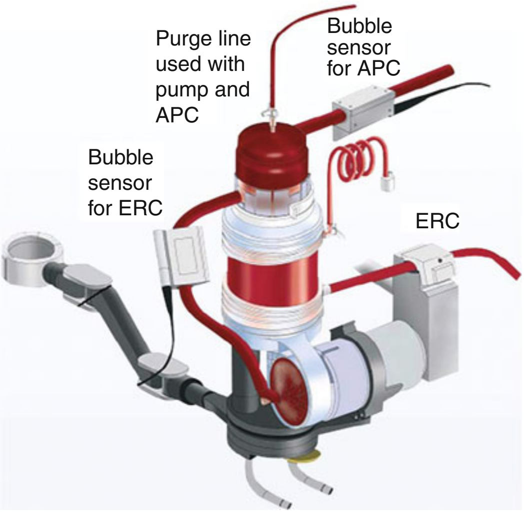

Fig. 3.12 Air purge control device (Courtesy of Sorin Group, Italy)

Description of the Air Purge Control (APC) System

The APC system consists of an APC control module, an APC sensor module, a bubble sensor for 3/8-in. tubing with a three-joint holder and ultrasonic gel. The APC purge line in the tubing set includes a one-way safety valve and is connected to the blood storage reservoir (Fig. 3.12). Air is aspirated out of the top of the Synergy bubble trap. It has a capacity of approximately 120 ml. The ERC is placed on the arterial line to the patient, with a second ultrasonic bubble sensor positioned between the bubble trap outlet and the inlet of the centrifugal pump head to trigger the ERC. This acts as a second level of security in case the APC is overwhelmed by entrained air. Both bubble sensors also have a bar graph on its control panel for visual confirmation of microembolic activity [57].

ROCSafe (Terumo)

The ROCSafe MPC is a minimized ‘closed-loop’ circulatory and respiratory support circuit. Its basic modular concept consists of a standard perfusion circuit (Terumo Europe N.V., Leuven, Belgium), including a Sarns™ Centrifugal Pump, a hollow-fibre oxygenator (CAPIOX® SX18X) and a 40 μm blood filter (AV6SV) in the arterial line. The circuit includes a venous de-airing

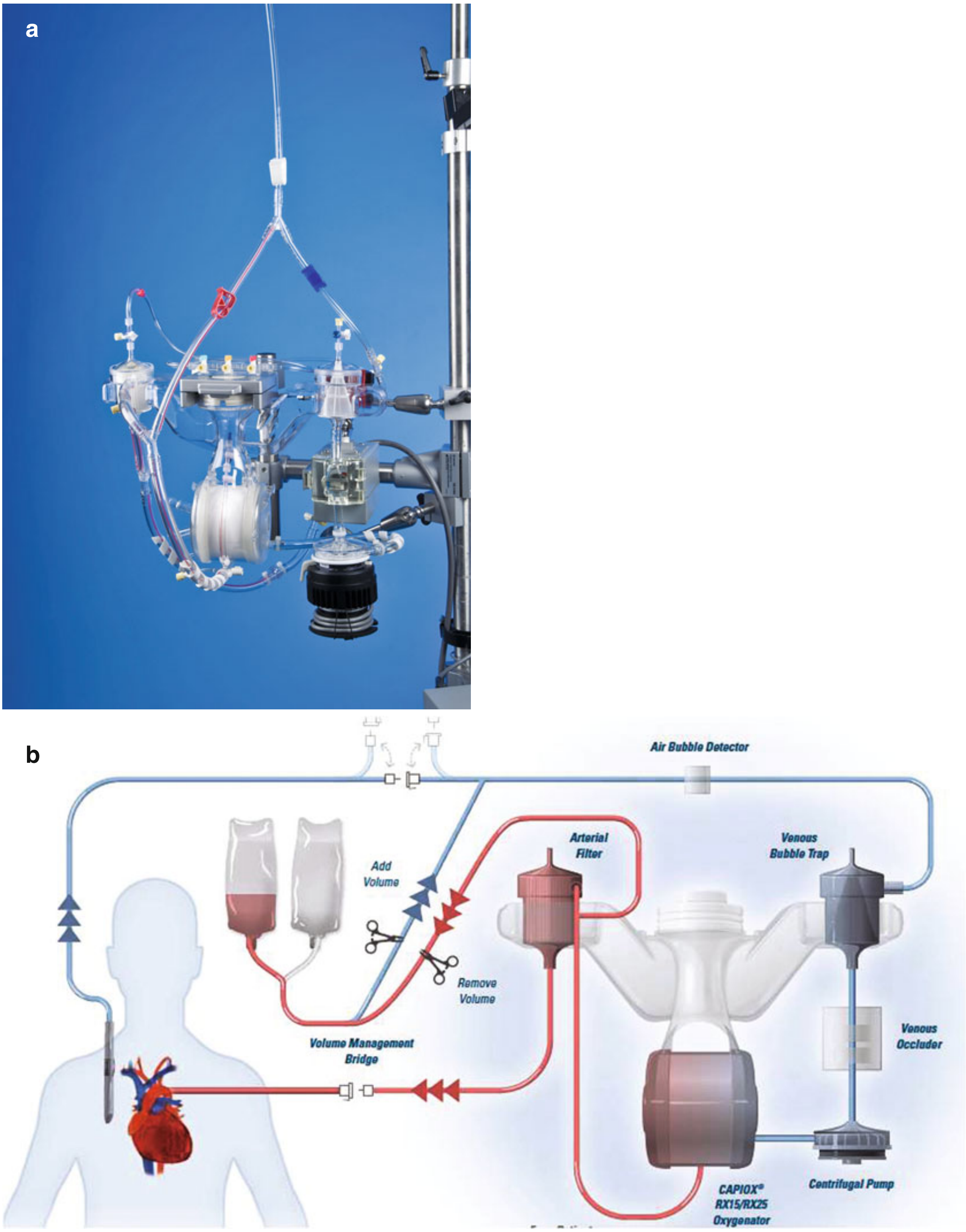

Fig. 3.13 ROCSafe Hybrid Perfusion System (**a**) and schematic view of the two different configurations (**b**) (Courtesy of Terumo)

unit, which consists of an ultrasound-controlled bubble detector (ABD), a 150 cm^3/170 µm bubble trap (BT15) and an electronic venous line occluder (EVO). The static prime volume of the system is approximately 800 ml. When air is detected by the ABD, an automatic command is given to the centrifugal pump to reduce speed to 1,500 rpm, which is a 'coasting' speed, creating neither forward nor reverse flow. This avoids negative pressure on the venous line during closure of the EVO. The EVO automatically closes the venous line in response to the speed reduction of the centrifugal pump. This allows for controlled manual de-airing of the bubble trap using a standard vacuum suction device (−200 mmHg). In cases of continuous air aspiration via the venous cannula, immediate suture of the leakage is mandatory. If this cannot be achieved sufficiently (e.g. large tear of the right atrium), a switch to an open system by integration of a pre-connected hard-shell reservoir is required within seconds. A soft reservoir can be integrated to the system for left ventricular blood venting [79]. The ROCSafe system is coated with X Coating™, Terumo's own biopassive polymer surface coating that reduces platelet activation and protein denaturing.

ROCSafe Hybrid Perfusion System is a hybrid system that instantly converts between a reservoir-less core configuration to a conventional configuration with a hard-shell venous reservoir. It uses CAPIOX® RX15 or RX25 oxygenator with a priming volume of 665 or 780 ml, respectively (Fig. 3.13).

CORx MPC (CardioVention)

The CORx MPC system (CardioVention Inc.) was the first closed-loop circuit using an integrated automatic de-airing device. It consisted of a centrifugal blood pump, an active venous air removal device (defoamer), a hollow fibre membrane oxygenator, an AirVac controller and a pump adapter. The AirVac controller powered the detection and facilitated removal of entrained air in the air-handling system of the disposable unit. The pump adapter was magnetic and allowed for the use of the Medtronic Biomedicus Bio-Console. [80]. The tubing was not bio-coated. The circuit was primed with 820 ml. This system is no longer manufactured.

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4

Perfusion Principles

Perfusion technique during surgery with MECC is of utmost importance in order to maintain optimal end-organ perfusion and avoid potentially lethal complications. Communication and continuous interaction and cooperation between the surgeon, the perfusionist and the anaesthesiologist is imperative to safely perform any procedure. As there is no venous reservoir, the patient's vascular system acts as a 'reservoir'. Moreover, air entrainment is far more difficult to handle compared to conventional extracorporeal circulation (CECC). Perfusion during surgery with MECC follows two main principles: *volume management* and *air handling*.

Preparation of the Circuit

The priming volume varies between various MECC systems, as presented in Table 2.4. In our institution, we use approximately 500 ml Voluven, 200 ml mannitol 20 %, and 300 ml Ringer's lactate. De-airing may differ depending on the type of circuit used.

Circuit Set-up

MECC aims to minimise artificial surface. Therefore, the circuit has to be kept close to the patients' head to reduce the length of the tubing (Fig. 4.1). In a standard set-up beyond the arterial and venous line, a line for delivering cardioplegia and a line for venting the aorta are employed. In our institution, we routinely use an extra line for venting the pulmonary artery (PA) trunk (Fig. 4.1). A separate line is used for de-airing the venous bubble trap (VBT) to the cell-saving device (Fig. 4.2).

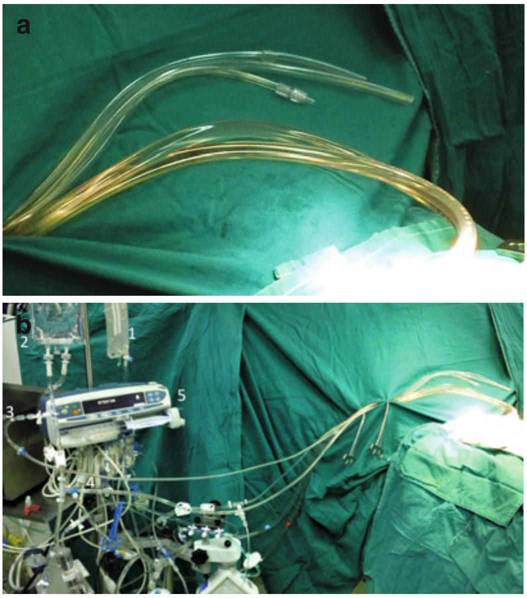

Fig. 4.1 The lines used during surgery with MECC: (**a**) The arterial and venous lines are placed separate from the other three lines (cardioplegia, pulmonary vent, aortic root vent), (**b**) *1* soft-shell reservoir, *2* prime bag, *3* aortic root vent, *4* pulmonary artery vent, *5* cardioplegia pump

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Fig. 4.2 The venous bubble trap connected to the circuit

Connecting the Circuit to the Patient

The arterial line is connected first; the venous line follows. Special care should be taken by the surgeon to avoid air entrainment into the tubes during cannulation. The vent to the PA is then placed and the perfusionist de-airs the line using the cell-saving device. The cardioplegia catheter to the ascending aorta (usually triple-lumen for: delivering cardioplegia, venting the aortic root and monitoring aortic root pressure) is placed after initiating CPB when pressure in the aorta is low.

Fig. 4.3 Retrograde autologous priming

Retrograde Autologous Priming (RAP)

RAP can reduce haemodilution, but it should be carefully applied only in haemodynamically stable patients so as to avoid myocardial ischaemia. RAP has been shown to increase plasma colloidal osmotic pressure and preserve extravascular lung water and fluid balance [1], as well as to decrease blood product use during CPB by maintaining higher haematocrit and decreasing pump prime [2]. Frequently, the anaesthesiologist has to administer vasoconstrictors (i.e. phenylephrine) so as to increase systemic vascular resistance. After releasing the clamp on the arterial part, the perfusionist lowers the prime bag below the level of the table. Arterial blood fills the circuit completely in a retrograde fashion driven by the patient's arterial pressure; the prime volume of the circuit then shifts back into the prime bag. The same procedure is repeated at the venous part of the circuit (Fig. 4.3).

Fig. 4.4 Mean arterial pressure (mmHg) during surgery with MECC (Adapted from Diez et al. [12])

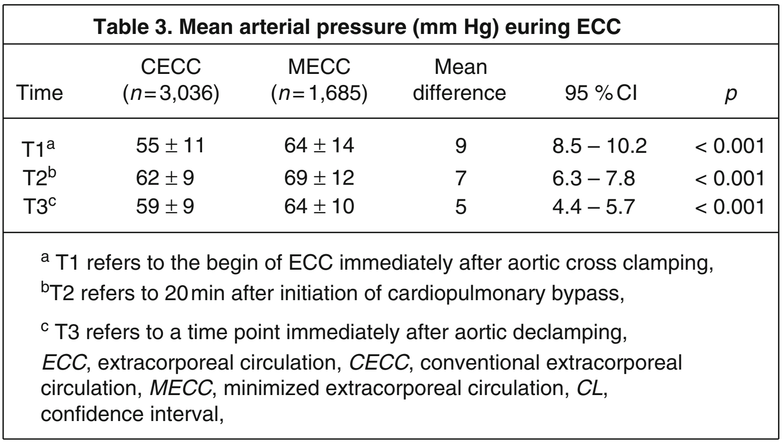


Table 3. Mean arterial pressure (mm Hg) euring ECC

Time	CECC ($n=3{,}036$)	MECC ($n=1{,}685$)	Mean difference	95 % CI	p
T1[a]	55 ± 11	64 ± 14	9	8.5 – 10.2	< 0.001
T2[b]	62 ± 9	69 ± 12	7	6.3 – 7.8	< 0.001
T3[c]	59 ± 9	64 ± 10	5	4.4 – 5.7	< 0.001

[a] T1 refers to the begin of ECC immediately after aortic cross clamping,
[b]T2 refers to 20 min after initiation of cardiopulmonary bypass,

[c] T3 refers to a time point immediately after aortic declamping,
ECC, extracorporeal circulation, *CECC*, conventional extracorporeal circulation, *MECC*, minimized extracorporeal circulation, *CL*, confidence interval,

Initiation of CPB

The perfusionist gradually increases the speed of the pump to provide adequate flow (target 2.4 L/min/m^2). For CABG procedures, normothermia is employed (35–37°C); lower temperature is utilised in complex and long-lasting procedures.

Haemodynamic Strategy During CPB

The target mean arterial pressure (MAP) is between 50 and 80 mmHg. A special feature of MECC which is of paramount importance is that the system maintains higher MAP in any flow increment compared to CECC (Fig. 4.4); interestingly, less vasoconstrictors are required for maintaining optimal perfusion pressure throughout the procedure (Fig. 4.5) [3]. When MAP is decreased, circulatory flow has to be increased up to 120 % of the calculated flow; if this strategy is not effective, phenylephrine is administered (starting with a bolus dose of 100 μg).

Administration of Cardioplegia

Warm blood Calafiore cardioplegia is used in MECC; this leads to less volume administration and preserves normothermia. The initial dose of potassium is usually 5.7 mmol/min for 2 min, the second dose is 3.4 mmol/min after 20 min and subsequent doses are 2.6 mmol/min every 20 min. Commonly during administration of cardioplegia, hyperkalemia causes transient vasodilation reflected as a drop in MAP which soon returns to normal.

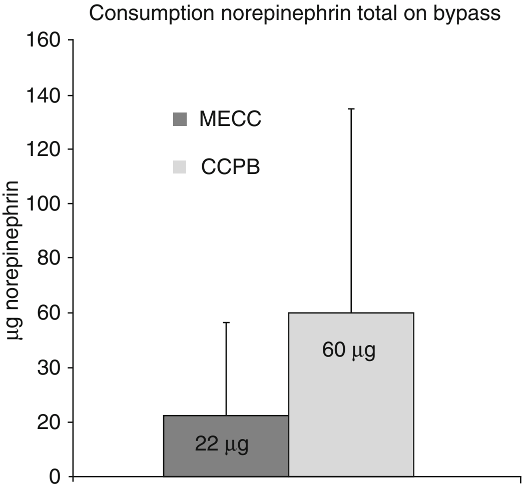


Fig. 4.5 Norepinephrine consumption total on bypass comparing MECC vs. CECC (Adapted from Bauer et al. [3])

Volume Management

MECC is a closed system and the patient himself acts as a 'reservoir'. Therefore, the pump flow is largely dependent on a balance between the volume load of the patient and the systemic vascular resistance (preload–afterload). Venous drainage in closed mini-bypass systems requires monitoring of venous line pressure [4]; this has to be maintained between –20 mmHg and –80 mmHg. In case of hypovolemia, pump flow will decrease. This may occur when there is a lot of blood loss in the surgical field or due to excessive diuresis (from bad anaesthetic management). Shifting patient to the Trendelenburg position, thus increasing the preload, volume replacement and/or administration of vasoconstrictors are the necessary corrective measures. On the other hand, a hypervolemic situation can cause difficulties in off-loading the heart and in obtaining a bloodless surgical field during construction of peripheral anastomoses. In this setting, we increase the pump flow, shift the patient to anti-Trendelenburg position, administer bolus vasodilators (i.e. nitroglycerin) and retract blood volume from the patient to the soft-shell reservoir. The latter is particularly important when performing valve surgery with MECC which prerequisites complete emptying of the heart.

Monitoring During CPB

Optimal end-organ perfusion can be assessed either with observational factors such as MAP and urine output or with biochemical markers. Level of lactate from arterial or venous blood gas samples is a readily available indicator of adequate perfusion. Measuring carbon dioxide elimination at the exhaust site of the oxygenator indirectly assesses the metabolic state of the patient. Many perfusionists use in-line venous saturation (SVO_2) and venous blood gases as measures of the overall adequacy of whole body tissue perfusion. These values have been shown by Ranucci et al. [5] to be poor predictors of anaerobic metabolism. Additionally, blood gas analyses are fundamental in determining the adequacy of perfusion. It is also important to monitor aortic root pressure during all phases of CPB which allows the perfusionist to regulate the use of the vent intermittently.

Post-conditioning

At the end of completion of distal anastomoses in CABG procedures, a post-conditioning strategy to optimise the stunned myocardium before releasing the cross clamp from the aorta can be applied. This comprises cycles of controlled perfusion of the heart with warm blood followed by venting the aortic root so as to wash out the toxic products from the ischaemic period. In our institution, we employ three alternating cycles of warm blood administration for 30 s followed by 30 s venting the aortic root. We believe that this strategy offers optimal conditions to the myocardium for the upcoming reperfusion period.

Reperfusion

Reperfusion is generally not necessary when using MECC. We usually start weaning from the bypass during construction of proximal graft anastomoses under partial aortic occlusion in CABG procedures.

Weaning off CPB

Ventilation and inotropic support start as soon as the aorta cross-clamp is removed. Gradual weaning from the bypass is usually employed during construction of proximal graft anastomoses. We target to wean off CPB with low CVP so as to easily return the blood from the circuit back to the patient. For this reason, low arterial pressure immediately after weaning off CPB is acceptable. Protamine is then administered titrated to neutralise heparin.

Management of Cell-Saved Blood

Since there is no cardiotomy reservoir in the MECC circuit, a cell-saver device is imperative to collect blood from the pleuro-pericardial cavities. The shed blood can be processed in the autotransfusion system to retrieve red blood cells and remove humoral factors [6–8]; after processing this, blood returns to the venous line of the circuit (Fig. 4.6). A recent technological advancement towards blood salvage during MECC is the development of an optoelectrical suction device (Cardiosmart AG, Muri, Switzerland) which could be integrated into the system. Aspiration of

Fig. 4.6 Cell-saver device connected to the venous line of the MECC circuit

blood is controlled by an optoelectrical sensor at the tip of the cannula, and suction mechanism is started only when the tip of it is in direct contact with the blood. The aspirated blood is directly retransfused into the venous line of the circuit, and therefore, no additional suction pump or reservoir is required (Fig. 9.3) [9].

Air Handling

Air entrainment into the circuit is the most dramatic complication during surgery with MECC. The perfusionist should be ready to immediately recognise this complication and promptly react. Contemporary MECC systems include safety features incorporated to the circuit such as VBT, ultrasonic bubble detector, level detector and arterial filter. Airtight insertion of cannulae to the heart is of great importance. Air entrapment to the circuit results in pump stop. The perfusionist then has to de-air the VBT by applying suction through the line which connects it to the cell-saving device while at the same time adds volume to the circuit so as to replace the air. If an arterial filter is incorporated into the system, de-airing process can be done through the suction port of it.

The ROCSafe™ MPC (Terumo Cardiovascular Systems) includes a venous de-airing unit, which consists of an ultrasound-controlled bubble detector (ABD), a 150 ml/170-µm bubble trap (BT15) and an electronic venous line occluder (EVO) (Fig. 4.7). When air is detected by the ABD, an automatic command is given to the centrifugal pump to reduce speed to 1,500 rpm, which is a ‘coasting’ speed, creating neither forward nor reverse flow. This avoids negative pressure on the venous line during closure of the EVO. The EVO automatically closes the venous line in response to the speed reduction of the centrifugal pump. This allows for controlled manual de-airing of the bubble trap using a standard vacuum suction device (–200 mmHg) [10].

The Synergy mini-bypass system and the ECC.O (Sorin Group, Italy) utilise the same extra safety features, that is, the air purge control (APC) system and the electronic remote clamp (ERC) that can effectively and automatically remove venous air via the purge line of the bubble trap (Fig. 4.8). In its automatic operating mode during CPB, the APC roller purge pump remains inactive. When the bubble sensor detects microembolic activity (approximately 100–150 µm or greater depending on the system flow rate), a bar graph on the control panel display lights up indicating micro-bubble activity, and the APC control module activates the APC roller pump to start removing air from the bubble trap. The roller

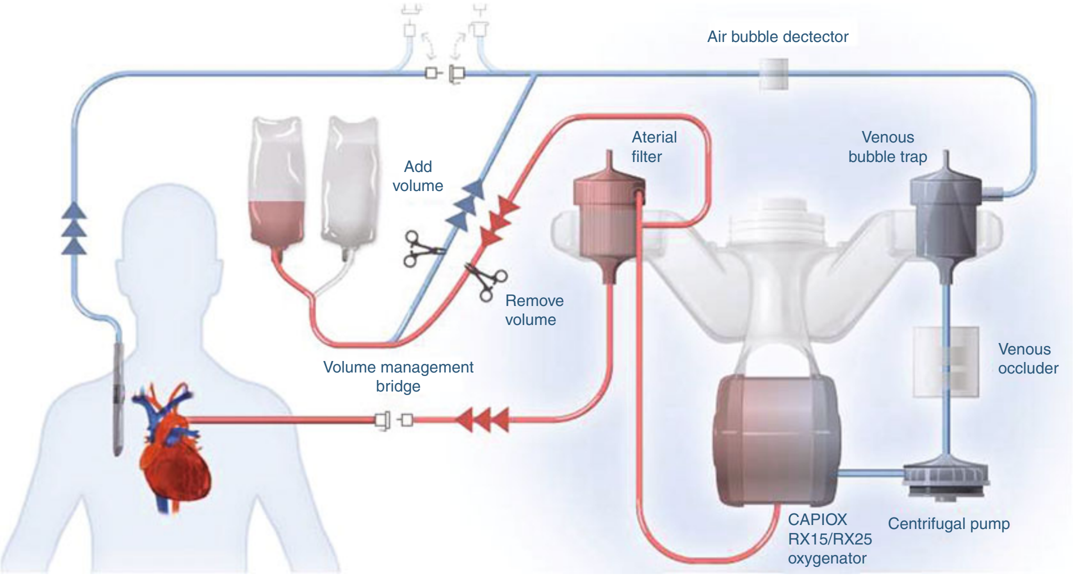
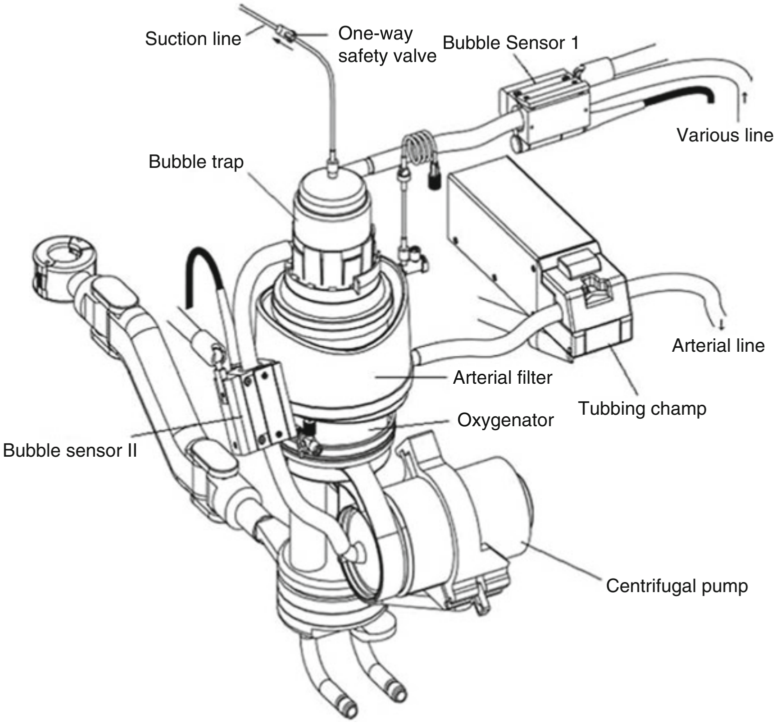


Fig. 4.7 Schematic representation of the ROCSafe™ MPC (Terumo Cardiovascular Systems)

Fig. 4.8 Schematic representation of the air purge control (APC) system used with ECC.O and Synergy systems (From Huybregts et al. [11])



pump starts running at the revolutions per minute preset by the perfusionist, thereby removing the air and a small amount of blood from the bubble trap. After expiration of the APC pump 'run-out' time, that is, the amount of time the perfusionist wants the system to run after the bubble sensor stops sensing air, the APC pump is stopped again. After expiration of the pump run time, the venous bubble trap can be visually inspected to ascertain if there was any residual air present [11].

Appendix

Schematic configuration of a typical MECC circuit (Fig. 4.9).

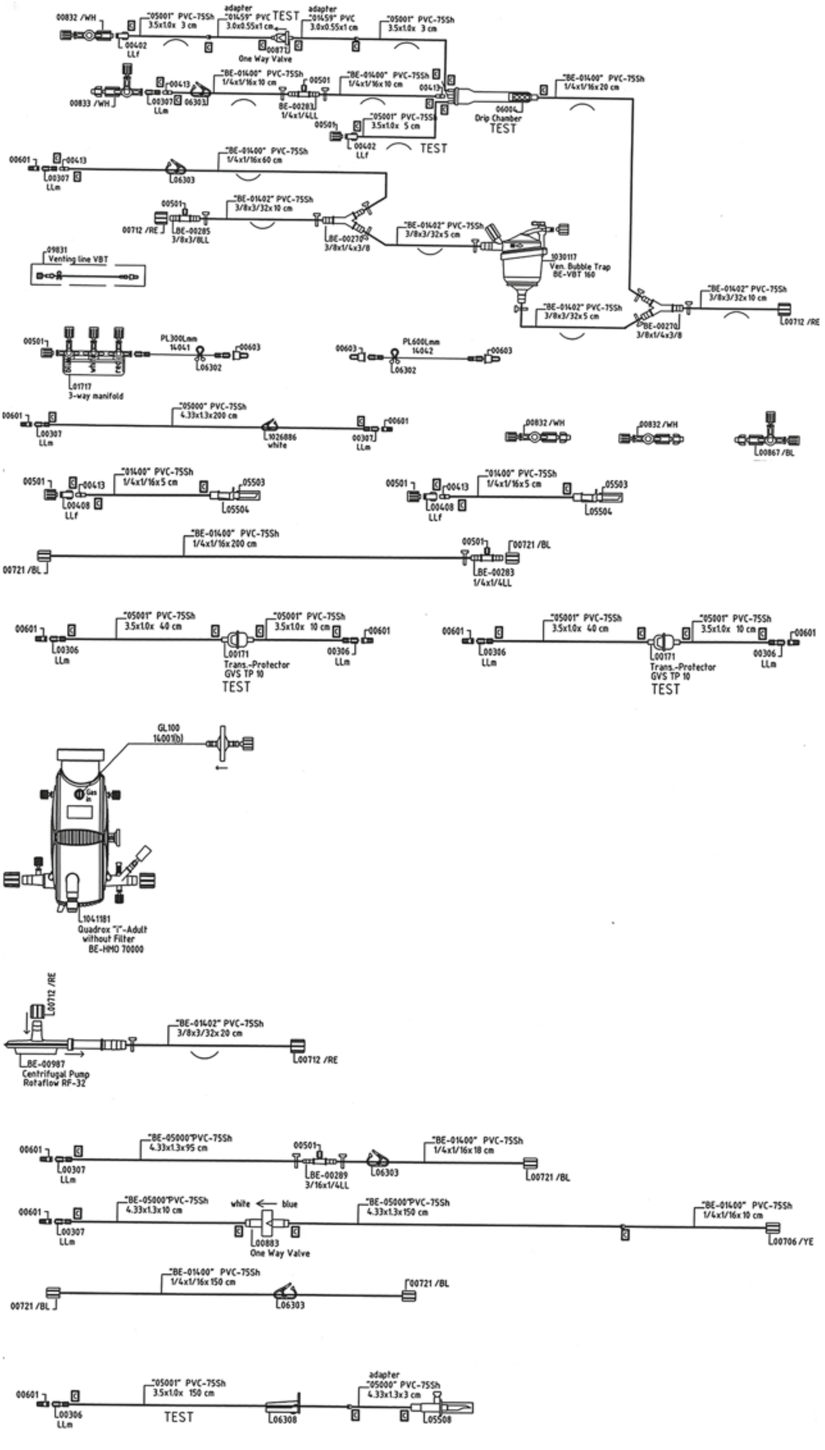


Fig. 4.9 AHEPA University Hospital MECC custom pack (Courtesy of Maquet)

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Surgical Considerations

5

Minimized cardiopulmonary bypass (CPB) systems represent a promising technology in heart surgery. The results from series of patients being operated on minimized extracorporeal circulation (MECC) are impressive, and the net outcome from their use is a stable intraoperative and postoperative course for the patient and a significantly reduced morbidity as well as lower perioperative mortality [1]. However, use of MECC demands a close multidisciplinary effort from the surgical team (surgeon, anaesthesiologist, perfusionist) comprising delicate and focused manoeuvres intraoperatively as well as a high level of cooperation from the team. Hence, a learning curve for obtaining the best performance is necessary [2]. Remadi et al. were among the first surgical teams who used the systems and first reported that the application of MECC requires the team to undergo a considerable learning curve [3]. As a result the report of a reduction in intraoperative blood loss after 50 cases with MECC was explained by this learning curve. Overall, teaching MECC has to be focused in the proper intraoperative setting, the consideration of tips and tricks, pitfalls, and drawbacks of the technique as well as the manoeuvres which are necessary from each one of the surgical team so as to perform a safe and stable procedure.

Regarding surgical strategy, in the set-up the MECC system has to be placed always as close as possible to the right side of the patient's head and not parallel to the patient like the conventional extracorporeal circulation (CECC). Short tubing is of great importance for system's qualities (Fig. 5.1). Standard cannulation technique for connecting the system to the patient with heparinized cannulae is used. Special care must be taken in managing any active drainage perfusion system, such as MECC, during cannulation procedure. Hence, 'airtight' cannulation site is secured with two silk ties around the tourniquets and cannula in order to ensure fixation after placement of the cannula. Ascending aorta is cannulated usually with an arterial 24 Fr cannula (Fig. 5.2). For the venous part a double-stage cannula is commonly used (32/40 Fr is usually adequate); two purse-string sutures and two snares for securing airproof sealing of the cannula is also of paramount importance. Arming the purse-strings with Teflon pledgets depends on surgeon's preference and on the quality of the right atrial appendage tissue. The venous cannula is then also doubly enforced with two silk ties (Fig. 5.3). Lines are connected with due diligence to avoid gaseous bubbles.

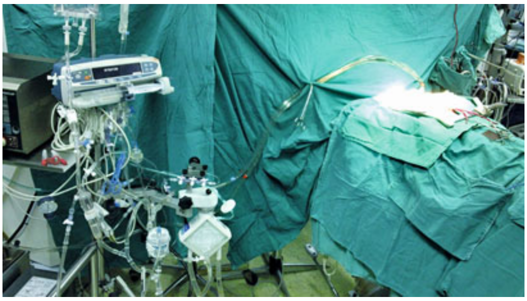

Fig. 5.1 Position of MECC system as close as possible to patient's head

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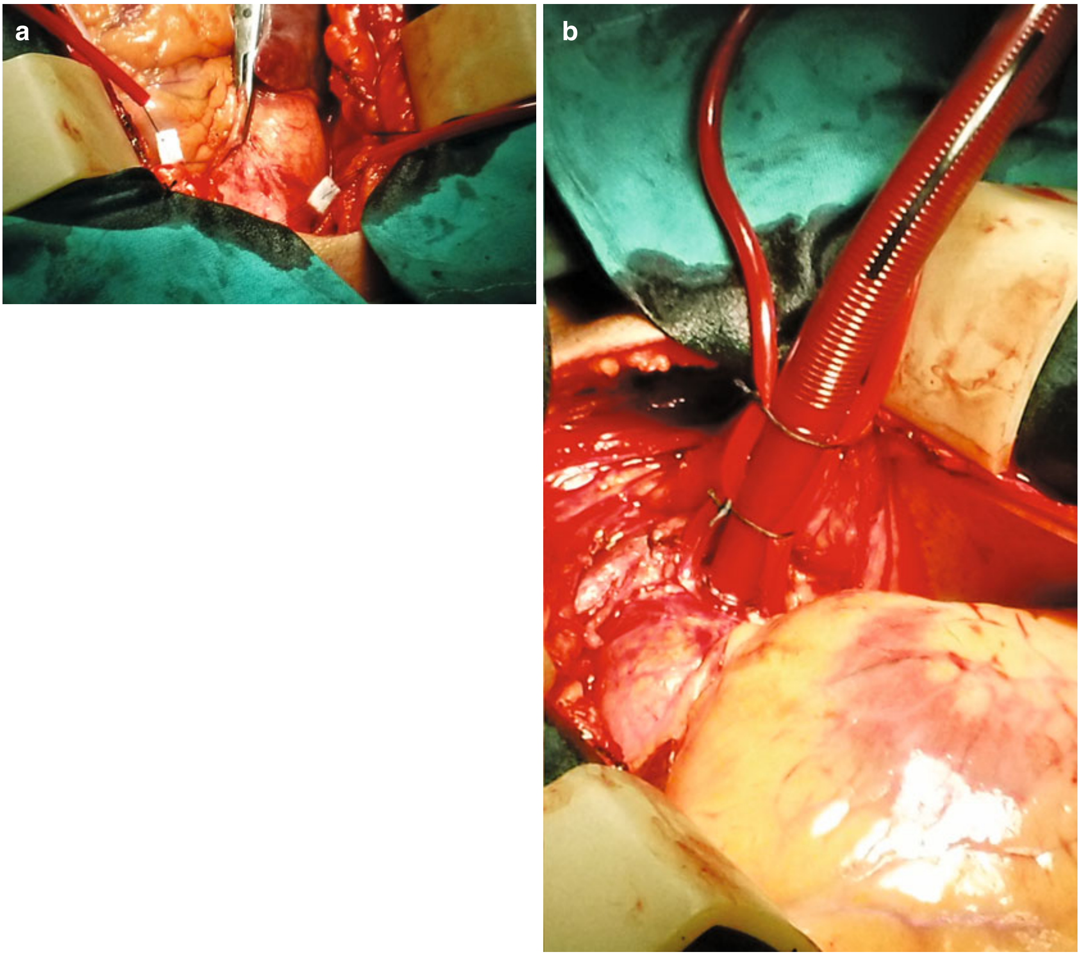

Fig. 5.2 Arterial aortic cannulation using two pledget-reinforced purse-string sutures (a); the cannula is secured with two silk ties (b).

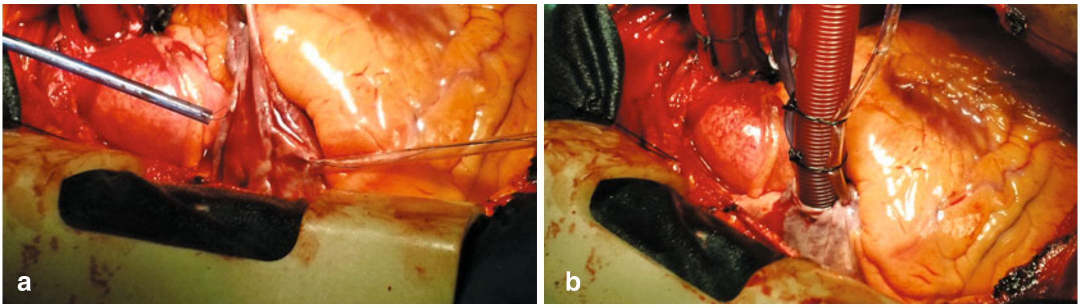

Fig. 5.3 Venous cannulation using two pledget-reinforced purse-string sutures (a); the cannula is secured with two silk ties (b).

It is important that there is accurate positioning of the venous cannula so as to achieve the optimum drainage from the vena cavae hence allowing minimum heart filling throughout the procedure. A useful trick is to use a swab externally into the pericardial cavity adjacent to the IVC compressing the right atrium after positioning the tip of the cannula accurately into

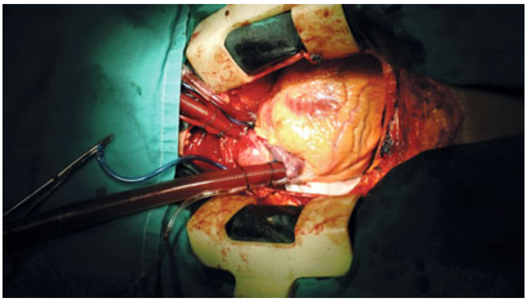

Fig. 5.4 Longitudinal positioning of the venous cannula and use of a swab externally into the pericardial cavity adjacent to the IVC for maintaining adequate venous return

Fig. 5.5 Three-stage cannula for venous return (MAQUET GmbH & Co KG)

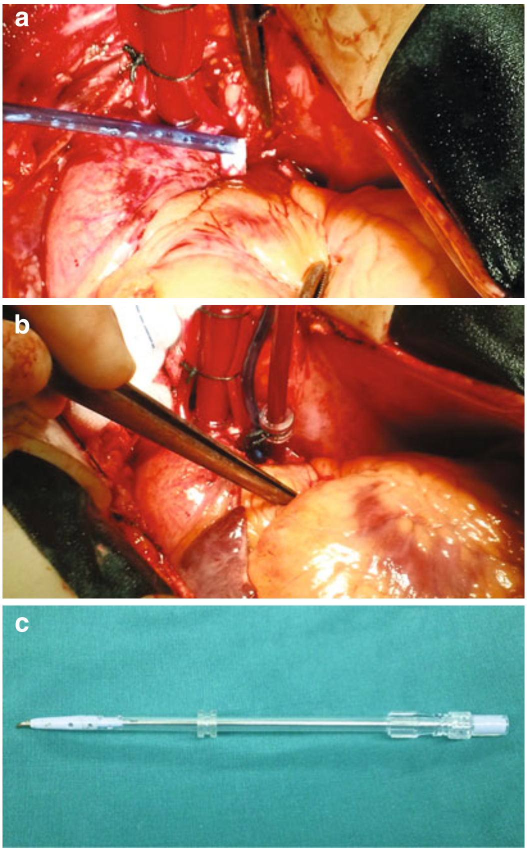

Fig. 5.6 Technique for pulmonary artery venting (**a**, **b**) using a standard venting catheter (**c**)

inferior vena cava (IVC) so that the cannula fits properly into its lumen and secures the venous drainage. Longitudinal positioning of the venous cannula has to be maintained continuously since bending or twisting it during heart displacement may result in poor venous drainage (Fig. 5.4). A three-stage cannula was introduced by some surgeons to overcome the issue of poor venous drainage (Fig. 5.5) [4]. This is an interesting modification of the standard cannulation set-up for CPB. However, we advocate alternatively the use of standard cannula along with pulmonary artery (PA) venting which is equally efficient for maximising venous drainage and does not need special consumables. We believe that venting through the PA trunk is the best site for alleviating the heart in MECC. A pledgetted prolene snare stitch is the best way to secure the site from air entrapment (Fig. 5.6).

Despite all the measures, it is frequent in MECC for the heart not to be completely unloaded during the procedure and for a persistent coronary flow to be observed in the arrested heart to the majority of patients. This may lead to difficulty in the construction of distal anastomoses in some patients. This minimal, residual perfusion of the arrested heart needs to be elucidated, but it is used as the explanation for improved myocardial protection observed during MECC use since it eliminates air embolisation of the coronary system [5]. For this reason, we advocate additional venting through the ascending aorta utilising a three-lumen catheter comprising a small (i.e. 7 Fr) venting needle, a cardioplegia route, and a line for root pressure monitoring. This vent may be used intermittently so as to alleviate a blood-filled left ventricle, limit coronary blood flow, and hence make surgery

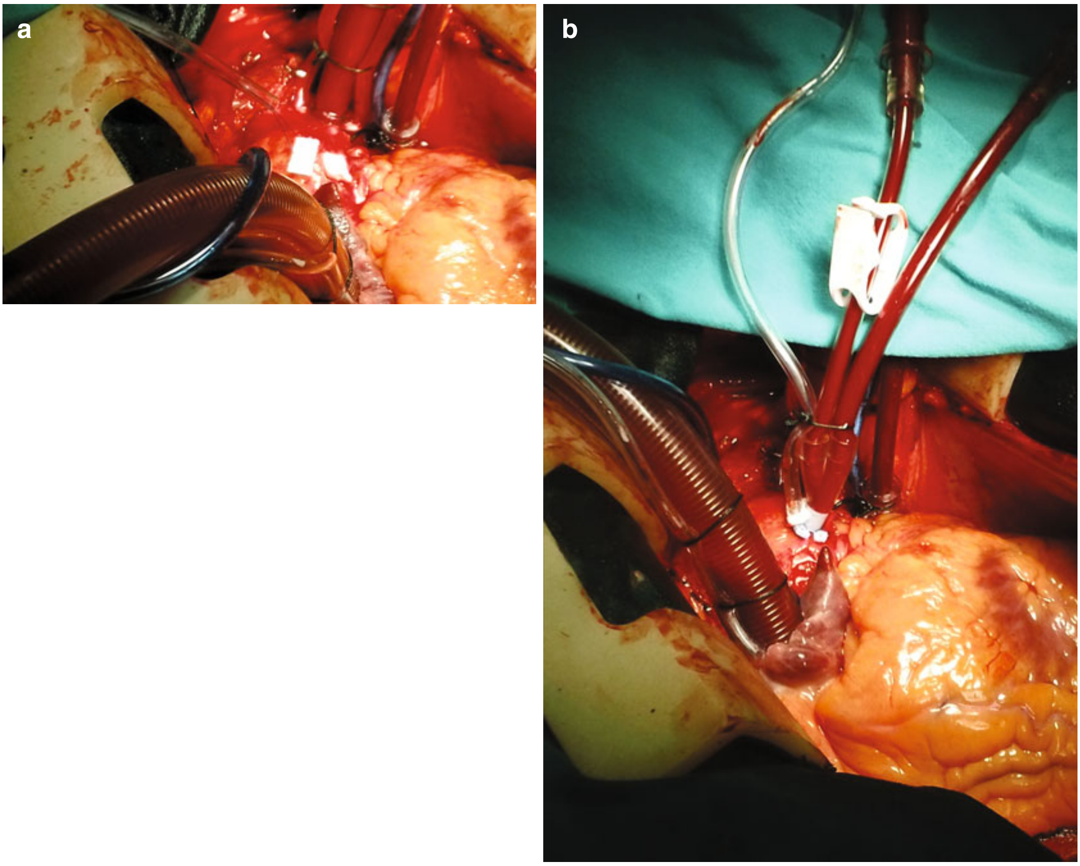

Fig. 5.7 Positioning of aortic root vent using two pledget-reinforced purse-string sutures (a,b)

comfortable. Special concern for not sucking air from the coronary arteries through the vent (which will be entrapped in the circuit) has to be undertaken. Continuous monitoring of the aortic root pressure is usually the threshold for venting. Furthermore, when using MECC for valve surgery, air is often sequestrated in the pulmonary veins, the myocardial trabeculae, and along the interventricular septum. Use of aortic root vent in valve cases is mandatory since the venting line is used for de-airing during reperfusion when the cross-clamp is removed (Fig. 5.7). Redirection of aspirating blood to a cell-saving device has been suggested [6]. However, we do not prefer this policy. Venting the heart and redirecting the blood into the circuit do not modify the system's qualities since there is no blood–air interaction. Thus, integration of an aortic root vent and using it discontinuously do not render the system as semi-closed. Alternatively, intraluminal shunts to the coronary arteries are frequently mandatory when no aortic root vent is being used. This technique seems to be beneficial since this limited coronary blood flow may result in better myocardial protection. In cases when volume-loaded circulation is present, a soft-bag closed reservoir connected to the circuit is beneficial for facilitating construction of distal anastomoses in a bloodless field.

After connecting the patient to the system, special care has to be taken for the prime volume of the circuit. The short tubing and hence small prime volume of the system is ideal for retrograde autologous priming (RAP). Haemodilution can be eliminated by using the RAP technique, as we always employ in our patients. It has been demonstrated that RAP in combination with autologous transfusion from a cell-saving device

Fig. 5.8 Retrograde autologous priming (RAP)

significantly reduces the need for blood transfusion [7]; it may also improve the postoperative result since low haematocrit during CPB has been associated with adverse outcomes (mortality, morbidity, and long-term survival) after CABG surgery [8]. Generally, RAP contributes to preservation of the haematocrit intraoperatively. However, this technique prerequisites a relevant strategy and proper manoeuvres from the anaesthesiologist: limitation of the intravenous fluids during the induction of anaesthesia and most of times some vasoconstriction using a small dose of phenylephrine. The aim is to withdraw 300–400 ml of blood from the patient into the circuit without significantly dropping the arterial pressure which carries the risk of myocardial ischemia. Nevertheless, since the optimal scenario of full RAP is not always feasible, utilising half RAP which is withdrawing only the prime from the arterial tubing (which comprises the 2/3 of the total priming volume of the circuit) and repriming it with autologous blood from the aorta is most of the time enough for avoiding haemodilution (Fig. 5.8).

After going on-CPB, the aorta is cross-clamped in the usual fashion, and preservation of the heart is achieved by infusion of Calafiore blood cardioplegia (Fig. 5.9). The initial dose of potassium is usually 5.7 mmol/min, the second dose is 3.4 mmol/min after 20 min, and subsequent doses are 2.6 mmol/min every 20 min. Normothermia (35–37°C) is the preferred operating technique for CABG and mild hypothermia (33–35°C) in valve cases with no need of epicardial cooling of the heart. Myocardial protection is accomplished usually using antegrade intermittent warm blood cardioplegia; however, retrograde cardioplegia installation through the coronary sinus could be employed. During CPB the cardiac index is maintained at 2.4 L/min/m^2 and acid–base management is generally regulated according to the alpha-stat protocol similarly to conventional CPB. Mean arterial pressure (MAP) is maintained between 50 and 80 mmHg. The major difference favouring MECC is that the MAP is always higher to any output of the system comparing to CECC (Fig. 5.2) and hence there is improved splanchnic perfusion (i.e. cerebral, renal, pulmonary, hepatic, intestinal). This is a core issue and the rationale for the superior results of MECC which provide higher MAP during CPB (Fig. 4.4), and as a result there is always need for reduced pump flows during the procedure and hence better organ perfusion as well as lower consumption of vasoactive drugs perioperatively (Fig. 4.5) [9, 10].

The distal anastomoses for a coronary artery bypass grafting (CABG) procedure are usually completed on an arrested heart; however, beating heart surgery on-MECC is feasible, that is, in cases of porcelain aorta. The proximal vein grafts anastomoses are established with the classic way utilising partial occlusion of the ascending aorta while the patient is rewarmed [11].

Throughout the procedure on-MECC, the shed blood is collected and processed with an autotransfusion device (Fig. 5.10). The washed red cells are redirected from the cell-saver device intermittently into the MECC circuit. Cleaning shed blood before retransfusion reduces blood activation and lipid embolism. At the end of the procedure, after discontinuing the CPB, the circuit is refilled with priming solution, and the residual autologous blood is redirected into the patient. Meticulous operative technique is mandatory and special effort must be given to avoid blood loss simulating the off-pump surgery measures.

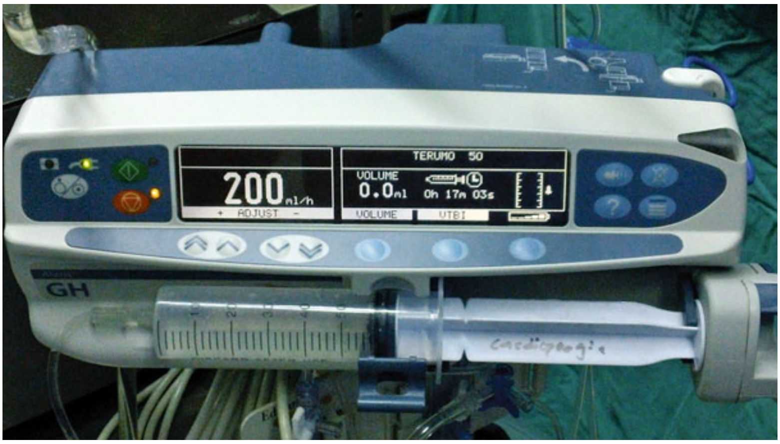

Fig. 5.9 Pump for infusion of Calafiore blood cardioplegia

Fig. 5.10 A cell-saver autotransfusion device (**a**) and its connection with the MECC circuit (**b**)

The heart manoeuvres on MECC are of specific importance for maintaining the output of the system. Displacement of the heart intraoperatively also simulates the off-pump CABG (OPCAB) manoeuvres of handling the heart; however, the main advantages operating on-MECC is that the heart is still, the field is bloodless, and the venous drainage as well as the cardiac output remain stable; hence, no blood stasis and congestion to the brain and no splanchnic hypoperfusion are evident as these may happen in OPCAB surgery.

The major difference of MECC from standard CPB is the absence of venous reservoir. Kinetic assistance is necessary for operating the system, and emptying of the heart can sometimes become difficult. Inadequate venous return is an issue that can lead to adverse patient outcomes. There are scenarios such as discontinuation of vent drainage, cardiac manipulation (particularly pulling the heart for accessing the circumflex coronary artery system), and kinking the venous cannula that can impede venous drainage and lower perfusion flows. Cooperation within the surgical team in ‘real-time’ is mandatory when operating on-MECC, and prompt as well as accurate measures must be undertaken in any of these scenarios. The surgeon must maintain active observation on the heart, and if the right atrium or right ventricle dilates due to undrained volume, he has to communicate immediately with the perfusionist so as to improve drainage [12].

In principle, reperfusion of the myocardium is not necessary in MECC since myocardial protection is superb. However, there is always some reperfusion time when constructing the proximal vein grafts’ anastomoses during CABG procedures. Throughout this time, the PA venting has to be stopped and removed if used, the ventilator has to be back on and the anaesthesiologist has to start all inotropic agents for supporting the heart. Weaning off CPB is gradual in MECC during this period so as by the end of the construction of the anastomoses the system works on a minimal flow (i.e. 2.5 L/min). The pump can then stop with the heart relatively empty (low CVP), and the blood volume from the circuit has to be redirected into the patient with gradual filling of the heart. For this reason, the venous cannula is not clamped before taking it out of the right atrium.

In summary, essential issues regarding the surgical considerations when using MECC systems are venous decompression, venting possibilities, air (entrapment, embolisation and handling), volume management in the presence of massive bleeding and advanced perfusion technique for obtaining the optimal result even in complex cases. Tips for overcoming these issues are described below.

As far as the venous return is concerned using MECC, rapid alterations of the pump flow result in right atrium distention which can affect visualisation during CABG. This scenario as discussed can be avoided by prompt communication between the surgeon and the perfusionist during the procedure. In addition, manoeuvres of the heart for exposing coronary arteries often dislodge the percutaneous venous cannula, thereby hindering venous return. Since the patient is literally ‘the venous reservoir’ of the system, stabilising the cannula to an optimal position and lowering the patient’s head can improve venous return. The anaesthetic input for optimising the pump flow during the procedure is indispensable (see anaesthetic management).

The venting issue using MECC has also been discussed. Furthermore, venting is a problem in minimally invasive valve surgery when performed on MECC. The set-up in this case comprises percutaneous femoral cannulae for both arterial and venous vessels and a left atrial (for mitral surgery) or ventricular (for aortic surgery through the aortic valve) sump drain; the blood is usually collected to the cell-saver device. Venting through the PA and aortic root is mandatory. De-airing is demanding: continuous CO_2 field flooding, placing the patient in the Trendelenburg position, stopping the pulmonary artery vent, resuming ventilation to vent out air from the pulmonary circulation and applying suction to the aortic root vent before unclamping the aorta have been proved successful in de-airing as confirmed by TEE examination [13, 14].

Using a conventional CPB circuit, air in the venous lines can be dealt with fairly promptly. On the other hand, the same amount of air in the

MECC system can lead to sudden cessation of the pump. Prompt de-airing of the system is needed as described in the perfusion chapter of the book. For this reason, application of an extra purse-string on the right atrium around the venous pipe to prevent accidental entry of air has already been discussed. As already mentioned there is a learning curve associated with use of MECC, but this is not a steep one and can be easily overcome. Generally, air entrapment requires a more careful cannulation technique [15]. However, there is always the risk of air entrapment caused by the negative venous line pressure and embolism mainly from the venous side and the venting sites. The MECC system is a closed-loop system, using kinetically assisted venous drainage, and it can result in subatmospheric pressures in the venous line as well as the centrifugal pump, causing bubble generation by the degassing of dissolved blood gasses. With conditions of reduced venous return (e.g. extreme blood loss, luxation of the heart or tube kinking), venous line pressure can transiently peak down to −300 mmHg or even lower [16]. Concerns have been raised against this issue [17].

Venous air travels easily through a CPB system resulting in gaseous microemboli in the arterial line prior to entering the patient's arterial circulation [18, 19]. It has been shown that the number of cerebral microemboli increases in CPB during drug bolus injections, blood sampling, low blood volume levels in the venous reservoir and infusions [20–22]. Microemboli entering the MECC system appeared also in the arterial outflow [23]. Some studies showed that the centrifugal pump fragments all macroemboli (diameter >500 μm) to microemboli [19, 24, 25], which, however, was not found in other studies [26].

Air microembolisation is considered to be the primary cause of neurological injury in cardiac surgery and de-airing when using MECC has been a matter of concern for some authors. Remadi et al. encountered incidents of air entering the venous cannula and passing into the oxygenator [27]. In the past, closed-loop minimised perfusion circuits were strongly criticised with respect to a potential risk of air embolisation and, therefore, have not been considered for open-heart surgery. Vacuum-augmented drainage is known to be susceptible to micro air aspiration into the circuit, although no fatal or major episodes have been described by any author. Nollert et al. reported that their study was discontinued prematurely because of two cases of air entering the MECC system around the venous cannula and accidental tear of right ventricle [6]. However, these adverse events resulted from two preventable mishaps: a leaky atrial purse-string and a defect in the right ventricle unintentionally caused. Both incidents were resolved uneventfully, but concerns were raised about the safety of the MECC system. Ultrasound-controlled air removal devices have been introduced to MECC, and many articles not only confirm the safety of mini-circuit but also report superior air elimination compared to CECC and reduced cerebral air microembolisation [17, 28]. In more than 450 MECC procedures, Remadi et al. encountered only three air intakes (problems in operative field) on the venous side. None of these three adverse events encountered consequences for the patients. For those cases, de-airing was achieved without any problems, and the air was stopped on the anterior part of the oxygenator [15].

Recently, improvements in MECC system or the so-called second generation of mini-bypass circuits introduced innovative de-airing and safety features to remove this potential concern [29]. The concept of using an integrated automatic de-airing device (called VBT, VARD, etc.) has been adopted and improved by several MECC companies (Fig. 5.11) [24, 25, 30–33]. This air filter at the drainage site is proved to effectively remove air bubbles from a closed circuit with a centrifugal blood pump [34]. Roosenhoff et al. demonstrated that a bubble trap integrated in a MECC system significantly reduces the volume of gaseous microemboli (20–500 μm) by 71 %. Large GME (>500 μm) are for the greater part (97 %) scavenged by the bubble trap. Therefore, the use of a bubble trap in a closed loop system is strongly advised and may further contribute to patient safety when using MECC [26]. Gaseous microemboli are currently detected by sensing systems with venous bubble trapping [35].

Due to the fact that MECC is a totally closed system, there is a risk of air embolism from the venous side, which can produce an airlock. A bubble detector is added to the venous side prior to the centrifugal pump, which detects any air emboli and can be removed by a separate line connected to the cell saver [36]. A double safety system with a bubble detector and alarm at the PA vent line as well as at the end of the venous line before entering the oxygenator has also been used in MECC. This alerts the perfusionist, allowing the trapped bubbles in the venous bubble trap to be vented to the cell saver by a separate line before reaching the arterial line [15]. Thus, when air enters the device through the venous return line, air bubbles are detected, and the device exerts evident visual and audible indications while removing the venous air. The air is automatically removed from the venous air removal device until its sensors detect no remaining air–blood mixture in the upper area of the device, and then it returns to standard setting [37].

In conclusion, MECC is technically less demanding than OPCAB surgery and allows maintaining peripheral (cerebral) safe perfusion in contrast to a certain risk in off-pump procedures. Remadi et al. have noticed excellent exposure for complete revascularisation [38] and, in more than 1,500 cases, found neither systemic injury nor occult air embolism, consistent with other reports [35, 39–41]. Air entrapment and handling is no longer a major problem using the systems. The use of an air removal device at the venous side of the MECC system could avoid air entering this system and may increase patient safety. Despite the potential risk of microembolisation using MECC, two recent studies reported a lower embolic load in patients perfused with these systems as compared to CECC during CABG [17, 23]. Finally, to prevent loss of blood in redo or complex cases or in the scenario of accidental blood loss, an optoelectrical suction device (Cardiosmart AG, Muri, Switzerland) can be integrated into the system. Aspiration of blood is controlled by an optoelectrical sensor at the tip of the suction cannula, and suction mechanism is started only when the tip of the suction cannula is in direct contact with the blood. The aspirated blood is directly retransfused into the venous line of the circuit, and therefore no additional suction pump or reservoir is required [5]. However, since this set-up renders the system as semi-closed and results in losing some of the qualities of the system, it is not preferred by many surgeons.

Fig. 5.11 De-airing device integrated to the MECC circuit

In conclusion, technical points which are of great importance for the surgical team when a MECC system is used include intermittent aortic root vent with continuous root pressure monitored by a transducer so as no embolisation of coronary arteries happen; intracardiac (i.e. valve) surgery prerequisites adequate venous return, and hence full emptying of the heart is mandatory for not wasting blood; smart-suction cannula may be a valuable addition in complex surgery; conversion to long-term support (ECMO) replacing only the oxygenator (if a hollow fibre one is used to a long-lasting diffusion oxygenator) and keeping the same set-up are feasible in cases of cardiogenic shock intraoperatively and failure from weaning off CPB. A close teamwork from all the participants in the operating theatre (surgeon, anaesthesiologist, perfusionist, scrub nurse) who continuously monitor the procedure and act promptly so as to maintain optimal operating conditions to perform surgery on MECC is of paramount importance.

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Anaesthetic Management

6

Cardiopulmonary bypass (CPB) technology is relatively old. Since the first cardiac surgical operations in the early 1950s, improvements in oxygenator design, in coagulation monitoring and greater understanding of blood damage by flow rates and shear stresses have contributed to the relatively safe modern circuit. Despite all this refinement, CPB is still associated with systemic inflammatory response syndrome (SIRS), which is translated into myocardial, renal, pulmonary and neurologic dysfunction. However, although these effects are often subclinical, they can contribute to adverse postoperative outcome. Over the past 10 years, miniaturized extracorporeal circulation (MECC) has been developed targeting in reducing the side effects of conventional extracorporeal circulation (CECC). MECC has adopted all modern technology and translated the results from research in its structures. The net outcome from the use of these systems is reduced perioperative morbidity and reduced procedural mortality as has been recently demonstrated in our meta-analysis [1]. Anaesthetic techniques have always evolved with changes in surgical practice. Anaesthetic considerations regarding use of MECC in cardiac surgery are discussed in this chapter with the rationale of enhanced recovery and implementation of fast track strategies based to the qualities of these systems.

The Pre-cardiopulmonary Bypass Period

The period of time between induction of anaesthesia and institution of CPB is characterised by widely varying surgical stimuli. Anaesthetic management during this high-risk period must strive to:

1. Optimise the myocardial oxygen supply/demand ratio and monitor for myocardial ischemia.
2. During this vulnerable time period, haemodynamics should be optimised in order to provide adequate organ perfusion. Taking into account the underlying cardiac pathology, we are trying to manipulate preload, afterload, contractility and heart rate in order to achieve optimal organ perfusion for every patient.
3. If a patient can be managed in a ‘fast-track’ basis, it is logical to use short-acting anaesthetic agents. For patients being operated on MECC, the lesser impact of SIRS tender them readily weanable from mechanical ventilation postoperatively. Most of these patients fulfill all extubation criteria shortly postoperatively. From this point of view, we can consider every MECC patient as a candidate for ‘fast-track’ anaesthesia.

The level of stimulation during the pre-CPB period is varying. Maintenance of an adequate depth of anaesthesia is critical for haemodynamic stability especially during high levels of stimulation. These include incision, sternal split, sympathetic nerve dissection, pericardiotomy and aortic cannulation. During this time it is very important to avoid adverse haemodynamic changes which could increase the risk of myocardial ischemia or dysrhythmias. These complications increase the risk for an adverse outcome for the patient and may cause alterations in the surgical plan leading to an emergency institution of bypass with failure to perform appropriate harvesting of

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the internal mammary artery. During this period, the treatment of any haemodynamic change should involve the administration of short-acting drugs like esmolol, nitroglycerin (as a bolus of 50–80 μg), phenylephrine and ephedrine. The use of agents with long half-lives could affect and compromise weaning from bypass. Until the mid-1990s, administration of large doses of opioids was a widespread practice in cardiac anaesthesia. Fentanyl is often given during anaesthesia for cardiac surgery using CPB. The impact of CPB on the pharmacokinetics of fentanyl has not been fully investigated. Many factors, including haemodilution, hypothermia, nonphysiological blood flow and pump-induced systemic inflammatory response have the potential to affect drug distribution and elimination [2]. During CPB fentanyl plasma concentration is unstable because it is influenced by a lot of factors like priming volume of the circuit, binding of fentanyl to the circuit tubing and membrane oxygenator, sequestration of fentanyl within the pulmonary circulation, altered protein binding after haemodilution and variable metabolism and excretion secondary to hypothermia. Although a stable plasma anaesthetic drug level can be maintained before CPB, the initiation of the bypass phase of cardiac surgery induces a decrease in plasma concentration of many drugs [3]. Taking into account the oxygenator type and the amount of priming volume, it should be necessary to rebolus fentanyl immediately before and after initiation of CPB or during the rewarming phase to maintain a constant blood level [4–6]. Three therapeutic objectives need to be fulfilled to optimise use of IV opioids in patients undergoing cardiac surgery:

1. Achieving and maintaining opioid concentrations that effectively control responses to surgical stimulation
2. Providing effective analgesia
3. Minimising the contribution of opioid-induced respiratory depression to the need for postoperative respiratory support.

Maximising the beneficial effects of opioids while also minimising the duration of postoperative respiratory depression requires greater precision in opioid administration.

Accurate and precise pharmacokinetic models are required in order to achieve and maintain the desired target drug concentrations. We think that target-controlled infusion models delivered through a reliable device could meet these criteria. Target-controlled infusion (TCI) incorporates the pharmacokinetic variables of an IV drug to facilitate safe and reliable administration. Maintaining a constant plasma or effect compartment concentration of an IV anaesthetic requires continuous adjustment of the infusion rate according to the pharmacokinetic properties of the drug. This can be achieved by computer-controlled infusion pumps, such as the devices for TCI. Despite the relative underestimation of propofol plasma concentrations reported in the literature, and the fact that the dosing schemes determined by the clinical requirements are not always optimally designed, maintenance of constant propofol plasma concentrations has been simplified in clinical practice by the use of TCI devices [7]. When the TCI administration of propofol is combined with opioids, propofol kinetics could be altered [8, 9].

Comparing to the other commonly used opioids like fentanyl and sufentanil, remifentanil has a unique pharmacokinetic profile through a widespread extrahepatic hydrolysis by nonspecific tissue and blood esterases. The ability to administer remifentanil continuously provides a stable analgesic and antinociceptive treatment to patient. Remifentanil has an onset time of 1 min and a recovery time of 9–20 min. The advantage with this drug is the possibility to titrate it every minute accordingly to the level of surgical stimulation without impending rapid recovery. Remifentanil appears to be an ideal analgesic component for total IV anaesthesia (TIVA) in combination with propofol because of its elimination via an independent pathway from that of propofol as well as its rapid elimination and favourable controllability.

In cardiac surgery the physical status of patients is usually severely impaired, and the sympathetic depression by anaesthetics pronounced, in comparison to healthy volunteers. Cardiac surgery is associated, apart from painful stimuli to severe disturbance of patient homeostasis (i.e. volume shift, blood loss, endocrine activation, CPB and marked SIRS). In our institution induction and maintenance of anaesthesia are performed with propofol (target: 1.5–2.5 ng/ml) and remifentanil (target: 7 ng/ml) during the whole procedure. We employ target-controlled propofol anaesthesia to keep the bispectral (BIS) index between 40 and 50. Similar BIS values have already been applied by Bauer et al. [10] during propofol–remifentanil anaesthesia in patients undergoing elective on-pump coronary artery bypass grafting.

Both drugs are administered with computer-controlled infusion devices. The TCI software is programmed on the basis of algorithms of Schwilden [11] and incorporates Schnider's [12] pharmacokinetic variable for propofol. Comparing to the Marsh pharmacokinetic model, the Schnider model takes age into account as a covariable. For the remifentanil infusion, the Minto model [13] is applied.

Many patients undergoing cardiac surgery do not tolerate unstable haemodynamics that can be precipitated by various noxious stimuli. Particularly, tachycardia that is strongly linked to the degree of sympathetic stimulation is a risk factor for perioperative myocardial ischaemia and infarction, especially in patients with coronary artery disease and those with a hypertrophic left ventricle [14]. Concomitant rises in blood pressure increase wall stress and may also cause decompensation in heart failure patients. Immediate on- and off-set of the analgesic effect of remifentanil makes it a perfect agent to instantly control painful stimuli during surgery. Remifentanil can easily be adjusted to each patient's analgesic needs without compromising recovery [15–18].

Haemodynamic alterations, especially during the pre-bypass period, have a great impact on cardiac morbidity. In addition, haemodynamics on and after CPB are frequently affected by the application of catecholamines and volume status and may not reflect stress responses [19]. We have noticed that the combination of remifentanil and propofol delivered with a TCI infusion pump suppressed efficiently haemodynamic responses during cardiac surgery and decreased episodes of hypertension and tachycardia associated with sympathetic stimulation.

Attenuation of neurohumoral responses to surgical stress has always been a main focus of cardiac anaesthesia. Anaesthetic management contributes extensively to the modulation of stress response after surgery thus facilitating weaning from ventilator support and enhancing recovery postoperatively. There is evidence from recently published data that TCI mode of administration of remifentanil led to intraoperative decrease in opioid consumption and also to attenuated opioid-induced hyperalgesia after cardiac surgery [19].

In our institution rocuronium is administered at a dose of 0.7–1.0 mg/kg for tracheal intubation, followed by a continuous infusion (10–15 mg/h) to maintain intraoperative paralysis. Comparing all other neuromuscular blocking agents, a rocuronium-induced neuromuscular blockade can be effectively and safely reversed with sugammadex, allowing prompt weaning from mechanical ventilation postoperatively if all other criteria are met. It is known that co-administration of rocuronium to remifentanil/propofol anaesthesia results in markedly reduced dose of rocuronium [20].

During the past decade, rapid postoperative recovery and earlier tracheal extubation have become priorities in the anaesthetic management of adults undergoing cardiac surgery. Current emphasis on rapid recovery and early tracheal extubation requires greater precision in administering opioids to keep their benefits (such as suppression of responses to noxious stimuli and postoperative analgesia) while reducing the duration of unintended postoperative respiratory depression and prolonged intensive care unit stay [21–23]. The oxygenator incorporated in MECC Maquet which we use in our institution contains a plasma-tight poly(4-methyl-1-pentene) membrane. This membrane constitutes a solid barrier between blood and gas and is therefore also described as a solid or diffusion membrane. The homogenous non-porous membrane and the complete separation of blood and gas phase provide improved biocompatibility with less blood traumatisation. Crossing of micro-bubbles caused by a lowered pressure on the blood side compared to the gas side as well as plasma leakage should not occur because of the tightness of the membrane [24, 25]. There were studies in the literature demonstrating a markedly decreased uptake of volatile anaesthetics into blood via this type of membrane oxygenators compared to conventional polypropylene membrane oxygenators [26, 27]. Therefore, propofol was considered preferable for maintenance of anaesthesia in patients operated on MECC to ensure a constant level of the applied anaesthetic agent. However, inability to use volatile agents which cause preconditioning of the myocardium could be a major potential disadvantage of the system [28]. Volatile anaesthetic agents are widely used for maintenance of anaesthesia in all kinds of surgical procedures. There is data in the literature supporting cardioprotective effects of volatile anaesthetic agents against the consequences of ischaemia–reperfusion injury associated with cardiac surgery. This effect seemed to be most pronounced when the agent was administered throughout the entire surgical procedure, including the bypass period [26, 27]. Use of volatile anaesthetics during cardiac surgery with CPB has been shown to reduce the extent of postoperative myocardial damage [26, 29–32], the incidence of postoperative myocardial infarction, ICU and in-hospital stay [32], and has even been associated with a lower postoperative one-year mortality [33]. Improvements in oxygenator design in MECC systems allowed the use of volatile anaesthetic during the CPB period. In our institution we perform anaesthesia induction with propofol and remifentanil using TCI administration and we maintain anaesthesia with remifentanil TCI and a volatile anaesthetic, such as sevoflurane. The use of the hollow fibre-type oxygenator in MECC circuits allows the use of a volatile agent throughout the entire surgical procedure, including the CPB period. Concerns regarding the impact of different volatile agents in the postoperative cognitive function have been expressed in the literature. In a study of Kanbak et al., isoflurane was associated with better neurocognitive functions than desflurane or sevoflurane after on-pump CABG. Sevoflurane was associated with the worst cognitive outcome, as assessed by neuropsychologic tests, and prolonged brain injury as detected by high S100B levels [34].

In a recently published study of Anastasiadis et al. [35], data on neurocognitive functioning in two different CPB settings (MECC vs. CECC) is provided. In this study, induction and maintenance of anaesthesia was performed with propofol only for both groups. This randomized study was designed to assess the net effect of the CPB circuit on neurocognitive performance after CABG surgery. The main finding was that there is better neurocognitive function after CABG on MECC compared with CECC at discharge from hospital and at 3 months postoperatively. It also found improved cerebral perfusion during CPB (using the technique of near infrared spectroscopy – NIRS), as indicated by the lower reduction in rSO_2 values. In this study, use of MECC seemed to attenuate neurocognitive impairment after coronary surgery compared with conventional CPB circuits. The study supported that this could be translated to a significant improvement in the quality of patients' life postoperatively.

The Fluid Management

Large priming volumes required in standard CPB can result in significant haemodilution with low postoperative haemoglobin concentration and haematocrit. When MECC is used, the haemodilution is much less pronounced due to less priming volume. Initial priming volume of the MECC Maquet system consisted of 500 ml of a balanced crystalloid/colloid solution (250 ml of hydroxyethyl starch 6 %, 200 ml of Ringer's Lactate solution and 50 ml of mannitol 20 %) [36]. Reduced haemodilution is partially responsible for the observed reduction in the requirement for blood products. Additionally, MECC lacks venous reservoir and cardiotomy suction. This further minimizes haemodilution and mechanical blood trauma. However, because the patient is literally 'the venous reservoir' for the system, tight control of vascular tone remains important. The effect of minimal haemodilution may be obviated if excessive crystalloid volume infusion is administered before and during the case. Volume management is challenging in MECC.

Intraoperative positioning of the patient (legs up and down) or application of a vasoconstrictor could be considered before volume administration. In case of hypotension observed prior to initiation of MECC, any cause of it (deep anaesthesia level, decreased venous return, impaired myocardial contractility, ischemia, dysrhythmia, decrease in systemic vascular resistance) has to be ruled out before volume infusion. After all these parameters including PCWP and CVP pressures have been checked, a fluid challenge of 100–300 ml may be given, and the response to it has to be closely monitored.

Heparinization

The initial dose of heparin for anticoagulation before institution of CPB with the MECC system is 150 units/kg. An ACT level of 300–350 s is safe and adequate for initiating CPB using the MECC system.

Retrograde Autologous Priming

Haemodilution in MECC could be further avoided using retrograde autologous priming (RAP) technique. After insertion of the aortic and the venous cannulae, the priming volume is completely removed, and the circuit fills in a retrograde fashion with autologous blood, thus minimising hemodilution and keeping a relatively high level of hematocrit during CPB [37]. Moderate hypotension during RAP can always occur. A phenylephrine boluses of 20–40 μg could be administered to support arterial pressure.

The Cardiopulmonary Bypass Period

During CPB, normothermia (35–37°C) and alpha-stat blood gas management is applied. Perfusion pressure is kept between 50 mmHg and 80 mmHg. Because haemodilution is markedly reduced, the diuresis during CPB can be decreased to 0.5–1 ml/kg/h. In MECC circuits, there is no venous reservoir. This requires an anaesthesiologist to interact with the surgeon and perfusionist to maintain ideal operating conditions and stable haemodynamics. The patient's intravascular volume is literally 'the venous reservoir' for the circuit. Administration of diuretic agents could further decrease intravascular volume and compromise venous return in the CPB circuit. Reliable indications of adequate perfusion during bypass are SvO_2 and rSO_2, if available.

The Post-cardiopulmonary Bypass Period: From Weaning to ICU Transport

Right after aortic clamp release and during the conduction of proximal anastomoses of the vein grafts, administration of the appropriate inotropic and vasoactive drugs and mechanical ventilation can be established. At this time, the venous return to the CPB and the pump flow could be gradually decreased. In MECC, a long reperfusion time is not necessary, and right after completion of the proximal anastomoses, the patient could be weaned from CPB, further minimizing the total CPB time, if all parameters are optimized. After termination of CPB the removed autologous blood is returned to the patient. After decannulation, protamine sulphate is being used to neutralize the anticoagulant activity of heparin. The standard dose of protamine following cardiopulmonary bypass is generally 1.0–1.5 mg of protamine per 100 IU of total heparin dose administered [38].

The main advantage of MECC is not the decrease in total dose of heparin used but the decreased need for protamine. Protamine has been found to be responsible for increased platelet aggregation and is associated with platelet dysfunction following CPB [39–41].

In our institution, protamine is given diluted in normal saline as short infusion via a peripheral vein in order to minimize the possibility of an anaphylactic reaction. Right after weaning off CPB due to the decreased intravascular volume, the mean arterial pressure can be relatively low. This is beneficial for the myocardium and gives the option to the perfusionist to gradually fill the patient with volume. Moreover, there is a great benefit from the high haematocrit maintenance and the avoidance of transfusions. Additionally, postoperative bleeding is mostly decreased because of the pump type and of the reduced total dose of heparin.

General anaesthesia causes collapse and induces ventilation/perfusion mismatch in the most dependent parts of the lungs in almost every patient [42, 43]. This can persist for hours or even days after surgery predisposing patients to postoperative complications [44, 45]. Despite the fact that MECC causes less injury to the lungs compared to conventional circuits [46], the CPB itself is an additional factor for lung collapse. Lung recruitment manoeuvres (RMs) are ventilatory strategies that aim to restore the aeration of normal lungs. They consist of a brief and controlled increment in airway pressure to open up collapsed areas of the lungs and sufficient positive end-expiratory pressure (PEEP) to keep them open afterwards. The application of RMs during anaesthesia normalizes lung function along the intraoperative period and contributes to successful application of fast-track protocols. There is physiological evidence that patients of all ages and any kind of surgery benefit from such an active intervention [47].

Several recruitment manoeuvres are described and proposed in the literature. In RMs from Tusman and Bohm [47], the driving pressure in a pressure-controlled mode of ventilation is adjusted to obtain a tidal volume of 8 ml/kg, and then PEEP is increased in steps of 5 cmH_2O, from 0 to 20 cmH_2O. PEEP levels between 10 and 15 cmH_2O are maintained until the haemodynamic status is evaluated. This is the so-called haemodynamic preconditioning phase. Provided that haemodynamics were already stable or have been stabilised successfully, the manoeuvre is continued. Once PEEP reaches 20 cmH_2O, the driving pressure is augmented to 20 cmH_2O to reach the opening pressure in healthy lungs (40 cmH_2O of plateau pressure). Those pressures are maintained for about ten respiratory cycles. The optimal closing pressure and thus the level of PEEP capable of keeping the lungs open can either be determined on the basis of theoretical considerations, knowledge and data from clinical studies or from own experience. If such information is neither available nor applicable for an individual patient, the closing pressure needs to be determined by a systematic decremental PEEP titration trial. Once re-collapsing of the lung has started, a second recruitment manoeuvre is applied to re-open the lungs before the final ventilatory settings at a PEEP 2 cmH_2O higher than the closing pressure are applied to keep the lung in an open state until the end of surgery [48]. In another study from Dorsa et al. [48] performed in patients undergoing off-pump CABG, alveolar recruitment technique occurred titrating PEEP in a lower level using fewer cycles for each level of PEEP comparing to RMs from Tusman and Bohm. The respirator was set to a respiratory rate of 8 breaths/min and a tidal volume between 7 and 9 ml/kg. For safety reasons, the maximum inspiratory pressure was kept below 40 cmH_2O. Every 3 cycles, PEEP was increased by 5 cmH_2O until it reached 15 cmH_2O. If a level of 40 cmH_2O was not achieved, the tidal volume was raised to 18 mL/kg, performing ten respiratory cycles (if it did not compromise haemodynamics). Then, the PEEP was reduced to 10 cmH_2O for 3 cycles and finally to 5 cmH_2O in order to maintain the already recruited alveoli. Contraindications included hypovolaemia, unstable haemodynamics, emphysema and bronchospasm. In this study, most of the patients were extubated in the operation room.

In our institution, after sternal closure and recruitment manoeuvres infusion of neuromuscular blocking agent stops. A dose of morphine 0.15 mg/kg and paracetamol 1,000 mg are administered to the patient intravenously; the maintenance agent propofol or volatile anaesthetic stops, and a dexmedetomidine infusion at a dose of 1 μg/kg/h starts. Dexmedetomidine is a short-acting, highly potent, selective a_2-adrenoceptor agonist. Dexmedetomidine combines unique analgesic, sedative, amnesic and anaesthesia-sparing properties with minimal respiratory depressant activity [49, 50]. Agonism at a_2-adrenoceptors in the spinal cord and in the locus ceruleus produces analgesia and sedation, respectively [51]. There is evidence in the literature that patients treated with dexmedetomidine after cardiac surgery experienced a lower incidence of postoperative delirium [52]. Dexmedetomidine has demonstrated an opioid-sparing effect [50, 53, 54] and may also counteract the effect of increased sympathetic activation, producing a dose-dependent bradycardic effect and a reduction in blood pressure secondary to a decrease in noradrenaline release and in centrally mediated sympathetic tone combined with an increase in vagal activity [55, 56]. Lin found [57] that patients receiving dexmedetomidine required 29 % less PCA morphine, adding further support to the analgesic effect of dexmedetomidine in clinical pain.

The ICU Period

In our institution, upon arrival at the ICU, a standardized protocol for postoperative care is implemented for all patients. Infusion rates for dexmedetomidine are titrated in order to achieve and maintain a Ramsay Sedation Score of 2–3, and morphine at a dose of 40 μg/kg/min is administered IV. All patients are extubated if the following criteria are met [58]:

1. State of consciousness: patient following simple commands (i.e. opening eyes and limb movements)
2. Haemodynamic stability: normotension, heart rate <100 beats/min, and no signs of low cardiac output syndrome or myocardial ischaemia without significant inotropic or vasoactive support
3. Spontaneous ventilation: respiratory rate <25 breaths/min with adequate ventilatory mechanics, oxygen saturation >95 %, 50 % FiO_2, and PaO_2/FiO_2 >200
4. Normothermia: temperature >36°C
5. Absence of active bleeding, activated coagulation time <120 s (collected 10 min after protamine)
6. Analgesia: no signs indicative of uncontrolled pain (in a pain scale [0–10] VAS <5).

For surgeons, anaesthesiologists and especially perfusionists, there is a learning curve for this technique. Refinements in anaesthetic technique can promote early recovery, while the use of a minimal invasive circuit for CPB provides safe and excellent operating condition for the surgeon and above all for the patient. Both can contribute to a major evolution in cardiac surgery.

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7

Clinical Outcome After Surgery with MECC Versus CECC Versus OPCAB

The number of cardiac surgical procedures increases worldwide. Coronary artery bypass grafting (CABG) is associated with improved long-term results in severe coronary artery disease compared to percutaneous techniques [1]. Refinements in surgical technique regarding valve procedures reduced morbidity and mortality even in high-risk patients [2]. Use of cardiopulmonary bypass (CPB) remains the gold standard perfusion strategy to perform cardiac surgery. Induction of systemic inflammatory response syndrome (SIRS) and the coagulation cascade during CPB, triggered mainly by the contact of blood with foreign surfaces and complement activation, is related to end-organ injury postoperatively [3].

Avoidance of extracorporeal circulation (ECC) emerged as a valuable alternative to conventional coronary surgery aiming to eliminate its deleterious effects on remote organs; however, this was not confirmed in large multicenter randomized studies [4]. MECC system has been introduced in clinical practice more recently than OPCAB in 1999. It is designed in order to dramatically reduce the side effects caused by CPB, thus resulting in a low inflammation response as for OPCAB and at the same time allowing for a complete myocardial revascularisation as for standard CPB [5]. The MECC is a compromise between OPCAB and standard CPB: This system provides an excellent surgical exposure with a stable cardiac output in order to perform an ideal anastomosis and decreases the inflammatory deleterious effects of the standard CPB. Thus, alternative revascularisation procedures with the MECC system should surpass conventional CPB, using best clinically proven strategies with respect to patient outcome and long-term graft patency [6].

Moreover, MECC can be effectively applied in aortic valve surgery as well as in other cardiac surgical procedures [7, 8]. This system acts as a closed, self-regulated circuit, which resembles a mechanical circulatory assist device rather than an ECC. The rationale is to increase biocompatibility by using a heparin-coated short circuit, reduce foreign surfaces requiring low priming volume and avoid air–blood interaction. Oxygenated blood enters the circulation with minimized haemodilution and mechanical trauma reducing SIRS and preserving coagulation. The advantageous outcome of closed and miniaturized circuits is supposedly derived from the following three components: (1) the elimination of cardiotomy suction, (2) the elimination of open venous reservoirs and (3) the extreme miniaturization of the circuit.

The important question raised by clinicians and health authorities is whether use of MECC influences patients' outcome. Numerous studies have evaluated the effect of MECC on various clinical and laboratory parameters. This heterogeneity of data dispersed in the literature as well as the fact that the net clinical outcome of this technology is still unclear impedes its penetration to routine practice. Several meta-analyses of randomized controlled trials (RCTs) have been published recently in an attempt to clarify most of these unresolved

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issues. The larger one comes from our institution [9]. Twenty-four RCTs comparing MECC versus CECC consisted the main group of this meta-analysis which included a total of 2,770 patients (1,387 allocated to MECC vs. 1,383 allocated to CECC); CABG was the procedure for 2,049 patients (1,026 operated on MECC vs. 1,023 operated on CECC), while 721 patients underwent aortic valve replacement (AVR) or aortic root surgery (361 operated on MECC vs. 360 operated on CECC). In this chapter, we aim to systematically present clinical outcome after coronary surgery with MECC compared to CECC, focusing on significant differences in biological and laboratory parameters that affect overall morbidity and mortality.

Clinical Outcomes Using MECC

Mortality

Even though MECC is in clinical practice for more than a decade, there is still scepticism about its benefits over CECC. Controversy exists mainly regarding operative mortality and long-term outcome which limits widespread use. Encouraging early results obtained from various cohort observational studies and confirmed by small mostly single-institutional RCTs indicated the superiority of MECC in minimizing the deleterious effects of CPB but failed to show any significant difference in hospital mortality between MECC and CECC that could allow a recommendation that all centres should adopt MECC as their standard of care.

Three meta-analyses, with different methodologies, have been published from 2009 in an attempt to 2011 to evaluate clinical implications from MECC use [10–12]. Biancari et al. included 13 RCTs in their meta-analysis with 562 patients operated with MECC and 599 operated with CECC. They analysed patients who underwent CABG, AVR or combined procedures [10]. Cumulative mortality was lower in MECC (1.1 vs. 2.2 %, $p=0.25$) without reaching statistical significance. Zangrillo et al. analysed 16 RCTs including 803 patients operated with MECC and 816 with CECC. Overall mortality was lower in patients operated on MECC (1 vs. 1.8 %) without reaching statistical significance [11]. In another meta-analysis by Harling et al., 29 studies were included with a total of 867 patients undergoing CABG or AVR surgery with MECC, while 879 patients were operated with CECC [12]. No significant difference in mortality was noticed between the two groups.

These studies did not allow drawing an unequivocal answer on the role of MECC, especially regarding effect on operative mortality. Limited total number of patients, inclusion of small underpowered studies, lack of subgroup analysis between CABG and AVR procedures and mixing of patients operated on CECC with those operated off-pump in control group were their main limitations, which prompted us to design an updated meta-analysis [9]. We analysed 24 RCTs comparing MECC versus CECC which included a total of 2,770 patients (1,387 allocated to MECC vs. 1,383 allocated to CECC), of whom 2,049 patients (1,026 operated on MECC vs. 1,023 operated on CECC) underwent CABG while 721 patients underwent aortic valve replacement (AVR) or aortic root surgery (361 operated on MECC vs. 360 operated on CECC). The main finding of the present study is the reduced mortality associated with MECC use in CABG procedures (Fig. 7.1). More specifically, mortality rate was 0.5 % (7/1,277 patients) in MECC group versus 1.7 % (22/1,273) in the control arm ($p=0.02$); this statistical significance was attributed to CABG procedure (6/1,062 [0.6 %] patients in MECC group vs. 20/1,058 [1.9 %] patients in CECC group; $p=0.03$), while no difference in mortality was observed in patients operated for AVR (1/215 [0.5 %] in MECC group vs. 2/215 [0.9 %] in the control arm; $p=0.57$). As described earlier, there was a trend already towards decreased mortality favouring MECC group in the previous meta-analyses, but this did not reach statistical significance. Our result is most probably attributed to the large number of patients

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Fromes 2002	0	30	0	30		Not estimable	2002
Abdel-Rahman 2005	0	101	1	103	6.1 %	0.34 [0.01, 8.36]	2005
Remadi 2006	3	200	5	200	30.1 %	0.59 [0.14, 2.52]	2006
Beghi 2006	0	30	0	30		Not estimable	2006
Skrabal 2007	0	30	0	30		Not estimable	2007
Huybregts 2007	0	25	0	24		Not estimable	2007
Ohata 2008	1	34	5	64	13.1 %	0.36 [0.04, 3.19]	2008
Schottler 2008	0	30	0	30		Not estimable	2008
Kofidis 2008	0	50	1	30	6.0 %	0.19 [0.01, 4.94]	2008
Ovcina I 2009	0	144	0	144		Not estimable	2009
Gunaydin 2009	1	20	2	20	10.2 %	0.47 [0.04, 5.69]	2009
Sakwa 2009	0	102	0	97		Not estimable	2009
Camboni 2009	0	52	3	40	7.0 %	0.10 [0.01, 2.03]	2009
Bauer 2010	0	18	0	22		Not estimable	2010
El-Essawi 2010	0	146	1	145	6.1 %	0.33 [0.01, 8.14]	2010
Anastasiadis 2010	1	50	2	49	10.6 %	0.48 [0.04, 5.47]	2010
Subtotal (95 % CI)		**1062**		**1058**	**89.4 %**	**0.39 [0.17, 0.90]**	
Total events	6		20				
Heterogeneity: Tau $^2 = 0.00$; Chi$^2 = 1.37$, df = 7 ($P = 0.99$); I$^2 = 0$ %							
Test for overall effect: $Z = 2.19$ ($P = 0.03$)							
b							
Remadi 2004	1	50	2	50	10.6 %	0.49 [0.04, 5.58]	2004
Bical 2006	0	20	0	20		Not estimable	2006
Castiglioni 2009	0	60	0	60		Not estimable	2009
Kutschka 2009	0	85	0	85		Not estimable	2009
Subtotal (95 % CI)		**215**		**215**	**10.6 %**	**0.49 [0.04, 5.58]**	
Total events	1		2				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 0.57$ ($P = 0.57$)							
Total (95 % CI)		**1277**		**1273**	**100.0%**	**0.40 [0.18, 0.88]**	
Total events	7		22				
Heterogeneity: Tau $^2 = 0.00$; Chi$^2 = 1.40$, df = 8 ($P = 0.99$); I$^2 = 0$ %							
Test for overall effect: $Z = 2.26$ ($P = 0.02$)							
Test for Subgroup differences: Chi $^2 = 0.03$, df = 1 ($P = 0.86$), I$^2 = 0$ %							

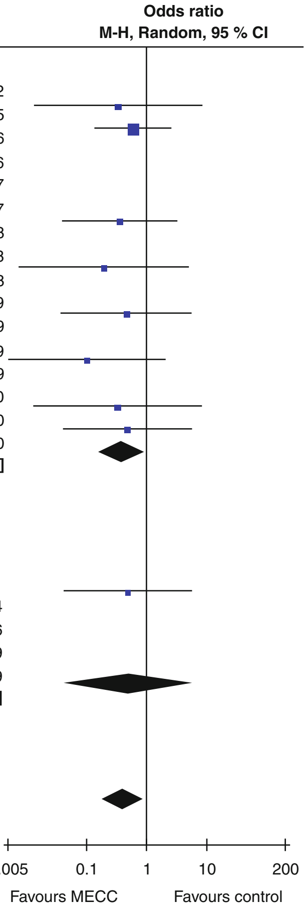


Fig. 7.1 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for overall mortality. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

included in the present meta-analysis (2,770 vs. 1,619 vs. 1,161 vs. 2,355 patients). Survival advantage during the early postoperative period observed in patients who underwent CABG with MECC represents the cumulative beneficial effect of MECC on end-organ protection and on various clinical and laboratory parameters that result in reduced overall morbidity. Considering this result, we advocate expansion of MECC technology to the extent that CECC should be completely abandoned in CABG procedures. This change will have important implications to the health care system. Well-designed RCTs with long-term outcome data are awaited before reaching a definite conclusion.

Surgical Parameters

Regarding procedural characteristics surgery with MECC is not expected to exert any positive effect on net cross-clamp time. This is true when the number of peripheral anastomoses is taken into consideration in coronary surgery. MECC allows for complete revascularisation as for CECC. Potential technical challenges resulting from reduced suction with MECC do not hinder the operation process [13]. Use of a main pulmonary artery vent further contributes to a clear surgical field. Moreover, learning curve required for adoption of MECC technology is not steep and does not influence operative characteristics. Cross-clamp times in different studies regarding CABG and AVR procedures are best shown and analysed in Fig. 7.2. In our thorough meta-analysis, we did not demonstrate any difference in cross-clamp time between MECC and CECC in CABG and AVR procedures.

Despite having similar cross-clamp time, total duration of CPB time is reduced in patients operated on MECC (Fig. 7.3). This is more evident in coronary procedures than in valve surgery. By analysing the data an important observation is that early studies failed to show any differences in cross-clamp times between MECC and CECC [14–16]. On the other hand, relatively recent studies show consistently reduced CPB time in MECC group [17–20]. This reflects more likely increased experience acquired by centres that use MECC routinely in coronary or aortic valve procedures. Taking into account that cross-clamp time does not differ in both procedures, it becomes evident that the observed reduction in total CPB time could be attributed to a reduction in the net reperfusion time required. This is a clear indicator of improved myocardial protection during surgery with MECC and reduced SIRS.

	MECC			Control				Mean difference	
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95 % CI**	**year**
a									
Fromes 2002	63	17	30	56	15	30	4.1 %	7.00 [–1.11, 15.11]	2002
Abdel-Rahman 2005	44	14	101	45	17	103	7.0 %	–1.00 [–5.27, 3.27]	2005
Beghi 2006	59	20	30	45	13	30	3.9 %	14.00 [5.46, 22.54	2006
Remadi 2006	31	12	200	33	9.5	200	8.8 %	–2.00 [–4.12, 0.12]	2006
Skrabal 2007	52	2.5	30	49.5	3	30	9.2 %	2.50 [1.10, 3.90]	2007
Valtoman 2007	58	17	20	65	19	20	2.7 %	–7.00 [–18.17, 4.17]	2007
Huybregts 2007	71	15	25	68	14.7	24	4.0 %	3.00 [–5.32, 11.32]	2007
Ohata 2008	93	28	34	107	34	64	2.3 %	–14.00 [–26.57, –1.43]	2008
Schottler 2008	61	19	30	61	18	30	3.4 %	0.00 [–9.37, 9.37]	2008
Kofidis 2008	42	12	50	46	11	30	6.2 %	–4.00 [–9.15, 1.15]	2008
Ovcina I 2009	65	19.2	144	70	11	144	7.6 %	–5.00 [–8.61, –1.39]	2009
Gunaydin 2009	76.8	13.42	20	74.5	14.31	20	3.8 %	2.30 [–6.30, 10.90]	2009
Camboni 2009	53	17.4	52	63.2	21.3	40	4.1 %	–10.20 [–18.32, –2.08]	2009
El-Essawi 2010	49	21	146	50	24	145	6.2 %	–1.00 [–6.18, 4.18]	2010
Bauer 2010	40	11	18	41	15	22	4.1 %	–1.00 [–9.07, 7.07]	2010
Anastasiadis 2010	65	17	50	72	22	49	4.3 %	–7.00 [–14.76, 0.76]	2010
Subtotal (95 % CI)			**980**			**981**	**81.7 %**	**–1.15 [–3.60, 1.30]**	
Heterogeneity: $Tau^2 = 13.63$; $Chi^2 = 55.14$, df =15 ($P < 0.00001$); $I^2 = 73$ %									
Test for overall effect: $Z = 0.92$ ($P = 0.36$)									
b									
Remadi 2004	40	20	50	46	17	50	4.6 %	–6.00 [–13.28, 1.28]	2004
Bical 2006	61	13	20	62	12	20	4.3 %	–1.00 [–8.75, 6.75]	2006
Castiglioni 2009	54	12.5	60	49	17	60	6.1 %	5.00 [–0.34, 10.34]	2009
Kutschka 2009	76.5	29.5	85	79	34	85	3.3 %	–2.50 [–12.07, 7.07]	2009
Subtotal (95 % CI)			**215**			**215**	**18.3 %**	**–0.60 [–5.88, 4.68]**	
Heterogeneity: $Tau^2 = 14.98$; $Chi^2 = 6.29$, df = 3 ($P = 0.10$); $I^2 = 52$ %									
Test for overall effect: $Z = 0.22$ ($P = 0.82$)									
Total (95 % CI)			**1195**			**1196**	**100.0 %**	**–1.04 [–3.20, 1.13]**	
Heterogeneity: $Tau^2 = 12.73$; $Chi^2 = 61.43$, df = 9 ($P < 0.00001$); $I^2 = 69$ %									
Test for overall effect: $Z = 0.94$ ($P = 0.35$)									
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 ($P = 0.97$); $I^2 = 0$ %									

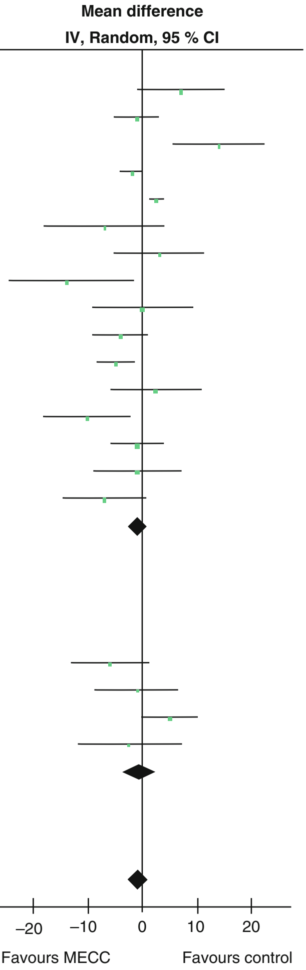


Fig. 7.2 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for cross-clamp time. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

Study or subgroup	MECC Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95 % CI	year
a									
Fromes 2002	61	20	30	79	22	30	4.3 %	–18.00 [–28.64, –7.36]	2002
Abdel-Rahman 2005	78	22	101	76	23	103	5.8 %	2.00 [–4.18, 8.18]	2005
Remadi 2006	63	19	200	65	18	200	6.6 %	–2.00 [–5.63, 1.63]	2006
Beghi 2006	99	28	30	78	19	30	3.9 %	21.00 [–8.89, 33.11]	2006
Skrabal 2007	85	3	30	92	4	30	6.9 %	–7.00 [–8.79, –5.21]	2007
Huybregts 2007	95	20	25	100	14.7	24	4.6 %	–5.00 [–14.80, 4.80]	2007
Valtonen 2007	77.5	19	20	85	21	20	3.8 %	–7.50 [–19.91, 4.91]	2007
Kofidis 2008	74	17	50	82	24	30	4.6 %	–8.00 [–17.80, 1.80]	2008
Ohata 2008	146	35	34	147	44	64	2.9 %	–1.00 [–16.96, 14.96]	2008
Schottler 2008	103	27	30	101	28	30	3.4 %	2.00 [–11.92, 15.92]	2008
Ovcina I 2009	111	28.1	144	115	27.4	144	5.7 %	–4.00 [–10.41, 15.17]	2009
Gunaydin 2009	98.7	18.78	20	94.5	16.55	20	4.2 %	4.20 [–6.77, 15.17]	2009
Camboni 2009	88.7	24	52	76	20	40	4.9 %	12.70 [3.70, 21.70]	2009
Sakwa 2009	75	20	102	97.5	30.6	97	5.5 %	–22.50 [–29.72, –15.28]	2009
El-Essawi 2010	75	27	146	79	34	145	5.5 %	–4.00 [–11.06, 3.06]	2010
Anastasiadis 2010	103	25	50	128	44	49	3.3 %	–25.00 [–39.31, –10.87]	2010
Bauer 2010	72	17	18	76	20	22	4.1 %	–4.00 [–1547, 747]	2010
Subtotal (95 % CI)			**1082**			**1078**	**79.9 %**	**–3.98 [–8.00, 0.03]**	

Heterogeneity: Tau^2 = 48.00; Chi^2 = 85.18, df =16 (P < 0.00001); I^2 = 81 %
Test for overall effect: Z =1.94 (P = 0.05)

Study or subgroup	MECC Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95 % CI	year
b									
Remadi 204	71	23	50	77	27	50	4.6 %	–6.00 [–15.83, 3.83]	2004
Bical 2006	79	14	20	79	12	20	5.1 %	0.00 [–8.37, 8.37]	2006
Castiglioni 2009	69	10	60	65	8.5	60	6.6 %	4.00 [0.68, 7.32]	2009
Kutschka 2009	103	37.9	85	106.9	44.9	85	3.8 %	–3.90 [–16.39, 8.59]	2009
Subtotal (95 % CI)			**215**			**215**	**20.1 %**	**0.39 [–4.50, 5.27]**	

Heterogeneity: Tau^2 = 10.06; Chi^2 = 4.98, df = 3 (P = 0.17); I^2 = 40 %
Test for overall effect: Z = 0.15 (P = 0.88)

Study or subgroup	MECC Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95 % CI	year
Total (95 % CI)			**1297**			**1293**	**100.0 %**	**–3.34 [–6.90, 0.21]**	

Heterogeneity: Tau^2 = 46.68; Chi^2 = 112.85, df = 20 (P < 0.00001); I^2 = 82 %
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Chi^2 = 22.69, df = 1 (P < 0.00001), I^2 = 95.6 %

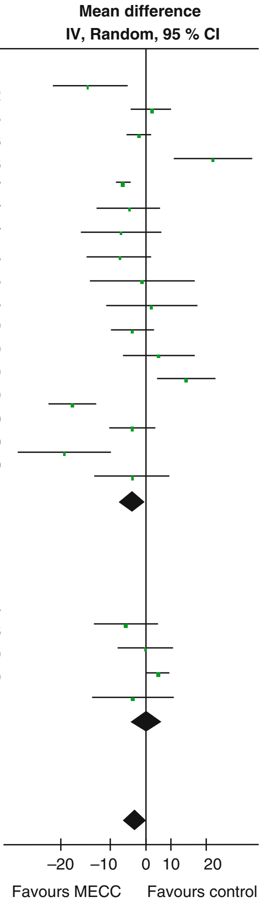


Fig. 7.3 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for total CPB time. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

Myocardial Protection

Damage to the myocardium during cardiac surgery is likely to be multifactorial. Ischaemia and reperfusion injury related to aortic cross-clamping as well as direct surgical trauma have been implicated in postoperative rises in cardiac specific enzymes which indicate myocardial injury. In addition, there is evidence that the CPB machine itself contributes to myocardial injury [21] due to triggering of inflammatory response [22–24]. Differentially from this pathway, pericardial suction blood itself contains high levels of CK and CK-MB, especially when the internal mammary artery is dissected and used for bypass. In the case of retransfusion, these enzymes reach circulation and elevate the systemic concentration [25].

The MECC system, even from the early period of its implementation, has shown promising results with regard to cardiac damage. Wiesenack et al. in their landmark paper on MECC report reduced rate of postoperative myocardial infarction when using MECC [26]. Immer et al. report the results of prospective measurement of cardiac enzymes following CABG in patients undergoing CPB with either MECC or CECC. Troponin I levels, indicative of myocardial injury, were significantly lower in the MECC group at 6, 12 and 24 h after surgery [27]. This study received criticism on the different cardioplegia regimens used, and it was considered that intraoperative myocardial protection was inadequate in the

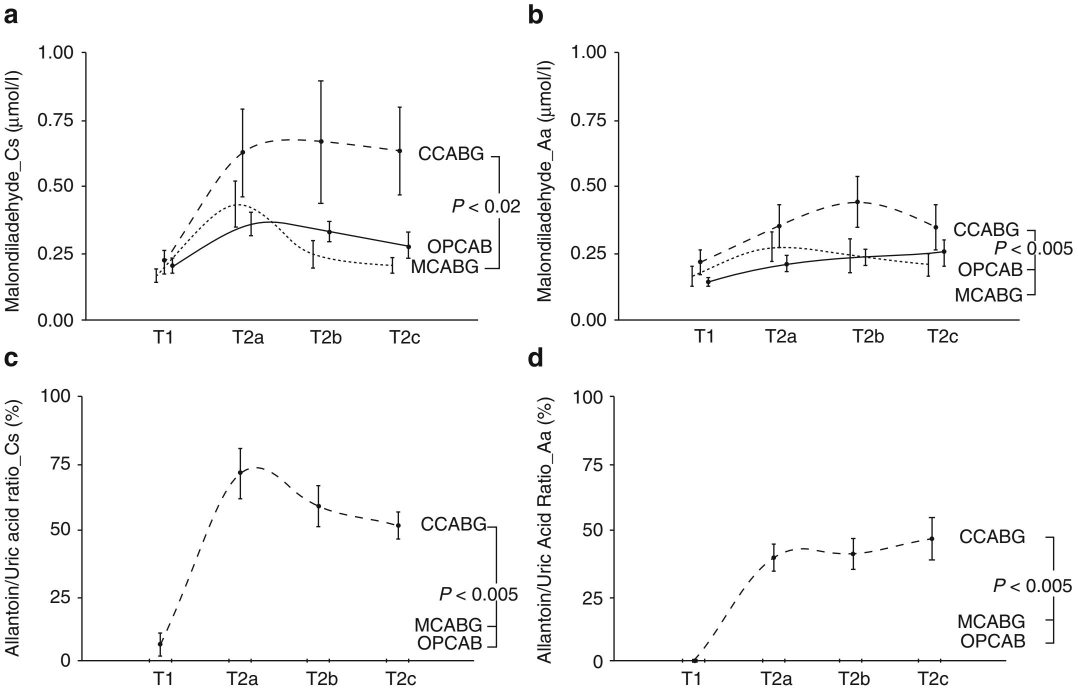
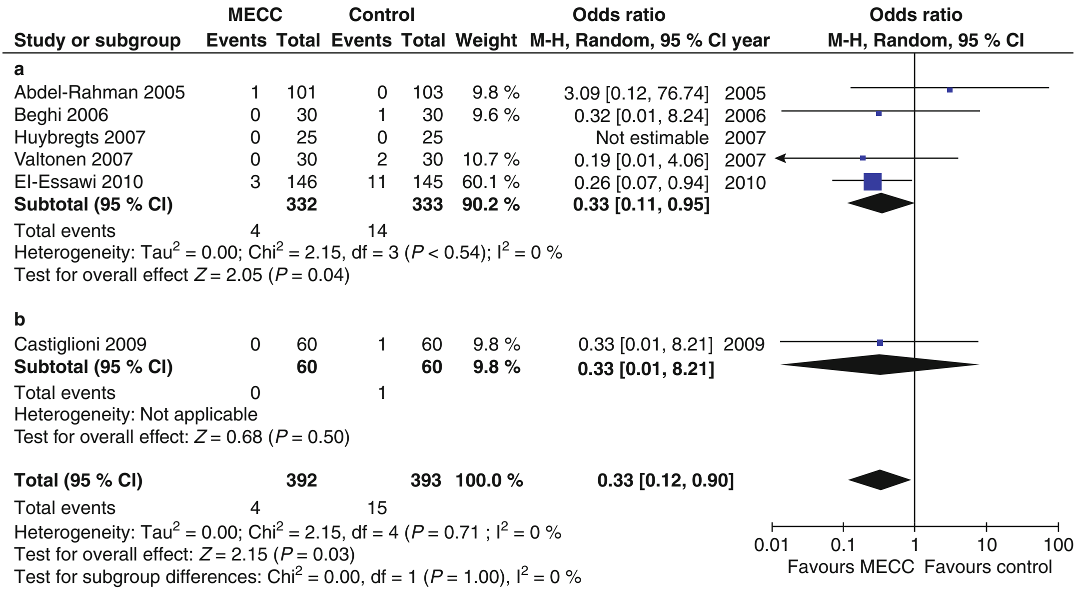


Fig. 7.4 Perioperative malondialdehyde levels in coronary sinus (**a**), or in the ascending aorta (**b**) and allantoin/uric acid ratios in the coronary sinus (**c**) or in the ascending aorta (**d**) (Adapted from van Boven et al. [31])

CECC group. In another prospective randomised study, Skrabal et al. showed that patients undergoing surgery with MECC had significantly lower levels of serum troponin T and creatine kinase-MB postoperatively than those who were operated on CECC [21]. Importantly, both groups in this study received the same cardioplegia regimen, which disputes the notion that inadequate cardioprotection may account for the differences in cardiac enzyme levels. Beneficial effect of MECC regarding myocardial protection was systematically observed in other series [28–30]. Van Boven et al. found significantly reduced global and myocardial oxidative stress in patients operated on MECC [31] (Fig. 7.4).

Analysing data from 24 RCTs in a meta-analysis, we found that surgery with MECC significantly reduced the risk of postoperative myocardial infarction (4/392 [1.0 %] patients in MECC group vs. 15/393 [3.8 %] patients in the control arm; $p=0.03$, Fig. 7.5). This effect was evident in CABG procedure (4/332 [1.2 %] patients in MECC group vs.14/333 [4.2%] patients in CECC group; $p=0.04$), while no difference was observed in patients operated for AVR (0/60 [0 %] in MECC group vs. 1/60 [1.7 %] in the control arm; $p=0.50$). MECC was also associated with statistically significantly reduced levels of peak troponin release (Fig. 7.6). Incidence of low cardiac output syndrome was significantly lower in MECC group (2/280 [0.7 %] patients in MECC group vs. 11/280 [3.9 %] patients in the control arm; $p=0.03$). Need for intra-aortic balloon pump favoured MECC group without reaching statistical significance (3/462 [0.6 %] patients in MECC group vs. 7/457 [1.5 %] patients in the control arm; Fig. 7.7). Interestingly, need for inotropic support was significantly reduced in patients operated on MECC (40/408 [9.8 %] patients in MECC group vs. 65/412 [15.8 %] patients in the control arm; $p=0.007$; Fig. 7.8). Furthermore, Harling et al. in a meta-analysis report significantly reduced incidence of postoperative arrhythmias [12].

There are many possible ways that use of MECC enhances myocardial protection. The absence of an aortic vent in the MECC setting results in the heart



Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Abdel-Rahman 2005	1	101	0	103	9.8 %	3.09 [0.12, 76.74]	2005
Beghi 2006	0	30	1	30	9.6 %	0.32 [0.01, 8.24]	2006
Huybregts 2007	0	25	0	25		Not estimable	2007
Valtonen 2007	0	30	2	30	10.7 %	0.19 [0.01, 4.06]	2007
El-Essawi 2010	3	146	11	145	60.1 %	0.26 [0.07, 0.94]	2010
Subtotal (95 % CI)		**332**		**333**	**90.2 %**	**0.33 [0.11, 0.95]**	
Total events	4		14				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.15, df = 3 ($P < 0.54$); I^2 = 0 %
Test for overall effect $Z = 2.05$ ($P = 0.04$)

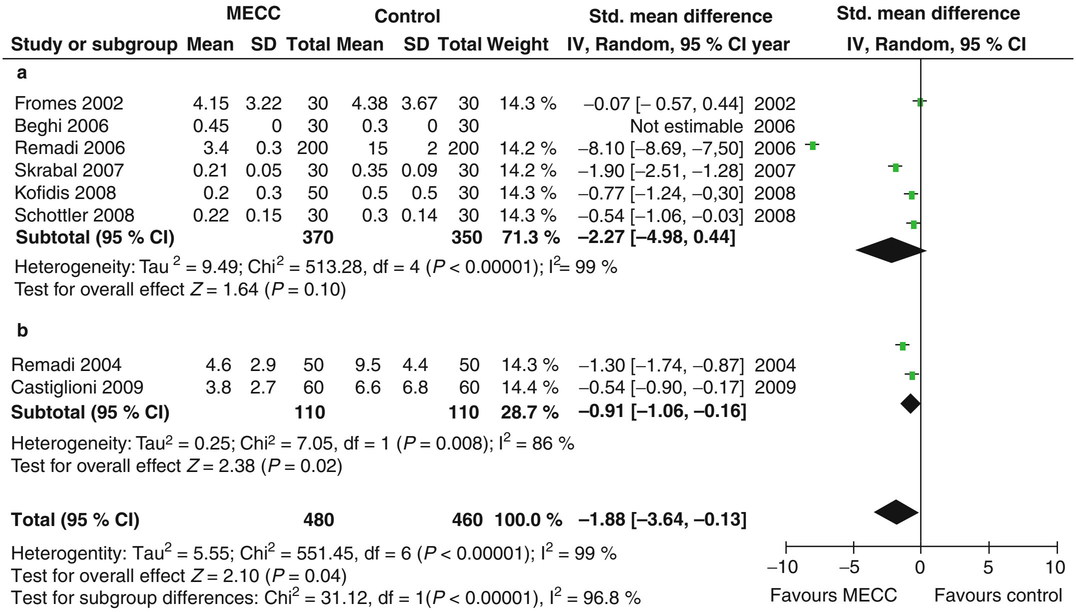
Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
b							
Castiglioni 2009	0	60	1	60	9.8 %	0.33 [0.01, 8.21]	2009
Subtotal (95 % CI)		**60**		**60**	**9.8 %**	**0.33 [0.01, 8.21]**	
Total events	0		1				

Heterogeneity: Not applicable
Test for overall effect: $Z = 0.68$ ($P = 0.50$)

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
Total (95 % CI)		**392**		**393**	**100.0 %**	**0.33 [0.12, 0.90]**	
Total events	4		15				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.15, df = 4 ($P = 0.71$; I^2 = 0 %
Test for overall effect: $Z = 2.15$ ($P = 0.03$)
Test for subgroup differences: Chi^2 = 0.00, df = 1 ($P = 1.00$), I^2 = 0 %

Fig. 7.5 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for postoperative myocardial infarction. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])



Study or subgroup	MECC Mean	MECC SD	MECC Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, Random, 95 % CI	year
a									
Fromes 2002	4.15	3.22	30	4.38	3.67	30	14.3 %	−0.07 [– 0.57, 0.44]	2002
Beghi 2006	0.45	0	30	0.3	0	30		Not estimable	2006
Remadi 2006	3.4	0.3	200	15	2	200	14.2 %	−8.10 [−8.69, −7,50]	2006
Skrabal 2007	0.21	0.05	30	0.35	0.09	30	14.2 %	−1.90 [−2.51, −1.28]	2007
Kofidis 2008	0.2	0.3	50	0.5	0.5	30	14.3 %	−0.77 [−1.24, −0,30]	2008
Schottler 2008	0.22	0.15	30	0.3	0.14	30	14.3 %	−0.54 [−1.06, −0.03]	2008
Subtotal (95 % CI)			**370**			**350**	**71.3 %**	**−2.27 [−4.98, 0.44]**	

Heterogeneity: Tau^2 = 9.49; Chi^2 = 513.28, df = 4 ($P < 0.00001$); I^2= 99 %
Test for overall effect $Z = 1.64$ ($P = 0.10$)

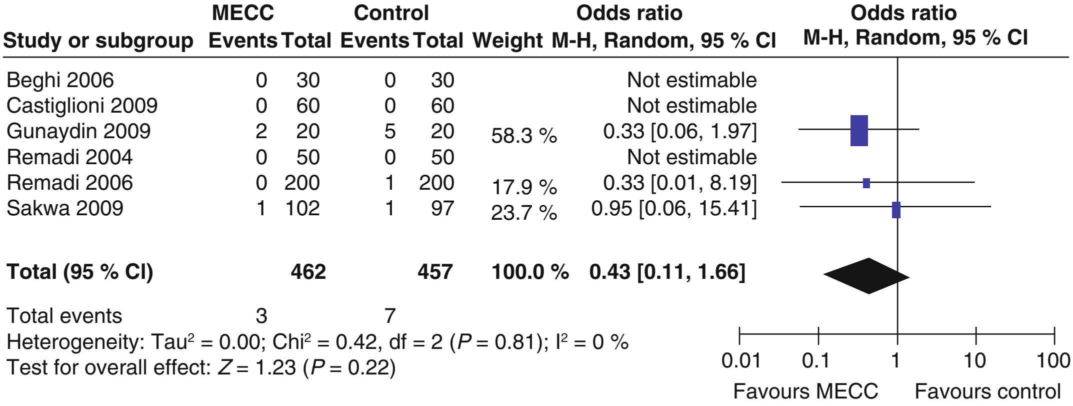
Study or subgroup	MECC Mean	MECC SD	MECC Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, Random, 95 % CI	year
b									
Remadi 2004	4.6	2.9	50	9.5	4.4	50	14.3 %	−1.30 [−1.74, −0.87]	2004
Castiglioni 2009	3.8	2.7	60	6.6	6.8	60	14.4 %	−0.54 [−0.90, −0.17]	2009
Subtotal (95 % CI)			**110**			**110**	**28.7 %**	**−0.91 [−1.06, −0.16]**	

Heterogeneity: Tau^2 = 0.25; Chi^2 = 7.05, df = 1 ($P = 0.008$); I^2 = 86 %
Test for overall effect $Z = 2.38$ ($P = 0.02$)

Study or subgroup	MECC Mean	MECC SD	MECC Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, Random, 95 % CI	year
Total (95 % CI)			**480**			**460**	**100.0 %**	**−1.88 [−3.64, −0.13]**	

Heterogentity: Tau^2 = 5.55; Chi^2 = 551.45, df = 6 ($P < 0.00001$); I^2 = 99 %
Test for overall effect $Z = 2.10$ ($P = 0.04$)
Test for subgroup differences: Chi^2 = 31.12, df = 1($P < 0.00001$), I^2 = 96.8 %

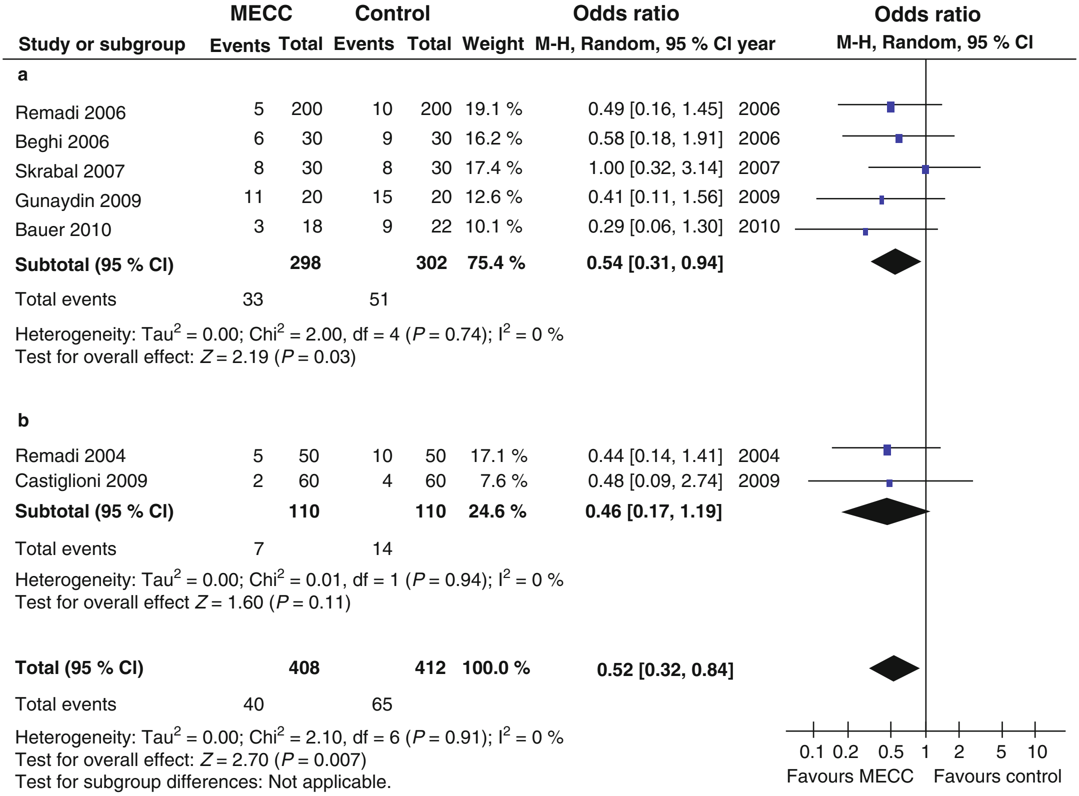
Fig. 7.6 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for peak troponin release postoperatively. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])



Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI
Beghi 2006	0	30	0	30		Not estimable
Castiglioni 2009	0	60	0	60		Not estimable
Gunaydin 2009	2	20	5	20	58.3 %	0.33 [0.06, 1.97]
Remadi 2004	0	50	0	50		Not estimable
Remadi 2006	0	200	1	200	17.9 %	0.33 [0.01, 8.19]
Sakwa 2009	1	102	1	97	23.7 %	0.95 [0.06, 15.41]
Total (95 % CI)		**462**		**457**	**100.0 %**	**0.43 [0.11, 1.66]**
Total events	3		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.42$, df = 2 ($P = 0.81$); $I^2 = 0$ %
Test for overall effect: $Z = 1.23$ ($P = 0.22$)

Fig. 7.7 Meta-analysis comparing MECC versus CECC (control) in CABG procedures, forest plot for the need of intra-aortic balloon pump postoperatively. *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])



Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Remadi 2006	5	200	10	200	19.1 %	0.49 [0.16, 1.45]	2006
Beghi 2006	6	30	9	30	16.2 %	0.58 [0.18, 1.91]	2006
Skrabal 2007	8	30	8	30	17.4 %	1.00 [0.32, 3.14]	2007
Gunaydin 2009	11	20	15	20	12.6 %	0.41 [0.11, 1.56]	2009
Bauer 2010	3	18	9	22	10.1 %	0.29 [0.06, 1.30]	2010
Subtotal (95 % CI)		**298**		**302**	**75.4 %**	**0.54 [0.31, 0.94]**	
Total events	33		51				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.00$, df = 4 ($P = 0.74$); $I^2 = 0$ %
Test for overall effect: $Z = 2.19$ ($P = 0.03$)

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
b							
Remadi 2004	5	50	10	50	17.1 %	0.44 [0.14, 1.41]	2004
Castiglioni 2009	2	60	4	60	7.6 %	0.48 [0.09, 2.74]	2009
Subtotal (95 % CI)		**110**		**110**	**24.6 %**	**0.46 [0.17, 1.19]**	
Total events	7		14				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 ($P = 0.94$); $I^2 = 0$ %
Test for overall effect $Z = 1.60$ ($P = 0.11$)

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
Total (95 % CI)		**408**		**412**	**100.0 %**	**0.52 [0.32, 0.84]**	
Total events	40		65				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.10$, df = 6 ($P = 0.91$); $I^2 = 0$ %
Test for overall effect: $Z = 2.70$ ($P = 0.007$)
Test for subgroup differences: Not applicable.

Fig. 7.8 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for need for inotropic support postoperatively. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

not being completely unloaded during the procedure, keeping a slight coronary flow in the majority of patients. This minimal residual perfusion reduces air in the coronary system and may in part explain improved myocardial protection [27]. It could also be attributed to the indirect effect of reduced SIRS during MECC surgery [11].

Neurologic Damage

Neurologic complications with transitory or permanent deficits remain a significant problem after CABG surgery. The incidence of type 1 neurologic events with stroke and transient or permanent deficit averages 3 %, and the rate of type 2 event with deterioration of intellectual function affects more than 50–80 % of patients after elective CABG [32]. Prolonged hypoperfusion and microembolisation during CPB have been related to postoperative neurological impairment [33]. Cerebral microembolisation is a well-recognised consequence of CPB. This has been demonstrated in clinical studies using Transcranial Doppler (TCD) and MRI [34] as well as in autopsy [35, 36]. Microemboli consist of both gaseous and solid particles believed to originate mainly from nonphysiologic surfaces and blood–air interfaces of the circuit and operative area. Venous air travels easily through a bypass system resulting in gaseous microemboli (GME) in the arterial line prior to entering the patient's arterial circulation [37]. GME have multiple potential sources of origin, such as surgical cannulation, cardiotomy suction, sampling and injection sites, the oxygenator, increased blood viscosity caused by hypothermic conditions, rapid warming of cold blood, increasing number of circuit connections, perfusionist interventions and turbulent flow in the tubing caused by increased flow rates [38, 39]. The number of cerebral microemboli increases in CECC systems during drug bolus injections, blood sampling, low blood volume levels in the venous reservoir and infusions [40, 41]. Microemboli activate the inflammatory response and may even obstruct the blood flow in the capillary vessels, causing ischaemia [42]. Microemboli may also lead to a decline in the cognitive function of the patient [43].

Cerebral perfusion during CPB is influenced by a number of factors, including haemodilution, hypotension, loss of pulsatile flow, impairment of the autoregulatory mechanisms of cerebral blood flow and embolic events. Furthermore, it might be the result of inflammatory changes that lead to increased permeability across the blood–brain barrier, resulting in cerebral oedema.

MECC is generally considered as a "neuroprotective" circuit. In a large prospective study including 1,674 patients undergoing CABG, Puehler et al. found that in the MECC group the stroke risk was decreased in comparison with that of the CECC group (2.3 vs. 4.1 %, $p < 0.05$) [5]. This finding was also confirmed in other studies [44]. Biancari and Zangrillo in two meta-analyses report reduction in neurologic damage after surgery with MECC [10, 11]. In our meta-analysis, which included significantly higher number of patients compared to the previous two, neurologic damage was not statistically different between the two techniques, though MECC was associated with reduced rate of neurologic events (22/953 [2.3 %] patients in MECC group vs. 38/950 [4.0 %] patients in the control arm; $p = 0.08$; Fig. 7.9) [9]. These data indicating improved neurologic outcome after surgery with MECC are strikingly interesting, as a major drawback of miniaturized CPB systems (for the lack of venous reservoir and arterial filter) is the potential entrapment of air with the risk of subsequent cerebral embolism. Emerging evidence coming from recent RCTs failed to demonstrate a positive effect of MECC in reducing risk of stroke [18–20, 45]. It is well established that the predominant cause of major neurological injury after cardiac surgery is the degree of aortic manipulation rather than the type of circuit used [46].

The observed trend towards improved neurologic outcome from MECC use, which is consistent in all meta-analyses, could be attributed mainly to the technologic advancements

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Abdel-Rahman 2005	0	101	1	103	3.2 %	0.34 [0.01, 8.36]	2005
Remadi 2006	1	200	7	200	7.3 %	0.14 [0.02, 1.14]	2006
Huy bregts 2007	0	25	0	24		Not estimable	2007
Ohata 2008	1	34	6	64	7.0 %	0.29 [0.03, 2.54]	2008
Kofidis 2008	1	50	1	30	4.1 %	0.59 [0.04, 9.83]	2008
Schottler 2008	0	30	1	30	3.1 %	0.32 [0.01, 8.24]	2008
Sakwa 2009	2	102	2	97	8.3 %	0.95 [0.13, 6.88]	2009
Camboni 2009	8	52	8	40	27.9 %	0.73 [0.25, 2.14]	2009
El-Essawi 2010	4	146	4	145	16.5 %	0.99 [0.24, 4.05]	2010
Bauer 2010	1	18	0	22	3.1 %	3.86 [0.15, 100.58]	2010
Subtotal (95 % CI)		**758**		**755**	**80.4 %**	**0.63 [0.33, 1.19]**	
Total events	18		30				
Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 4.68$, df = 8 ($P = 0.79$); $I^2 = 0$ %							
Test for overall effect: $Z = 1.44$ ($P = 0.15$)							
b							
Remadi 2004	2	50	7	50	12.3 %	0.26 [0.05, 1.30]	2004
Kutschka 2009	1	85	1	85	4.2 %	1.00 [0.06, 16.25]	2009
Castiglioni 2009	1	60	0	60	3.1 %	3.05 [0.12, 76.39]	2009
Subtotal (95 % CI)		**195**		**195**	**19.6 %**	**0.53 [0.14, 2.01]**	
Total events	4		8				
Heterogeneity: $Tau^2 = 0.08$, $Chi^2 = 2.10$, df = 2 ($P = 0.35$); $I^2 = 5$ %							
Test for overall effect: $Z = 0.94$ ($P = 0.35$)							
Total (95 % CI)		**953**		**950**	**100.0 %**	**0.60 [0.34, 1.06]**	
Total events	22		38				
Heterogeneity: $Tau^2 = 0.08$, $Chi^2 = 6.85$, df = 11 ($P = 0.81$); $I^2 = 0$ %							
Test for overall effect: $Z = 1.74$ ($P = 0.08$)							

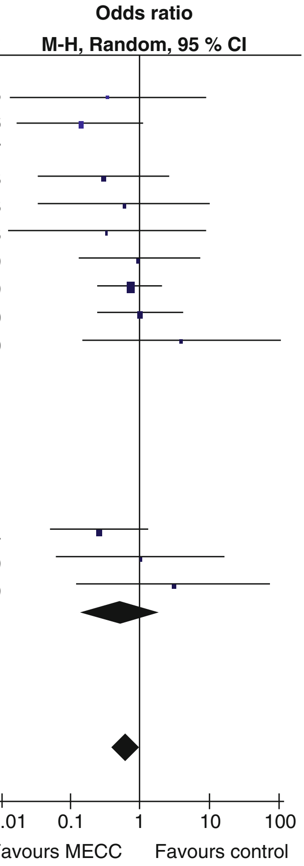


Fig. 7.9 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for neurologic damage *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

incorporated in these systems: (1) heparin coating of the artificial surfaces which resemble the physiologic endothelium [47], (2) avoidance of recirculation of shed blood along with cellular debris and lipid microparticulates with elimination of the venous reservoir and the cardiotomy suction [48, 49] as well as (3) maintenance of higher mean perfusion pressure during CPB [18, 26]. Perthel et al. reported a significantly lower rate of gaseous microemboli in the arterial line of MECC compared to CECC [50]. In a landmark paper, Liebold et al. evaluated cerebral oxygenation by near-infrared spectroscopy during surgery with MECC versus CECC. They observed a significantly lower oxyhaemoglobin level in the CECC group. MECC was associated with significantly lower total embolic count (733 ± 162 in the MECC group vs. 1,591 ± 555 in the CECC group, $p = 0.02$). Microemboli were identified as gaseous in 76 % of patients operated on CECC and 77 % of patients operated on MECC. A preserved perfusion pressure with the use of MECC has been observed as well [49]. In a randomized study published recently by the group from Finland, reduced retinal microembolisation was found after the use of MECC compared with CECC, suggesting a decreased embolic load to the brain [51].

Neurocognitive Dysfunction

Postoperative cognitive decline (POCD) is characterized as impairment in attention, cognition, recognition, orientation, memory and learning. It may result in prolonged hospitalisation and increased morbidity and mortality, while it has an adverse impact on quality of life after surgery. It occurs in 40–50 % of patients and has been reported in as high as 79 % of patients in the early postoperative period [33]. Cerebral microembolism and hypoperfusion have been proposed to be the major mechanisms for cognitive dysfunction after cardiac surgery [52, 53]. All these factors cause tissue ischaemia and hypoxia, resulting in neurodegeneration. Neurodegeneration is accompanied by both acute necrotic and delayed apoptotic neuron death [54]. Cerebral oxygen desaturation, as measured intraoperatively with near-infrared spectroscopy, is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery with CPB [55].

Our group has extensively studied the effect of MECC on neurocognitive outcome in patients operated for CABG. In a randomized study published in 2011, we found that there is better neurocognitive function after CABG with MECC compared to CECC at discharge from hospital and at 3 months postoperatively. This could potentially have a positive impact on the quality of life of these patients [56]. Moreover, the same study revealed that MECC offered improved cerebral perfusion during CPB, as indicated by the lower reduction in rSO_2 values and cerebral desaturation episodes, as measured with cerebral oxymetry monitoring. Cerebral desaturation episodes adversely affect neurocognitive outcome. This is in accordance with the findings of Liebold et al. who reported that patients who underwent CABG on MECC experienced preserved cerebral tissue oxygenation and reduced cerebral microembolisation compared to patients who underwent surgery with the conventional circuit.

Many factors could explain this outcome. Avoidance of cardiotomy suction and processing of shed blood with a cell saver has been proved to play a key role in this setting [57]. Other features of the MECC circuit such as reduced SIRS, reduced haemodilution and improved haemodynamic performance contribute to improved neurocognitive performance after surgery.

End-Organ Dysfunction

CPB may result in periods of relative tissue ischaemia of the heart and of other organs, contributing to organ dysfunction and even failure. CPB is associated with a generalized inflammatory response and splanchnic oedema formation that is thought to be related to microvascular barrier injury [58]. The reversal of periods of ischaemia can lead to reperfusion injury typified by the generation of reactive oxygen species, elevation of intracellular calcium concentrations, inflammation and ultimately cell death [59]. In the first clinical observational study on MECC in coronary surgery, Wiesenack et al. revealed that maximum values of lactate concentration during bypass were significantly higher in the control group compared to the MECC group [26]. Though the interpretation of elevated lactate concentrations is limited by several confounding variables, measurement of blood lactate levels is widely used to assess the adequacy of tissue perfusion. Based on regional blood flow and lactate exchange measurements, Takala et al. stated that hyperlactatemia after cardiac surgery is a sign of inadequate or marginal tissue perfusion of the hepatosplanchnic region, as well as other tissues [60]. Several studies that used sensitive and specific markers on end-organ function showed improved functioning after surgery with MECC compared to CECC. Van Boven et al. measured the levels of MDA and the allantoin/uric acid ratios of patients undergoing surgery with both MECC and CECC. They found reduced levels of oxidative stress among the MECC patients following removal of the aortic cross-clamp and subsequent reperfusion [61].

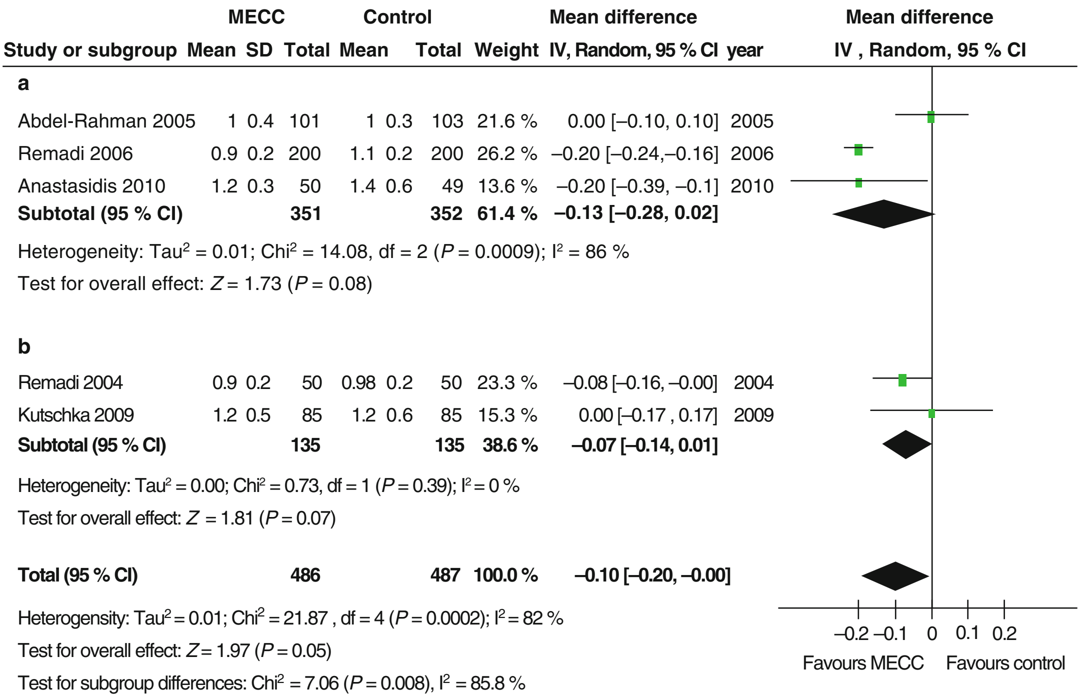
Renal Injury

Acute renal failure after a cardiac operation is one of the strongest independent predictors for mortality. Therefore, preservation of kidney function during CPB is of paramount importance. Diez et al. concluded that MECC could not prevent acute kidney injury but attenuate early renal dysfunction after coronary bypass grafting [62].

They found that within the first postoperative 48 h, significantly fewer patients in the MECC group developed a decline in eGFR (30.7 %) compared with patients after CECC (45.5 %) with a mean difference of 14.8 % ($p<0.001$). However, the incidence of eGFR decrease by ≥50 % did not differ between both groups. This implies MECC does not prevent development of acute renal failure but preserves better renal function within the early postoperative period.

Huybregts also evaluated the impact of MECC systems on renal tubular injury by measurement of urine *N*-acetyl-glucosaminidase (NGAL) and IL-6. Both markers were significantly increased in the CECC group compared with MECC and most likely, as the authors argue, due to the lower haematocrit and haemoglobin values triggering a more severe organ-dependent inflammation and hypoxia [63]. These results were confirmed by other studies [64]. It is reasonable to support that MECC systems seem to exert a renoprotective effect. Our study adds to the growing evidence that patients operated on minimised CPB systems may benefit in several terms. Analysing the data of these studies, it becomes evident that reduced haemodilution and transfusion requirements combined with a higher mean arterial pressure and systemic vascular resistance during CPB were the main contributing factors for the improved outcome. In another series by Benedetto et al., MECC was associated with an absolute reduction in acute kidney injury occurrence of 13.5 % [65].

Analysing data emerging from 24 RCTs regarding renal function in patients having elective coronary surgery with MECC versus CECC, we found that renal function was better preserved in patients operated on MECC as reflected by peak creatinine levels (WMD = –0.10 [–0.20, –0.00], $p=0.05$; Fig. 7.10) [9]. However, incidence of postoperative acute renal failure (peak creatinine >2 mg/dl) was similar between groups (9/201 [4.5 %] patients in MECC group vs. 11/218 [5.0 %] patients in the control arm; $p=0.50$; Fig. 7.11).



	MECC			Control				Mean difference	
Study or subgroup	Mean	SD	Total	Mean		Total	Weight	IV, Random, 95 % CI	year
a									
Abdel-Rahman 2005	1	0.4	101	1	0.3	103	21.6 %	0.00 [–0.10, 0.10]	2005
Remadi 2006	0.9	0.2	200	1.1	0.2	200	26.2 %	–0.20 [–0.24,–0.16]	2006
Anastasidis 2010	1.2	0.3	50	1.4	0.6	49	13.6 %	–0.20 [–0.39, –0.1]	2010
Subtotal (95 % CI)			**351**			**352**	**61.4 %**	**–0.13 [–0.28, 0.02]**	
b									
Remadi 2004	0.9	0.2	50	0.98	0.2	50	23.3 %	–0.08 [–0.16, –0.00]	2004
Kutschka 2009	1.2	0.5	85	1.2	0.6	85	15.3 %	0.00 [–0.17 , 0.17]	2009
Subtotal (95 % CI)			**135**			**135**	**38.6 %**	**–0.07 [–0.14, 0.01]**	
Total (95 % CI)			**486**			**487**	**100.0 %**	**–0.10 [–0.20, –0.00]**	

(a) Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 14.08$, df = 2 ($P = 0.0009$); $I^2 = 86$ %

Test for overall effect: $Z = 1.73$ ($P = 0.08$)

(b) Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 1 ($P = 0.39$); $I^2 = 0$ %

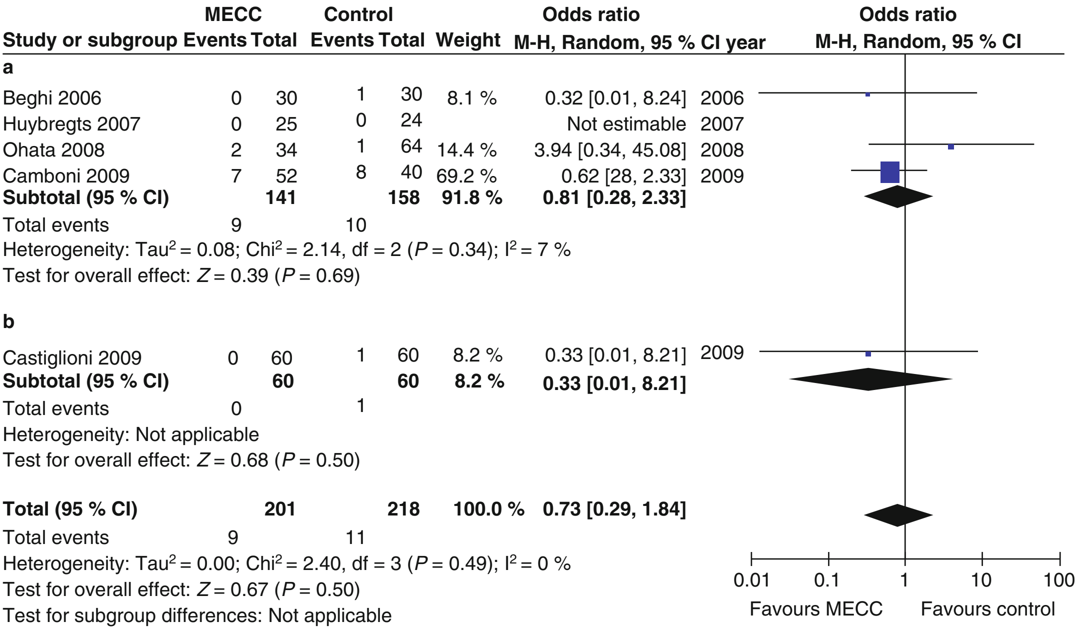
Test for overall effect: $Z = 1.81$ ($P = 0.07$)

Heterogensity: $Tau^2 = 0.01$; $Chi^2 = 21.87$, df = 4 ($P = 0.0002$); $I^2 = 82$ %

Test for overall effect: $Z = 1.97$ ($P = 0.05$)

Test for subgroup differences: $Chi^2 = 7.06$ ($P = 0.008$), $I^2 = 85.8$ %

Fig. 7.10 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot peak postoperative creatinine levels *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])



Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Beghi 2006	0	30	1	30	8.1 %	0.32 [0.01, 8.24]	2006
Huybregts 2007	0	25	0	24		Not estimable	2007
Ohata 2008	2	34	1	64	14.4 %	3.94 [0.34, 45.08]	2008
Camboni 2009	7	52	8	40	69.2 %	0.62 [28, 2.33]	2009
Subtotal (95 % CI)		**141**		**158**	**91.8 %**	**0.81 [0.28, 2.33]**	
Total events	9		10				

Heterogeneity: Tau^2 = 0.08; Chi^2 = 2.14, df = 2 (P = 0.34); I^2 = 7 %
Test for overall effect: Z = 0.39 (P = 0.69)

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
b							
Castiglioni 2009	0	60	1	60	8.2 %	0.33 [0.01, 8.21]	2009
Subtotal (95 % CI)		**60**		**60**	**8.2 %**	**0.33 [0.01, 8.21]**	
Total events	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
Total (95 % CI)		**201**		**218**	**100.0 %**	**0.73 [0.29, 1.84]**	
Total events	9		11				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.40, df = 3 (P = 0.49); I^2 = 0 %
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable

Fig. 7.11 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot development of acute renal failure. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

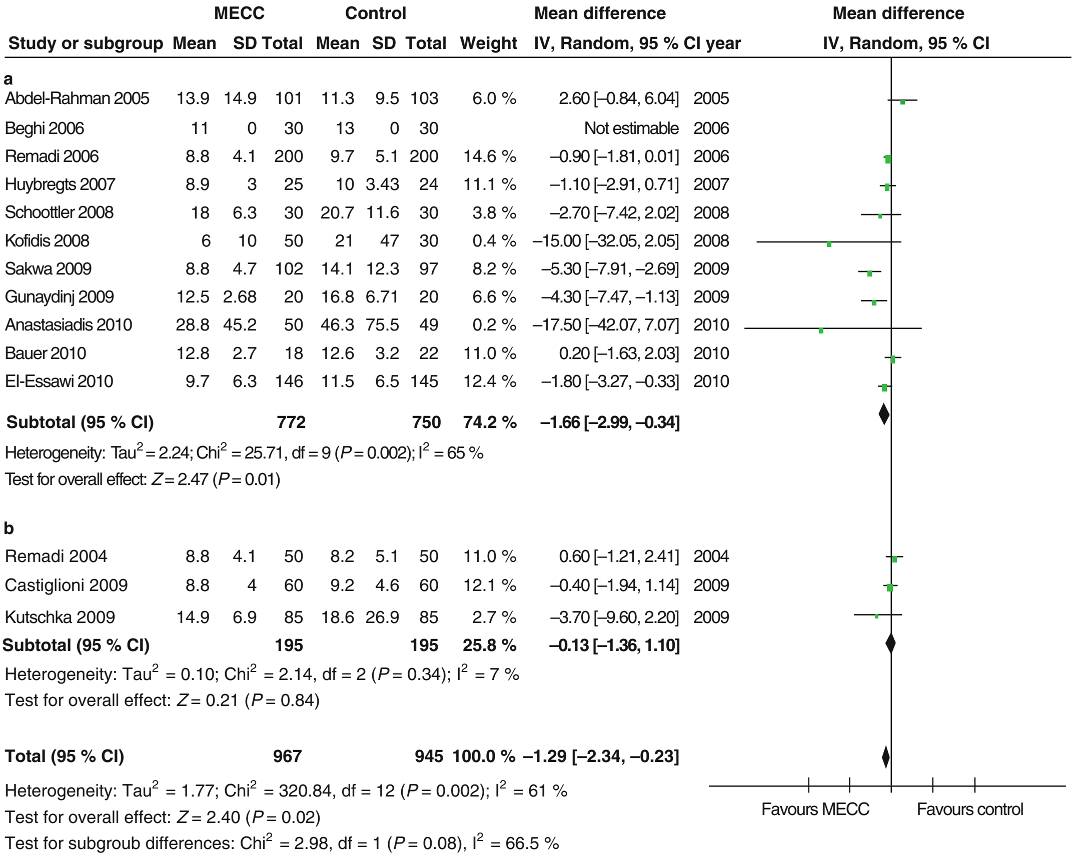
Haemodynamic characteristics of MECC could provide an explanation for this phenomenon. A significant independent association was found between the lowest haematocrit during bypass and acute kidney injury, with significant benefits on renal function after reduction of the bypass prime volume [66]. Moreover, MECC has been shown to provide an elevated mean arterial pressure compared with conventional cardiopulmonary bypass. The increased perfusion pressure and the greater intravascular volume resulting from the removal of a venous reservoir may provide better capillary perfusion of all organs, including the kidney.

Lung Injury

There are very few studies that investigate lung injury during perfusion with MECC. Van Boven et al. have looked at CC16, a Clara cell protein, which serves as a very sensitive index of lung injury which may be elevated following acute alveolar injury [67]. They found reduced levels when MECC was used instead of CECC. Postoperative pulmonary dysfunction is related to overwhelming total lung water content post-CPB [68]. By significantly reducing haemodilution during surgery with MECC, the possibility of lung injury is reduced.

In clinical terms it has been reported that by using MECC the duration of intubation is decreased [27]. Biancari et al. in their meta-analysis report reduced duration of mechanical ventilation [10] with MECC. This finding was subsequently confirmed in our meta-analysis which showed that duration of mechanical ventilation was significantly reduced after surgery with MECC (WMD = −1.29 [−2.34, −0.23], $p = 0.02$; Fig. 7.12). The difference was attributed to CABG procedures, while in AVR duration of mechanical ventilation was similar.

Considering the marked improved myocardial protection obtained during surgery with MECC with reduced need for mechanical ventilation, it is expected that MECC should result in reduced duration of ICU stay. This was evident in our meta-analysis [9]. ICU stay was significantly lower in



Study or subgroup	MECC Mean	MECC SD	MECC Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95 % CI	year
a									
Abdel-Rahman 2005	13.9	14.9	101	11.3	9.5	103	6.0 %	2.60 [–0.84, 6.04]	2005
Beghi 2006	11	0	30	13	0	30		Not estimable	2006
Remadi 2006	8.8	4.1	200	9.7	5.1	200	14.6 %	–0.90 [–1.81, 0.01]	2006
Huybregts 2007	8.9	3	25	10	3.43	24	11.1 %	–1.10 [–2.91, 0.71]	2007
Schoottler 2008	18	6.3	30	20.7	11.6	30	3.8 %	–2.70 [–7.42, 2.02]	2008
Kofidis 2008	6	10	50	21	47	30	0.4 %	–15.00 [–32.05, 2.05]	2008
Sakwa 2009	8.8	4.7	102	14.1	12.3	97	8.2 %	–5.30 [–7.91, –2.69]	2009
Gunaydinj 2009	12.5	2.68	20	16.8	6.71	20	6.6 %	–4.30 [–7.47, –1.13]	2009
Anastasiadis 2010	28.8	45.2	50	46.3	75.5	49	0.2 %	–17.50 [–42.07, 7.07]	2010
Bauer 2010	12.8	2.7	18	12.6	3.2	22	11.0 %	0.20 [–1.63, 2.03]	2010
El-Essawi 2010	9.7	6.3	146	11.5	6.5	145	12.4 %	–1.80 [–3.27, –0.33]	2010
Subtotal (95 % CI)			**772**			**750**	**74.2 %**	**–1.66 [–2.99, –0.34]**	
Heterogeneity: $Tau^2 = 2.24$; $Chi^2 = 25.71$, df = 9 ($P = 0.002$); $I^2 = 65$ %									
Test for overall effect: $Z = 2.47$ ($P = 0.01$)									
b									
Remadi 2004	8.8	4.1	50	8.2	5.1	50	11.0 %	0.60 [–1.21, 2.41]	2004
Castiglioni 2009	8.8	4	60	9.2	4.6	60	12.1 %	–0.40 [–1.94, 1.14]	2009
Kutschka 2009	14.9	6.9	85	18.6	26.9	85	2.7 %	–3.70 [–9.60, 2.20]	2009
Subtotal (95 % CI)			**195**			**195**	**25.8 %**	**–0.13 [–1.36, 1.10]**	
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 2.14$, df = 2 ($P = 0.34$); $I^2 = 7$ %									
Test for overall effect: $Z = 0.21$ ($P = 0.84$)									
Total (95 % CI)			**967**			**945**	**100.0 %**	**–1.29 [–2.34, –0.23]**	
Heterogeneity: $Tau^2 = 1.77$; $Chi^2 = 320.84$, df = 12 ($P = 0.002$); $I^2 = 61$ %									
Test for overall effect: $Z = 2.40$ ($P = 0.02$)									
Test for subgroub differences: $Chi^2 = 2.98$, df = 1 ($P = 0.08$), $I^2 = 66.5$ %									

Fig. 7.12 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for duration of mechanical ventilation. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

MECC group ($p < 0.001$, Fig. 7.13) for both CABG and AVR procedures. At the same time total length of postoperative in-hospital stay did not differ between groups ($p = 0.14$, Fig. 7.14).

Other Organs

Transient splanchnic tissue hypoxia is demonstrated to occur even after uncomplicated CPB in low-risk patients more likely due to alterations in blood flow at the microcirculatory level [69]. The liver is another organ prone to ischaemic injury with a reported incidence of 1.1 % of severe early ischaemic liver injury following cardiac surgery. This is characterized by elevated liver transaminases and carries a mortality of up to 65 % [70]. Prasser et al. measured serum levels of alanine aminotransferase (ALT) and excretion of indocyanine green (a non-toxic dye metabolised solely by the liver) in patients undergoing CABG and found no significant differences between MECC and CECC groups [71].

Huybregts studied intestinal injury during surgery with MECC [63]. He found reduced levels of urine intestinal fatty acid-binding protein (IFABP) in patients operated on MECC. IFABP is a cytosolic protein readily released into the circulation after enterocytes damage; it is released into the blood stream and excreted by kidney early in the course of intestinal ischaemia [72]. Elevated urine IFABP levels predict the development of gastrointestinal complications after CPB and correlate with clinical development of the systemic inflammatory response syndrome in critically ill patients [73].

	MECC			Control				Mean difference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95 % CI	year
a									
Abdel-Rahman 2005	18	17	101	19	19	103	10.4 %	−1.00 [−5.95, 3.95]	2005
Remadi 2006	42.2	3.6	200	48.2	4.3	200	28.4 %	−6.00 [−6.78, −5.22]	2006
Beghi 2006	34	0	30	55	0	30		Not estimable	2006
Skrabal 2007	26.4	0	30	24	0	30		Not estimable	2007
Schoottler 2008	31	14	30	34	21.6	30	4.0 %	−3.00 [−12.21, 6.21]	2008
Kofidis 2008	27	18	50	35	46	30	1.3 %	−8.00 [−25.20, 9.20]	2008
Ovcina I 2009	53.04	0	144	62.4	0	144		Not estimable	2009
Gunaydin 2009	67.2	25.76	20	100.8	28.98	20	1.3 %	−33.60 [−50.59, −16.61]	2009
El-Essawi 2010	26.8	24.6	146	28.6	33.1	145	6.8 %	−1.80 [−8.50, 4.90]	2010
Anastasiadis 2010	72.9	64.3	50	120	171.6	49	0.1 %	−47.10 [−98.35, 4.15]	2010
Subtotal (95 % CI)			**801**			**781**	**52.3 %**	**−5.87 [−10.72, −1.02]**	

Heterogeneity: Tau^2 = 20.29; Chi^2 = 18.40, df = 6 (P = 0.005); I^2 = 67 %
Test for overall effect: Z = 2.37 (P = 0.02)

	MECC			Control				Mean difference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95 % CI	year
b									
Remadi 2004	42.2	3.6	50	48.2	4.3	50	25.1 %	−6.00 [−7.55, −4.45]	2004
Castiglioni 2009	18.4	6.4	60	22.4	6.5	60	21.2 %	−4.00 [−6.31, −1.69]	2009
Kutschka 2009	38.4	38.4	85	57.6	67.2	85	1.4 %	−19.20 [−35.65, −2.75]	2009
Subtotal (95 % CI)			**195**			**195**	**47.7 %**	**−5.44 [−8.04, −2.84]**	

Heterogeneity: Tau^2 = 2.64; Chi^2 = 4.68, df = 2 (P = 0.10); I^2 = 57 %
Test for overall effect: Z = 4.10 (P < 0.0001)

Total (95 % CI)			**996**			**976**	**100.0 %**	**−5.28 [−7.26, −3.30]**	

Heterogeneity: Tau^2 = 3.45; Chi^2 = 23.37, df = 9 (P = 0.005); I^2 = 61%
Test for overall effect: Z = 5.22 (P < 0.00001)
Test for subgroup differences: Chi^2 = 0.30, df = 1 (P = 0.59), I^2 = 0%

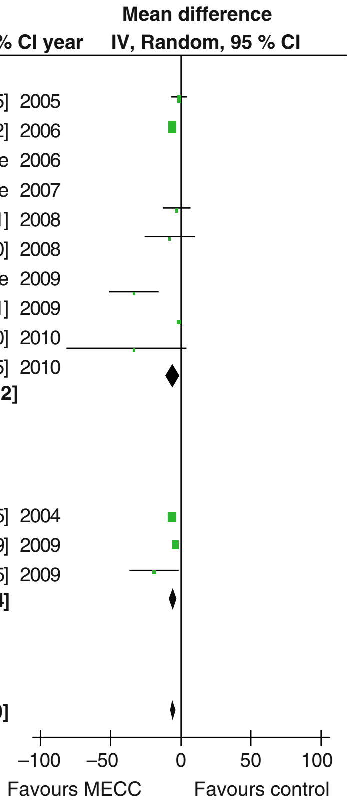
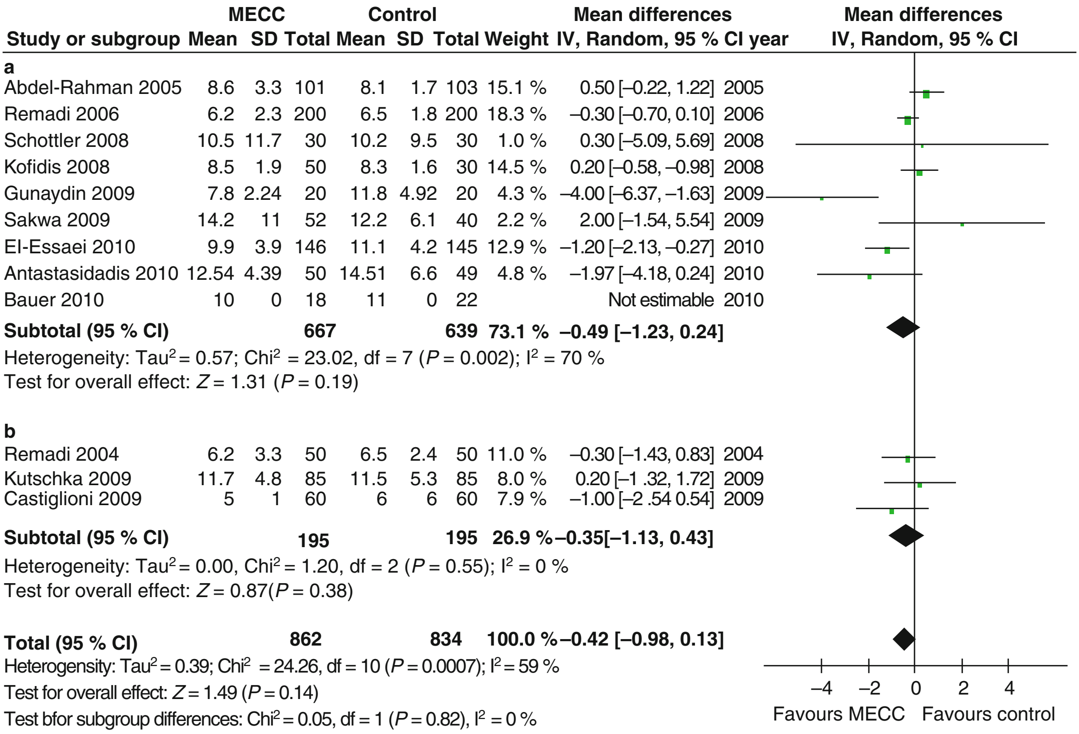


Fig. 7.13 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for duration of ICU stay. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *ICU* intensive care unit, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

Inflammatory Response

CPB stimulates a systemic inflammatory response (SIRS) mediated through the interaction of air, blood and synthetic components in the CPB apparatus. The inflammation is further driven by the physical trauma of surgery and the effects of ischaemia and reperfusion [74–76]. Its generation is regulated by the activation of complement, macrophages, neutrophils and proinflammatory cytokines such as interleukins (IL)-6 and IL-8 [77]. Neutrophils are the predominant cell type involved in the inflammatory response after CPB, with mast cells and basophils fulfilling lesser roles. Neutrophil activation can occur in response to complement or as a reaction to heparin–protamine. The ensuing SIRS can significantly derange the haemodynamic stability of patients even for long periods after the cessation of CPB, potentially increasing the time required in the ICU [78].

Several studies have investigated the inflammatory response triggered by MECC in comparison to CECC. MECC features are designed to limit the level of SIRS encountered. Circuit tubing is coated and length is reduced which translates into a reduced total artificial surface. The centrifugal pump, as analysed in Chap. 2, is less traumatic to the blood elements. Moreover, requirement for protamine administration is lower during MECC. Accurate assessment of inflammatory response is a complex task due to the fact that there is no universal agreement about which markers are the most indicative of an inappropriate inflammatory response during cardiac surgery. Inevitably, a wide variety of markers have been employed by different groups



Study or subgroup	MECC Mean	SD	Total	Control Mean	SD	Total	Weight	Mean differences IV, Random, 95 % CI	year
a									
Abdel-Rahman 2005	8.6	3.3	101	8.1	1.7	103	15.1 %	0.50 [–0.22, 1.22]	2005
Remadi 2006	6.2	2.3	200	6.5	1.8	200	18.3 %	–0.30 [–0.70, 0.10]	2006
Schottler 2008	10.5	11.7	30	10.2	9.5	30	1.0 %	0.30 [–5.09, 5.69]	2008
Kofidis 2008	8.5	1.9	50	8.3	1.6	30	14.5 %	0.20 [–0.58, –0.98]	2008
Gunaydin 2009	7.8	2.24	20	11.8	4.92	20	4.3 %	–4.00 [–6.37, –1.63]	2009
Sakwa 2009	14.2	11	52	12.2	6.1	40	2.2 %	2.00 [–1.54, 5.54]	2009
El-Essaei 2010	9.9	3.9	146	11.1	4.2	145	12.9 %	–1.20 [–2.13, –0.27]	2010
Antastasidadis 2010	12.54	4.39	50	14.51	6.6	49	4.8 %	–1.97 [–4.18, 0.24]	2010
Bauer 2010	10	0	18	11	0	22		Not estimable	2010
Subtotal (95 % CI)			**667**			**639**	**73.1 %**	**–0.49 [–1.23, 0.24]**	
b									
Remadi 2004	6.2	3.3	50	6.5	2.4	50	11.0 %	–0.30 [–1.43, 0.83]	2004
Kutschka 2009	11.7	4.8	85	11.5	5.3	85	8.0 %	0.20 [–1 .32, 1.72]	2009
Castiglioni 2009	5	1	60	6	6	60	7.9 %	–1.00 [–2 .54 0.54]	2009
Subtotal (95 % CI)			**195**			**195**	**26.9 %**	**–0.35[–1.13, 0.43]**	
Total (95 % CI)			**862**			**834**	**100.0 %**	**–0.42 [–0.98, 0.13]**	

a: Heterogeneity: Tau^2 = 0.57; Chi^2 = 23.02, df = 7 (P = 0.002); I^2 = 70 %
Test for overall effect: Z = 1.31 (P = 0.19)

b: Heterogeneity: Tau^2 = 0.00, Chi^2 = 1.20, df = 2 (P = 0.55); I^2 = 0 %
Test for overall effect: Z = 0.87(P = 0.38)

Total: Heterogensity: Tau^2 = 0.39; Chi^2 = 24.26, df = 10 (P = 0.0007); I^2 = 59 %
Test for overall effect: Z = 1.49 (P = 0.14)
Test bfor subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.82), I^2 = 0 %

Fig. 7.14 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for total length of hospital stay. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

evaluating different endpoints. The number of patients in each study is low; thus, reaching a conclusion is made difficult.

It is postulated that MECC could lead to a reduction in the incidence of SIRS. Standard postoperative measures of inflammation include leukocyte count and C-reactive protein (CRP). Remadi et al. reported significantly higher CRP levels in patients receiving CECC than in those treated with MECC at 24 and 48 h postoperatively [6]. Fromes et al. described the trend in monocyte levels intraoperatively and for a 24-h period after. They demonstrated that in both CECC and MECC patients, the monocyte count drops following the initiation of bypass and then increases again postoperatively, peaking at 24 h. This initial decline was attributed to the dilutional effect of commencing bypass and the later rise to the mounting inflammatory response. The drop in monocyte level was greater in the CECC group, probably as a result of greater dilution. Interestingly, the monocyte count rose significantly less in the MECC group, suggesting that a weaker inflammatory process was generated [28].

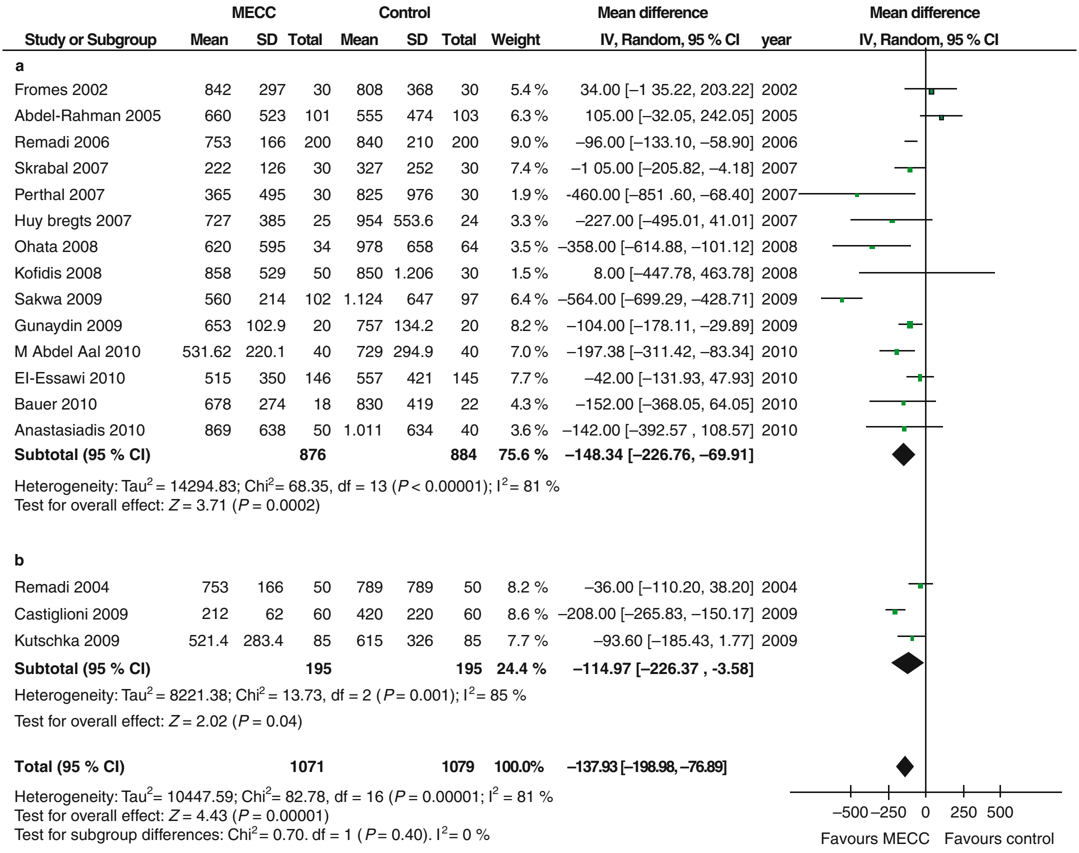
Some cytokines, such as IL-1β, IL-6 or tumour necrosis factor a (TNF-a), have been used as inflammatory markers after CPB [79]. Liebold et al. compared a minimized and closed extracorporeal circuit with a centrifugal pump and a membrane oxygenator as the only active component with a conventional CPB system. Patients operated with the MECC system demonstrated significantly lower peak levels of IL-6 [80]. Fromes et al. measured the levels of IL-1β, IL-6 and tumour necrosis factor α (TNF-α) at six time intervals during and after CPB (up to 24 h postoperatively) [28]. They detected significant increase in IL-6 levels, peaking 6 h postoperatively. Furthermore, the levels of IL-6 were significantly lower in MECC patients than in those in which CECC was used. There was also a rise in serum TNF-α, with MECC levels again being lower than those seen with CECC. Abdel-Rahman et al. found a containment in both polymorphonuclear elastase and terminal complement complex releases in a CorX mini-CPB system [68]. The same system was explored by Wippermann et al. which could demonstrate a decreased thrombin formation, lower levels of plasmin–antiplasmin complex and a decreased IL-6 release [81].

Immer et al. measured serum IL-6 and SC5b-9, which is a terminal complement complex that is often raised in inflammation, at six time points in the first 24 h following surgery in patients undergoing CABG [27]. The levels of IL-6 and SC5b-9 were significantly higher following surgery in the CECC group than in the MECC group. This provides further evidence that MECC is less proinflammatory than CECC. Other investigators, however, have been unable to demonstrate any significant difference in IL-6 levels in MECC and CECC patients [14, 82]. Ohata and Fromes showed that use of a MECC system resulted in significantly lower levels of neutrophil elastase than conventional CPB, which is a specific marker of neutrophil activation. These results demonstrate that mini-CPB attenuates the inflammatory reactions associated with CABG.

Haematologic Parameters: Postoperative Bleeding

MECC is designed in a way to protect the different pathways of the coagulation mechanism. It became evident that MECC is associated with reduced postoperative bleeding and reduced need for blood transfusion. Thus, it is considered one of the most potent blood-conserving strategies in cardiac surgery [83]. This recommendation came from numerous studies that examined integrity of the coagulation pathway, postoperative bleeding and need for blood transfusion after surgery with MECC. This was evidenced in all meta-analyses that investigated clinical outcome after surgery with MECC [9–12]. In the meta-analysis performed by our group, postoperative bleeding was significantly lower in patients operated on MECC (WMD $= -137.93$ [-198.98, -76.89], $p < 0.001$, Fig. 7.15), while rate of re-exploration for bleeding favoured MECC group without reaching statistical significance (15/557 [2.7 %] patients in MECC group vs. 24/537 [4.5 %] patients in the control arm; $p = 0.14$, Fig. 7.16). Furthermore, use of MECC significantly reduced the risk of red blood cells (RBC) transfusion (55/315 [17.5 %] patients in MECC group vs. 135/313 [43.1 %] patients in the control arm; $p < 0.001$, Fig. 7.17). Rate of FFP transfusion was similar between groups. Platelet count was preserved in MECC group (WMD $= 39.01$ [22.90, 55.13], $p < 0.001$, Fig. 7.18) [9].

MECC systems literally integrate all the advances from the clinical research towards minimizing the side effects from CPB on blood elements. Thus, the beneficial effects of these systems derive from the implementation of all these advances in one technology. This refers to the use of closed rather than open venous reservoirs in the CPB circuits which results in less systemic blood activation, less amount of blood loss, less need for colloid–crystalloid infusion and less need for donor blood [84]. Moreover, use of centrifugal instead of roller pump to the circuit reduces platelet aggregation and results in lower susceptibility to postoperative thrombotic complications [85]. Furthermore, coating techniques stand as an important step towards higher haemocompatibility of blood-contacting surfaces in the artificial devices used for ECC. Thus, heparin-bonded devices demonstrate lessened humoral and cellular activation, improved platelet protection and reduced SIRS. Integration to the ECC circuit of both centrifugal pump and heparin coating further improves CPB biocompatibility [86]. In MECC a reduced dose of heparin is followed by a low-dose administration of protamine, based on a heparin–protamine titration method, and this restores the blood coagulation but the platelet responses to thrombin during heparin neutralisation; overdose of protamine activates platelets and may predispose patients to excessive bleeding after cardiac surgery [87]. Rahe-Meyer assessed platelet aggregation and coagulation parameters and found that platelet function was less affected by the MECC than by the CECC [88].



	MECC			Control				Mean difference		Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95 % CI	year	IV, Random, 95 % CI
a										
Fromes 2002	842	297	30	808	368	30	5.4 %	34.00 [–1 35.22, 203.22]	2002	
Abdel-Rahman 2005	660	523	101	555	474	103	6.3 %	105.00 [–32.05, 242.05]	2005	
Remadi 2006	753	166	200	840	210	200	9.0 %	–96.00 [–133.10, –58.90]	2006	
Skrabal 2007	222	126	30	327	252	30	7.4 %	–1 05.00 [–205.82, –4.18]	2007	
Perthal 2007	365	495	30	825	976	30	1.9 %	-460.00 [–851 .60, –68.40]	2007	
Huy bregts 2007	727	385	25	954	553.6	24	3.3 %	–227.00 [–495.01, 41.01]	2007	
Ohata 2008	620	595	34	978	658	64	3.5 %	–358.00 [–614.88, –101.12]	2008	
Kofidis 2008	858	529	50	850	1.206	30	1.5 %	8.00 [–447.78, 463.78]	2008	
Sakwa 2009	560	214	102	1.124	647	97	6.4 %	–564.00 [–699.29, –428.71]	2009	
Gunaydin 2009	653	102.9	20	757	134.2	20	8.2 %	–104.00 [–178.11, –29.89]	2009	
M Abdel Aal 2010	531.62	220.1	40	729	294.9	40	7.0 %	–197.38 [–311.42, –83.34]	2010	
El-Essawi 2010	515	350	146	557	421	145	7.7 %	–42.00 [–131.93, 47.93]	2010	
Bauer 2010	678	274	18	830	419	22	4.3 %	–152.00 [–368.05, 64.05]	2010	
Anastasiadis 2010	869	638	50	1.011	634	40	3.6 %	–142.00 [–392.57 , 108.57]	2010	
Subtotal (95 % CI)			**876**			**884**	**75.6 %**	**–148.34 [–226.76, –69.91]**		
Heterogeneity: $Tau^2 = 14294.83$; $Chi^2 = 68.35$, df = 13 ($P < 0.00001$); $I^2 = 81$ %										
Test for overall effect: $Z = 3.71$ ($P = 0.0002$)										
b										
Remadi 2004	753	166	50	789	789	50	8.2 %	–36.00 [–110.20, 38.20]	2004	
Castiglioni 2009	212	62	60	420	220	60	8.6 %	–208.00 [–265.83, –150.17]	2009	
Kutschka 2009	521.4	283.4	85	615	326	85	7.7 %	–93.60 [–185.43, 1.77]	2009	
Subtotal (95 % CI)			**195**			**195**	**24.4 %**	**–114.97 [–226.37 , -3.58]**		
Heterogeneity: $Tau^2 = 8221.38$; $Chi^2 = 13.73$, df = 2 ($P = 0.001$); $I^2 = 85$ %										
Test for overall effect: $Z = 2.02$ ($P = 0.04$)										
Total (95 % CI)			**1071**			**1079**	**100.0%**	**–137.93 [–198.98, –76.89]**		
Heterogeneity: $Tau^2 = 10447.59$; $Chi^2 = 82.78$, df = 16 ($P = 0.00001$; $I^2 = 81$ %										
Test for overall effect: $Z = 4.43$ ($P = 0.00001$)										
Test for subgroup differences: $Chi^2 = 0.70$. df = 1 ($P = 0.40$). $I^2 = 0$ %										

Fig. 7.15 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for postoperative blood loss. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

Avoidance of cardiotomy suction not only reduces the recirculation of the debris and lipids from the shed mediastinal blood but also reduces haemolysis [89], restores haemostasis and attenuates postoperative bleeding. The combination of tubing coating and avoidance of shed blood recirculation has been shown to maintain physiological coagulation levels and markedly reduce red blood cell trauma in ECC procedures [90].

MECC systems are closed and have less tubing length, hence offer low prime volume (<500 ml) requirements compared to the standard prime volume (three times more) of the open CPB circuits integrated in CECC systems. Haemodilution can be literally eliminated by using the retrograde autologous priming (RAP) technique, which we use as a standard procedure in our institution. RAP in combination with autologous transfusion significantly reduces the need for blood transfusion. A low haematocrit during CPB has been associated with adverse outcomes (mortality, morbidity and long-term survival) after CABG surgery [91]. In our meta-analysis haemodilution, as calculated by haematocrit drop after CPB, was found to be significantly lower in MECC group (WMD = –6.72 [–13.28, –0.17], $p = 0.04$); consequently, haematocrit at the end of CPB was significantly higher in patients operated on MECC (WMD = 3.47 [2.11, 4.83], $p < 0.001$, Fig. 7.19).

Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Beghi 2006	0	30	1	30	4.7 %	0.32 [0.01, 8.24]	2006
Bical 2006	0	20	0	20		Not estimable	2006
Kofidis 2008	1	50	1	30	6.2 %	0.59 [0.04, 9.83]	2008
Schottler 2008	2	30	0	30	5.2 %	5.35 [0.25, 116.31]	2008
Sakwa 2009	0	102	1	97	4.8 %	0.31 [0.01, 7.80]	2009
Bauer 2010	1	18	1	22	6.1 %	1.24 [0.07 , 21.24]	2010
El-Essawi 2010	9	146	16	145	67.8 %	0.53 [0.23, 1.24]	2010
Subtotal (95 % CI)		**396**		**374**	**94.7 %**	**0.61 [0.30, 1.25]**	
Total events	13		20				
Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 2.59$, df = 5 ($P = 0.76$); $I^2 = 0\%$							
Test for overall effect: $Z = 1.36$ ($P = 0.18$)							
b							
Castiglioni 2009	0	60	2	60	5.3 %	0.19 [0.01, 4.11]	2009
Subtotal (95 % CI)		**60**		**60**	**5.3 %**	**0.19 [0.01, 4.11]**	
Total events	0		2				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 1.05$ ($P = 0.29$)							
Total events		**456**		**434**	**100.0 %**	**0.57 [0.28, 1.15]**	
Total events	13		22				
Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 3.09$, df = 6 ($P = 0.80$); $I^2 = 0\%$							
Test for overall effect: $Z = 1.56$ ($P = 0.12$)							
Test for subgroup differences: Not applicable							

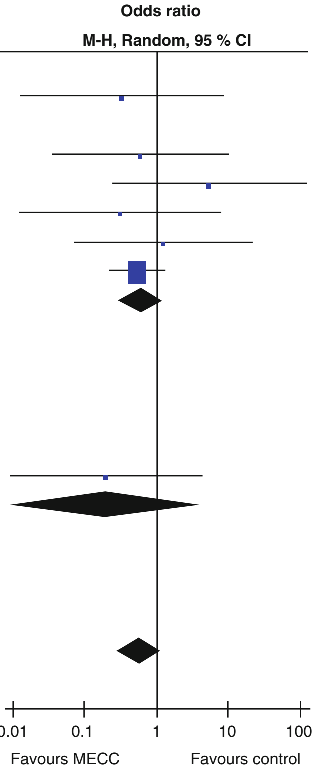
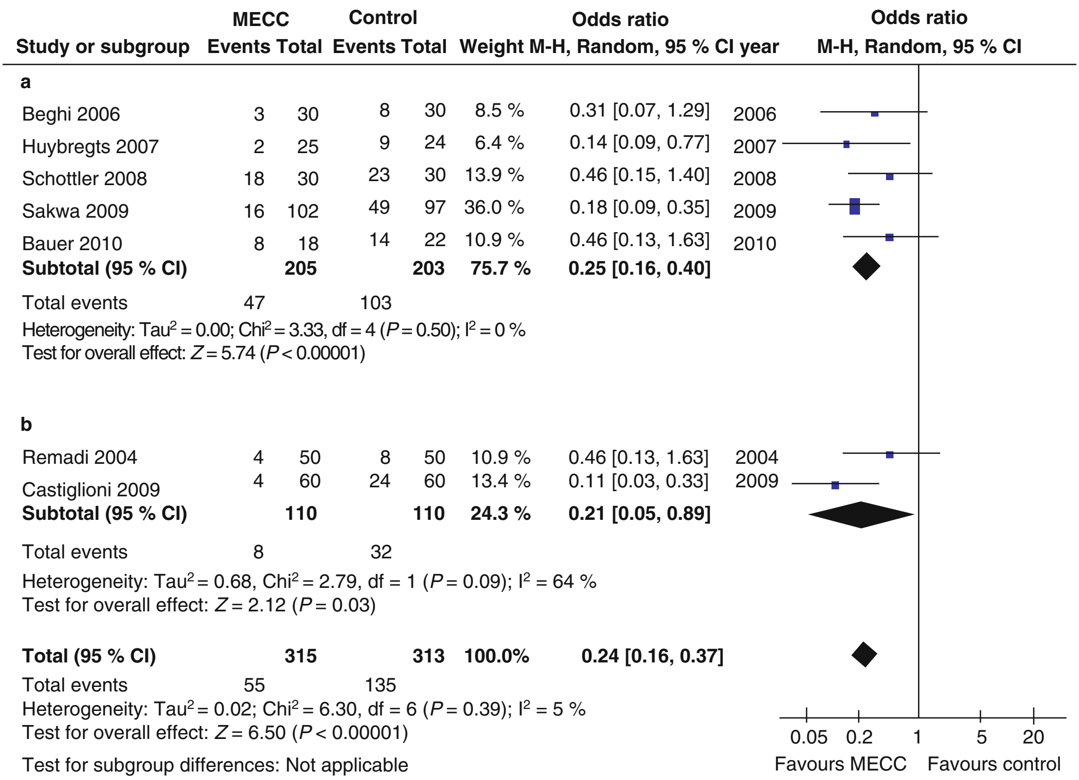


Fig. 7.16 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for the rate of re-exploration for bleeding. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

Atrial Fibrillation

Atrial fibrillation (AF) after open-heart surgery is a frequent clinical problem, and in large series incidences of 20–40 % have been reported regarding CABG procedures [92, 93]. AF is triggered by the inflammation associated with CPB [94, 95] and is responsible for significant morbidity, increased cost of medication and prolongation of hospital stay [96].

Immer et al. demonstrated an 11 % incidence of postoperative AF in patients who received MECC compared to 39 % in CECC participants ($p < 0.001$) [27]. At discharge, 96 % of the CECC patients and 94 % of the MECC patients who developed postoperative AF had converted to a stable sinus rhythm. In another series by Panday et al., postoperative AF or atrial flutter occurred in 25 % of the MECC group and in 35.6 % of the CECC group ($p = 0.05$) [97]. Apart from individual studies the incidence of AF was found significantly reduced in two recently published meta-analyses [9, 12]. In the one performed by our group, occurrence of postoperative AF was significantly less frequent in MECC group (130/652 [19.2 %] patients in MEEC group vs. 174/631 [27.6 %] patients in the control arm; $p = 0.01$, Fig. 7.20); this effect was attributed exclusively to CABG procedures, while after AVR, surgery rates were similar. Part of this improved early outcome with MECC could be due to a reduction in the incidence of SIRS that could trigger AF. Moreover, reduced priming volume of the MECC system and the higher haematocrit during CPB contribute to a decrease in the usual volume compartment shift, traditionally observed in patients undergoing cardiac surgery [27].



Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Beghi 2006	3	30	8	30	8.5 %	0.31 [0.07, 1.29]	2006
Huybregts 2007	2	25	9	24	6.4 %	0.14 [0.09, 0.77]	2007
Schottler 2008	18	30	23	30	13.9 %	0.46 [0.15, 1.40]	2008
Sakwa 2009	16	102	49	97	36.0 %	0.18 [0.09, 0.35]	2009
Bauer 2010	8	18	14	22	10.9 %	0.46 [0.13, 1.63]	2010
Subtotal (95 % CI)		**205**		**203**	**75.7 %**	**0.25 [0.16, 0.40]**	
Total events	47		103				
b							
Remadi 2004	4	50	8	50	10.9 %	0.46 [0.13, 1.63]	2004
Castiglioni 2009	4	60	24	60	13.4 %	0.11 [0.03, 0.33]	2009
Subtotal (95 % CI)		**110**		**110**	**24.3 %**	**0.21 [0.05, 0.89]**	
Total events	8		32				
Total (95 % CI)		**315**		**313**	**100.0%**	**0.24 [0.16, 0.37]**	
Total events	55		135				

a: Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.33, df = 4 (P = 0.50); I^2 = 0 %
Test for overall effect: Z = 5.74 (P < 0.00001)

b: Heterogeneity: Tau^2 = 0.68, Chi^2 = 2.79, df = 1 (P = 0.09); I^2 = 64 %
Test for overall effect: Z = 2.12 (P = 0.03)

Total: Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.30, df = 6 (P = 0.39); I^2 = 5 %
Test for overall effect: Z = 6.50 (P < 0.00001)

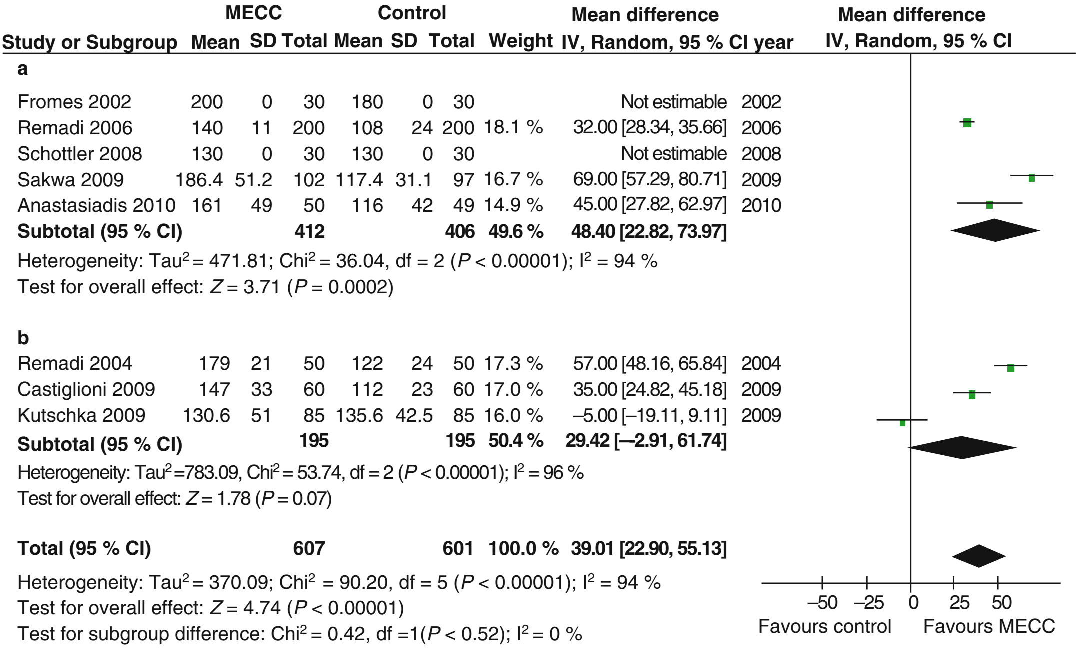
Test for subgroup differences: Not applicable

Fig. 7.17 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for rate of RBC transfusion. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation, *RBC* red blood cells (From Anastasiadis et al. [9])

MECC Versus OPCAB

The technique of "off-pump" coronary artery bypass grafting (OPCAB) emerged in the early 90's as a valuable alternative to conventional coronary surgery aiming to eliminate its deleterious effects on remote organs. However, this was not confirmed in large multicenter randomized studies [98]. A major limitation is that off-pump techniques apply only in coronary surgery (OPCAB) and preclude all other cardiac surgical pathology. OPCAB requires a significant learning curve from the surgeon. Moreover, it is technically more demanding due to anatomical constraints or haemodynamic instability. Concerns regarding incomplete revascularisation and lack of proven clinical benefits have limited OPCAB from being performed routinely [99]. Moreover, ROOBY study recently showed a worse 1-year clinical outcome and poor graft patency in patients operated on beating heart [4]. MECC was introduced later than OPCAB. It attenuates the side effects from CPB while at the same time allows for complete revascularisation with on an arrested heart and a clear and unobstructed field.

Mazzei et al. performed the first randomized comparison between patients operated with MECC and OPCAB [100]. The 1-year mortality rates were 2.7 and 3.4 % in the MECC and OPCAB groups, respectively, (p<0.99). Both overall survival and angina-free survival rates were not statistically different between the study groups at any time point. OPCAB and MECC were associated with similar degrees of mean IL-6 release; the difference was not statistically



	MECC			Control				Mean difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95 % CI	year
a									
Fromes 2002	200	0	30	180	0	30		Not estimable	2002
Remadi 2006	140	11	200	108	24	200	18.1 %	32.00 [28.34, 35.66]	2006
Schottler 2008	130	0	30	130	0	30		Not estimable	2008
Sakwa 2009	186.4	51.2	102	117.4	31.1	97	16.7 %	69.00 [57.29, 80.71]	2009
Anastasiadis 2010	161	49	50	116	42	49	14.9 %	45.00 [27.82, 62.97]	2010
Subtotal (95 % CI)			**412**			**406**	**49.6 %**	**48.40 [22.82, 73.97]**	
b									
Remadi 2004	179	21	50	122	24	50	17.3 %	57.00 [48.16, 65.84]	2004
Castiglioni 2009	147	33	60	112	23	60	17.0 %	35.00 [24.82, 45.18]	2009
Kutschka 2009	130.6	51	85	135.6	42.5	85	16.0 %	–5.00 [–19.11, 9.11]	2009
Subtotal (95 % CI)			**195**			**195**	**50.4 %**	**29.42 [–2.91, 61.74]**	
Total (95 % CI)			**607**			**601**	**100.0 %**	**39.01 [22.90, 55.13]**	

a: Heterogeneity: $Tau^2 = 471.81$; $Chi^2 = 36.04$, df = 2 ($P < 0.00001$); $I^2 = 94$ %

Test for overall effect: $Z = 3.71$ ($P = 0.0002$)

b: Heterogeneity: $Tau^2 = 783.09$, $Chi^2 = 53.74$, df = 2 ($P < 0.00001$); $I^2 = 96$ %

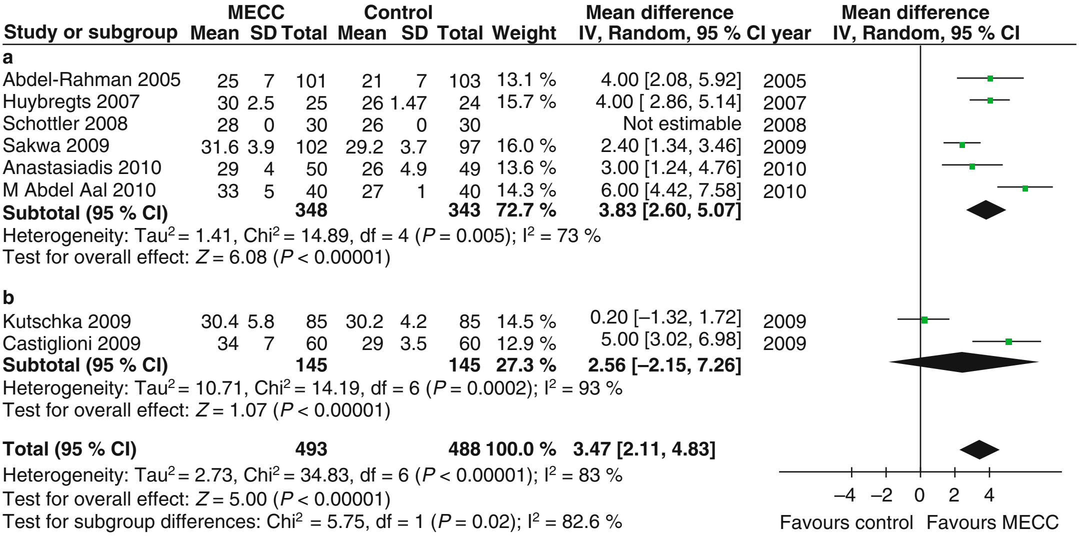
Test for overall effect: $Z = 1.78$ ($P = 0.07$)

Total: Heterogeneity: $Tau^2 = 370.09$; $Chi^2 = 90.20$, df = 5 ($P < 0.00001$); $I^2 = 94$ %

Test for overall effect: $Z = 4.74$ ($P < 0.00001$)

Test for subgroup difference: $Chi^2 = 0.42$, df =1($P < 0.52$); $I^2 = 0$ %

Fig. 7.18 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot platelet count at the end of CPB. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *CPB* cardiopulmonary bypass, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])



	MECC			Control				Mean difference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95 % CI	year
a									
Abdel-Rahman 2005	25	7	101	21	7	103	13.1 %	4.00 [2.08, 5.92]	2005
Huybregts 2007	30	2.5	25	26	1.47	24	15.7 %	4.00 [2.86, 5.14]	2007
Schottler 2008	28	0	30	26	0	30		Not estimable	2008
Sakwa 2009	31.6	3.9	102	29.2	3.7	97	16.0 %	2.40 [1.34, 3.46]	2009
Anastasiadis 2010	29	4	50	26	4.9	49	13.6 %	3.00 [1.24, 4.76]	2010
M Abdel Aal 2010	33	5	40	27	1	40	14.3 %	6.00 [4.42, 7.58]	2010
Subtotal (95 % CI)			**348**			**343**	**72.7 %**	**3.83 [2.60, 5.07]**	
b									
Kutschka 2009	30.4	5.8	85	30.2	4.2	85	14.5 %	0.20 [–1.32, 1.72]	2009
Castiglioni 2009	34	7	60	29	3.5	60	12.9 %	5.00 [3.02, 6.98]	2009
Subtotal (95 % CI)			**145**			**145**	**27.3 %**	**2.56 [–2.15, 7.26]**	
Total (95 % CI)			**493**			**488**	**100.0 %**	**3.47 [2.11, 4.83]**	

a: Heterogeneity: $Tau^2 = 1.41$, $Chi^2 = 14.89$, df = 4 ($P = 0.005$); $I^2 = 73$ %

Test for overall effect: $Z = 6.08$ ($P < 0.00001$)

b: Heterogeneity: $Tau^2 = 10.71$, $Chi^2 = 14.19$, df = 6 ($P = 0.0002$); $I^2 = 93$ %

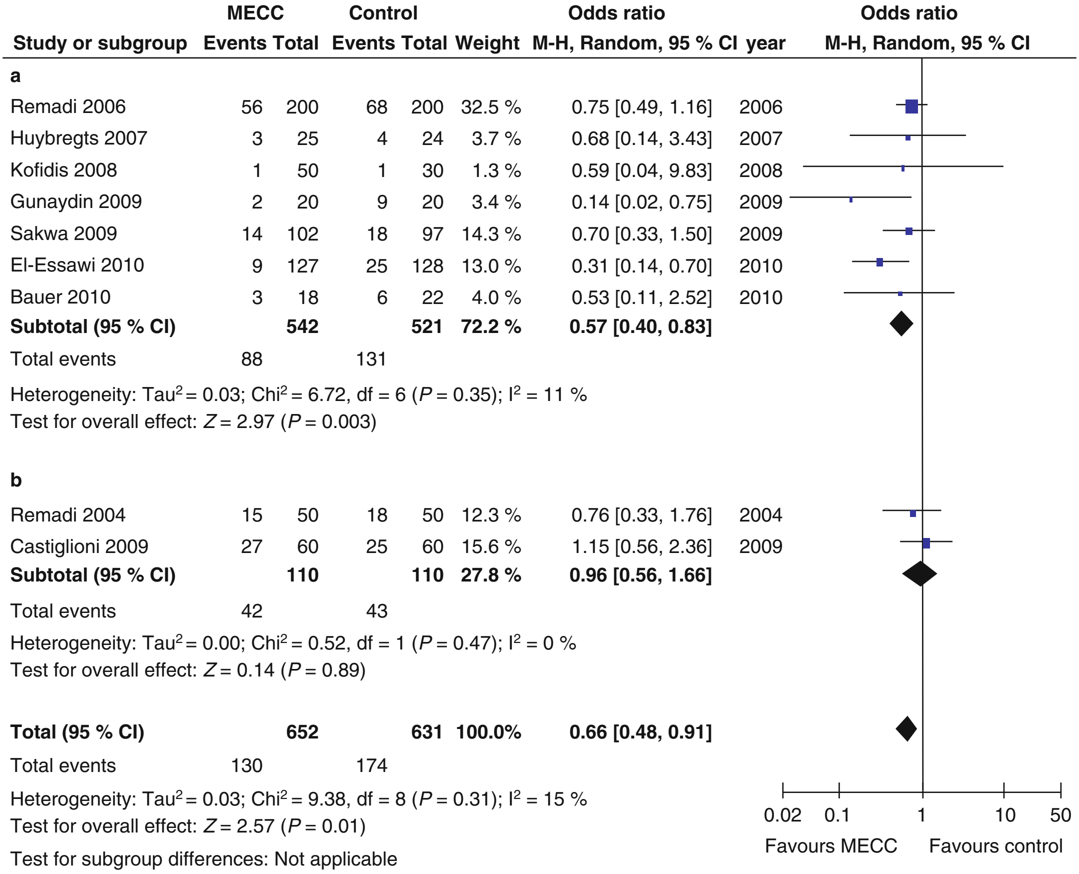
Test for overall effect: $Z = 1.07$ ($P < 0.00001$)

Total: Heterogeneity: $Tau^2 = 2.73$, $Chi^2 = 34.83$, df = 6 ($P < 0.00001$); $I^2 = 83$ %

Test for overall effect: $Z = 5.00$ ($P < 0.00001$)

Test for subgroup differences: $Chi^2 = 5.75$, df = 1 ($P = 0.02$); $I^2 = 82.6$ %

Fig. 7.19 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for the haematocrit at the end of CPB. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *CPB* cardiopulmonary bypass, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])



Study or subgroup	MECC Events	MECC Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95 % CI	year
a							
Remadi 2006	56	200	68	200	32.5 %	0.75 [0.49, 1.16]	2006
Huybregts 2007	3	25	4	24	3.7 %	0.68 [0.14, 3.43]	2007
Kofidis 2008	1	50	1	30	1.3 %	0.59 [0.04, 9.83]	2008
Gunaydin 2009	2	20	9	20	3.4 %	0.14 [0.02, 0.75]	2009
Sakwa 2009	14	102	18	97	14.3 %	0.70 [0.33, 1.50]	2009
El-Essawi 2010	9	127	25	128	13.0 %	0.31 [0.14, 0.70]	2010
Bauer 2010	3	18	6	22	4.0 %	0.53 [0.11, 2.52]	2010
Subtotal (95 % CI)		**542**		**521**	**72.2 %**	**0.57 [0.40, 0.83]**	
Total events	88		131				
b							
Remadi 2004	15	50	18	50	12.3 %	0.76 [0.33, 1.76]	2004
Castiglioni 2009	27	60	25	60	15.6 %	1.15 [0.56, 2.36]	2009
Subtotal (95 % CI)		**110**		**110**	**27.8 %**	**0.96 [0.56, 1.66]**	
Total events	42		43				
Total (95 % CI)		**652**		**631**	**100.0%**	**0.66 [0.48, 0.91]**	
Total events	130		174				

a: Heterogeneity: $\mathrm{Tau}^2 = 0.03$; $\mathrm{Chi}^2 = 6.72$, df = 6 ($P = 0.35$); $I^2 = 11\ \%$
Test for overall effect: $Z = 2.97$ ($P = 0.003$)

b: Heterogeneity: $\mathrm{Tau}^2 = 0.00$; $\mathrm{Chi}^2 = 0.52$, df = 1 ($P = 0.47$); $I^2 = 0\ \%$
Test for overall effect: $Z = 0.14$ ($P = 0.89$)

Total: Heterogeneity: $\mathrm{Tau}^2 = 0.03$; $\mathrm{Chi}^2 = 9.38$, df = 8 ($P = 0.31$); $I^2 = 15\ \%$
Test for overall effect: $Z = 2.57$ ($P = 0.01$)
Test for subgroup differences: Not applicable

Fig. 7.20 Meta-analysis comparing MECC versus CECC (control) in (**a**) CABG procedures, (**b**) AVR procedures and total; forest plot for atrial fibrillation. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [9])

significant at any time point. In the MECC group, serum levels of S-100 protein were not significantly higher than those found in the OPCAB group. This suggests that brain injury during ECC is mainly due to the release of inflammatory mediators with the potential to alter the blood–brain barrier. He concludes that the degree of systemic inflammatory reaction end-organ damage after coronary revascularisation with the heart arrested and with the use of MECC is comparable to that seen in patients who were operated on without any form of CPB [100]. Larger prospective adequately powered studies are needed, however, to provide a definitive answer on this topic.

Van Boven studied oxidative stress during CABG comparing three techniques: CECC, MECC and OPCAB [31]. He found a reduced level of oxidative stress during surgery with MECC and OPCAB compared to CECC. Panday in a recent study including 329 patients operated with MECC or OPCAB found similar morbidity between patients operated with MECC or OPCAB [97]. However, completeness of revascularisation was significantly compromised in OPCAB patients.

By analysing studies comparing MECC versus OPCAB, no statistically significant differences were found in nearly all variables [9]: mortality, RBC transfusion, IL-6 levels, need for intra-aortic balloon pump and total length of postoperative in-hospital stay. ICU stay was found to favour significantly the OPCAB group (WMD = 1.50 [0.67, 2.34], $p < 0.001$). We can conclude, therefore, that MECC, using cardioplegic arrest, appears to be an equal or even superior strategy in contemporary coronary surgery in comparison to OPCAB and CECC because it is associated with a reduction of peri- and postoperative morbidity. MECC offers a surgical setting in which completeness of revascularisation is warranted and high-risk patients can be operated upon relatively safely [97].

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MECC in Valve Surgery

8

Use of MECC for aortic valve replacement (AVR) was first reported in 2004 [1]. The main advantages of MECC for AVR were reported to include significantly reduced chest tube drainage, lower haemodilution and higher haematocrit [2–4]; it also allows for higher time course of haematocrit at all time points during the operation [2]. This translates in less transfusional requirements [1, 5]. MECC use also results in lower C-reactive protein and serum IL-6 levels suggesting beneficial effects of the system on cardiac and respiratory function [1, 4, 6], as well as TNF-α, neutrophil elastase and IL-10. Moreover, increase in elastase, IL-10 and TNF-α levels after weaning off MECC is less pronounced compared to CECC [7]. MECC is associated with a higher platelet count postoperatively [1–3], better preservation of renal function [1, 5], lower neurologic event rate [1] and improved myocardial protection [1–3]. Hence, MECC offers an alternative to conventional CPB for AVR which is safe, effective and reproducible [5, 6].

In the setting of open heart surgery like aortic valve surgery, venting of the heart is mandatory, and the advantage of the MECC system in reducing systemic inflammation could disappear as the closed system is modified in a semi-closed one with increased blood–air contact (Fig. 8.1). However, existing data indicates that in aortic valve surgery, MECC system is still associated with lower inflammation response than the standard CPB circuit [7]. Using MECC with aortic root and pulmonary artery vent and connecting them to a venous bubble trap provides a closed and secure system which permits AVR without losing its biologic advantage. Placement of the vent in the right superior pulmonary vein precludes the elimination of the blood–air interaction and converts the system into semi-closed one. A high level of skill and expertise from all the team using the technique to perform coronary artery bypass grafting must be developed before applying MECC for AVR. This technique is considered to be more difficult than CECC because of the potential for air embolism and bleeding complications, even though the procedure initially seems to be quite simple [4].

Combined AVR and CABG using MECC is also feasible and provides better clinical results than standard CPB in regard to blood transfusion requirements, without compromising operative morbidity or mortality and postoperative results [9]. In general, MECC may effectively minimize some key events of CPB-triggered inflammatory pathways and further improve the safety of AVR procedure. It should be considered as an additional step towards further reduction in surgical trauma, especially in patients with a high risk of bleeding (e.g. patients with cirrhosis, liver disease and thrombocytopenia) [2, 8].

Remadi et al. prospectively evaluated the MECC system for AVR and showed better clinical results with preservation of renal function, decreased cardiac enzyme release and platelet count preservation. Their study also showed that haemodilution and blood transfusions could be potentially avoided with this perfusion

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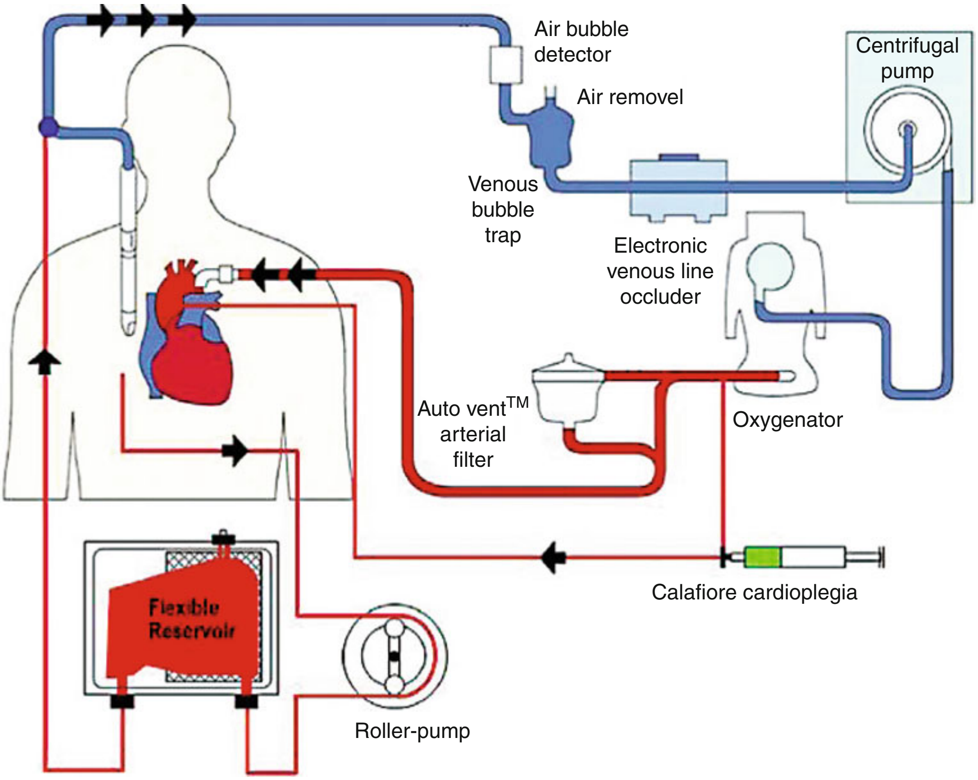
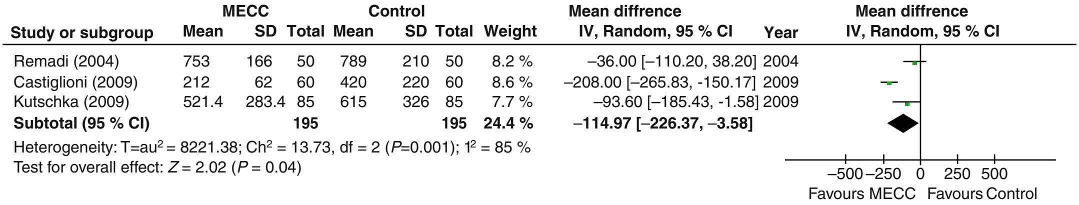


Fig. 8.1 Standard set-up for valve procedures incorporating air-handling devices (Adapted from Kutschka et al. [8])

approach [1]. Castiglioni et al. randomized 120 patients and found that AVR with the MECC system has demonstrated better postoperative clinical results in terms of need for transfusion, platelet consumption and myocardial damage as compared to the standard CPB. In patients who underwent surgery with the MECC system, neither intraoperative perfusion accidents nor the need of switching to conventional CPB was reported [3]. Our group published a meta-analysis on outcome after surgery with MECC in 2011 including 24 randomized studies. The subgroup of patients operated for AVR was analysed separately. This included 721 patients who underwent AVR or aortic root surgery (361 patients operated on MECC vs. 360 patients operated on CECC) from five studies [10]. AVR with MECC was associated with reduced postoperative bleeding (Fig. 8.2), less need for blood transfusion, reduced peak troponin T levels postoperatively and preserved platelet count. Reduction in morbidity was associated with reduced ICU stay (Fig. 8.3).

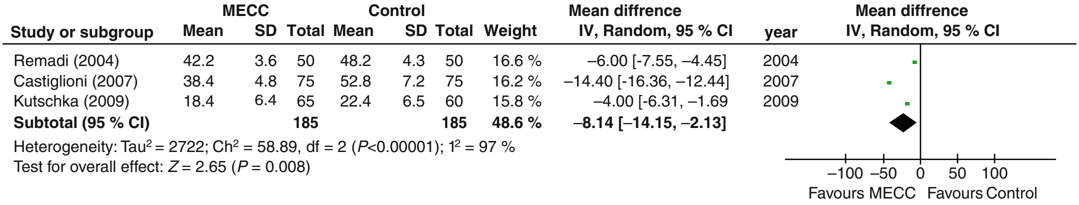
Over the last 10 years, minimal access techniques for AVR have been evolving, demonstrating better clinical outcomes by reducing pain, improving cosmetics, reducing bleeding and allowing earlier functional recovery and a shorter hospital stay, thereby reducing total cost. Until now most of these operations have been performed with CECC [11, 12]. The definition of minimally invasive cardiac surgery incorporates avoidance of median sternotomy and/or cardiopulmonary bypass. The addition of MECC to routine minimally invasive AVR (mini-AVR) will further 'minimize' the risk of postoperative complications [13]. In this operation, continuous CO_2 field flooding, placing the patient in the Trendelenburg position before unclamping the aorta, stopping the pulmonary artery vent, hand ventilation to vent out air in



Study or subgroup	MECC Mean	MECC SD	MECC Total	Control Mean	Control SD	Control Total	Weight	Mean diffrence IV, Random, 95 % CI	Year
Remadi (2004)	753	166	50	789	210	50	8.2 %	–36.00 [–110.20, 38.20]	2004
Castiglioni (2009)	212	62	60	420	220	60	8.6 %	–208.00 [–265.83, -150.17]	2009
Kutschka (2009)	521.4	283.4	85	615	326	85	7.7 %	–93.60 [–185.43, -1.58]	2009
Subtotal (95 % CI)			**195**			**195**	**24.4 %**	**–114.97 [–226.37, –3.58]**	

Heterogeneity: T=au^2 = 8221.38; Ch^2 = 13.73, df = 2 (P=0.001); 1^2 = 85 %
Test for overall effect: Z = 2.02 (P = 0.04)

Fig. 8.2 Meta-analysis comparing MECC vs. CECC in AVR procedures; forest plot for postoperative blood loss. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [10])



Study or subgroup	MECC Mean	MECC SD	MECC Total	Control Mean	Control SD	Control Total	Weight	Mean diffrence IV, Random, 95 % CI	year
Remadi (2004)	42.2	3.6	50	48.2	4.3	50	16.6 %	–6.00 [-7.55, –4.45]	2004
Castiglioni (2007)	38.4	4.8	75	52.8	7.2	75	16.2 %	–14.40 [-16.36, –12.44]	2007
Kutschka (2009)	18.4	6.4	65	22.4	6.5	60	15.8 %	–4.00 [-6.31, –1.69	2009
Subtotal (95 % CI)			**185**			**185**	**48.6 %**	**–8.14 [–14.15, –2.13]**	

Heterogeneity: Tau^2 = 2722; Ch^2 = 58.89, df = 2 (P<0.00001); 1^2 = 97 %
Test for overall effect: Z = 2.65 (P = 0.008)

Fig. 8.3 Meta-analysis comparing MECC vs. CECC in AVR procedures; forest plot for length of postoperative ICU stay. *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *CI* confidence interval, *CECC* conventional extracorporeal circulation, *MECC* minimal extracorporeal circulation (From Anastasiadis et al. [10]

the pulmonary tree, and the aortic root vent have been proved successful in removing air, as confirmed by transoesophageal echocardiography examination [14]. However, absolute contraindication for the procedure (utilising MECC) is a septal defect because we have a venous cannula in place, and a septal defect can be the source of an airlock through the open aortic root. In addition, there could be relative contraindications such as annular abscess, morbid obesity, femoral artery calcification and chest wall deformities, although they may be amenable for a minimal access approach with slight modifications [14].

MECC improves the early postoperative outcome after aortic root surgery compared to standard extracorporeal perfusion. MECC resulted in a decrease of postoperative bleeding and in a significant reduction of transfusion requirements. Reduced C-reactive protein levels, reflecting less early systemic inflammatory response and markedly shortened mean stay on ICU were found to be the results from the use of MECC [8].

Regarding mitral valve surgery using MECC, this is not only feasible but it also provides good clinical results without compromising operative morbidity or mortality [15–18]. Patients undergoing mitral valve surgery with the MECC system have high postoperative haemoglobin and relatively low blood transfusion requirements [16, 17]. There are, though, some considerations that need to be mentioned on use of MECC for the mitral valve surgery. Access to the mitral valve is preferably achieved through the interatrial groove of Waterstone. Transeptal approach through the right atrium can lead to some disadvantages; however, an open right atrium augments the risk for air embolisation through the pulmonary artery vent. Venting should be stopped when this occurs. This will result in an inadequate venting of the left side. Consequently, more blood loss will be present in the left atrium which needs removal by cell-saver drainage leading to increased loss of blood plasma, hereby diminishing an important advantage of MECC [19]. Furthermore, regarding tricuspid valve surgery concomitant with MVR or as an isolated procedure, right atrial opening may increase the risk of air embolisation of the system. However, alternative techniques, as discussed in the surgical considerations chapter, such as placement of the cannula to the superior vena cava directly and use of a long cannula from the femoral vein to the inferior vena cava along with snare tapes proximal to the heart, secure the integrity of the closed system. In general, use of a venous bubble trap integrated to the system together with avoidance of pulmonary artery venting throughout the tricuspid valve surgery allow for the standard set-up to be used safely.

The recent advances in minimally invasive surgical techniques and instrumentation, cardiac anaesthesia and perfusion technology have enabled minimally invasive mitral valve surgery (mini-MVR) to be performed more efficiently. These smaller non-sternotomy incisions translate into reduced wound pain, decreased rate of wound infection, reduced blood loss, less transfusion requirements, earlier discharge from hospital, faster recovery times and earlier return to normal activity [19]. MECC use for mini-MVR has demonstrated a higher haematocrit level and better platelet preservation resulting in lower transfusion requirements and allows the patient to gain the advantages from the minimally invasive surgery [20].

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MECC in Non-coronary and Non-valve Procedures

9

Miniaturized CPB systems offer a new way of practising cardiac surgery, that is not only operating over coronaries but also dealing with heart valves. MECC exerts a considerable beneficial effect on postoperative mortality as well as morbidity [1]. However, extracorporeal circulation is mandatory in other pathologies and may be valuable for performing thoracic surgery. Furthermore, as described in 'Future Perspectives' chapter, MECC systems have already enabled performing open-heart surgery without blood transfusion in selected paediatric patients (small infants and children) [2, 3]. In this population, conventional CPB circuits are large relative to the patient size, and hence, MECC offers a new potential for improving the outcome from heart surgery in congenital diseases.

Regarding other cardiac pathologies, aortic surgery still remains a challenge for the cardiac surgeon not only due to the demanding operating skills it necessitates but also due to the cautious setting-up it requires for obtaining good results from surgery. The incidence of ischaemic complications associated with repair of descending and thoracoabdominal aortic aneurysms has been significantly reduced by the use of distal aortic perfusion with moderate hypothermia, cerebral spinal fluid drainage and segmental sequential clamping techniques. Hence, CPB is used in such cases to prevent the occurrence of visceral and renal ischaemia and to reduce the afterload on the heart during graft replacement. However, because the maintenance of proximal perfusion, the adequacy of left heart bypass (LHB) and the ability to ventilate patients on one lung are all dependent on ventricular and pulmonary function, high-risk patients with descending and/or thoracoabdominal aortic aneurysms in the presence of cardiopulmonary insufficiency or instability present a difficult challenge for the surgical team. Traditional closed LHB circuits become nonfunctional in the event of cardiac arrest or refractory arrhythmias that create haemodynamic instability and are unable to provide necessary pulmonary support if the patient fails to ventilate adequately on one lung during thoracotomy. Furthermore, converting a patient from closed LHB to traditional venoarterial CPB is frequently difficult, especially when the perfusionist works without the benefit of extra personnel available to assist during such crises [4]. Moreover, paraplegia and paraparesis, visceral and renal ischaemia are the most serious complications in cases of thoracoabdominal aortic surgery [5].

Use of MECC system with percutaneous cannulae insertion through the femoral vessels from Palombo et al. has proved to be safe, effective and relatively simple to carry out compared to conventional CPB. The mean flow rate for distal aortic perfusion and selective visceral perfusion were 2.5 and 700 ml/min, respectively. The distal aortic perfusion pressure was 80 mmHg in all cases except in the patient who developed paraplegia in whom the distal aortic perfusion pressure never exceeded 50 mmHg [6]. In addition, distal aortic perfusion with partial CPB through cannulation of the femoral vein and artery has

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several advantages such as lung support during one-lung ventilation, while it carries the risk of coagulopathy and resultant lung complications. MECC enables a reduction in the heparin dose if using a closed-loop system, which may solve the problem of coagulopathy. Furthermore, avoidance of cardiotomy suction resulted in suppressed postoperative hyperfibrinolysis [7]. Shiiya et al. found that in distal aortic perfusion during surgery of the descending thoracic aorta, the use of cardiotomy suction is associated with elevated FDP and D-dimer levels, even when a fully heparin-coated semi-closed CPB system is used. Lower ACT level with the use of cardiotomy suction was associated with higher FDP and D-dimer levels, whereas such a relationship does not exist when cardiotomy suction was not used [8]. In general, avoiding CPB in thoracic aortic surgery provides an attractive option. Cooley introduced the clamp-and-sew technique for reconstruction of the descending thoracic aorta [9]. However, this procedure is very delicate and demands particular technical surgical skills. Time consumed for constructing the anastomoses of the interpositioned synthetic graft is critical for development of intraoperative spinal cord and visceral ischaemia. Use of conventional CPB through peripheral (femoral) or central cannulation technique in order to perfuse abdominal viscera and the brain has become prevalent [10]. Otherwise, a passive Gott shunt bypassing the operating aorta or a partial left heart bypass using conventional CPB can be applied [11]. Nevertheless, these techniques have the limitation that lung function is not supported. MECC systems may help to overcome all the hazards from the CPB use in cases of thoracoabdominal aortic surgery and further improve the results [12].

In our department, MECC has been used for complex cardiac cases such as left ventricular aneuyrysmectomy or Dor procedures, intracardiac tumour resections and inferior vena cava tumours. It has proved to be safe and effective and enabled us to design new protocols for dealing with such patients aiming mainly to gain from the advantages of MECC. Reduced SIRS, haematocrit preservation and reduced need for transfusion requirements as well as better intraoperative splanchnic perfusion which all translate into a warm, less oedematous, with less lung injury and low lactates, immediately postoperatively led us to justify anaesthesia protocols with intraoperative target-controlled infusion (TCI) anaesthesia and fast-track extubation and mobilisation protocols for the patients. This is of outmost importance in such a cohort of patients where morbidity may be translated quite easily to mortality. Hence, uneventful postoperative course does not only refer to recovery but also to survival.

An important field in contemporary cardiac surgery is heart failure with left ventricular assist device (LVAD) implantation where the use of MECC can be applied with several issues that have to be addressed. Even though the standard technique is implantation of the device on-CPB, a number of LVADs can be inserted safely and reproducibly without the use of CPB [13]. Conventional CPB circuits trigger a systemic inflammatory response that may worsen organ dysfunction in heart failure patients. Moreover, avoidance of haemodilution and the inflammatory response convey benefit by preserving coagulation and minimizing the need for blood and blood product transfusion [14]. Complement activation, neutralisation of heparin by protamine and multiple blood transfusion each cause elevation of pulmonary vascular resistance which may exacerbate right heart failure in LVAD patients.

The left thoracotomy approach for LVAD implantation is particularly amenable to the off-pump method because the ventricular apex is easily accessible without displacement. The alternative implantation technique through a median sternotomy is considered mandatory in patients with profound atherosclerosis of the descending thoracic aorta that require anastomosis of the outflow graft to the ascending aorta or when multiple cardiac procedures are performed. In such circumstances, CPB is often required due to marked displacement of the heart for exposing left ventricular apex, while suturing the restraining cuff and coring of apical muscle. This maneuvre may cause significant haemodynamic deterioration and ventricular fibrillation in unstable patients. It is therefore advisable to have a perfusion system standing by to prevent cerebral injury, and given its advantages, MECC may serve as the best system for this use [15]. Regarding off-pump LVAD implantation, this may provide a simple and effective alternative to conventional LVAD implantation using CPB. Nevertheless, a ‘safety net’ must be provided in the event of life-threatening dysrhythmia or haemodynamic deterioration. MECC can provide this insurance without the disadvantages of conventional CPB. The main advantage of MECC stand-by technique when used in the setting of an LVAD implantation is that both arterial and venous cannulation and decannulation can be performed minimally invasive with the Seldinger technique and that the circuit can be used to reintroduce cell-saved blood rapidly into the circulation, if required. Alternatively, only the guidewires to the femoral vessels can be left in place in order to avoid spoiling cannulae. Furthermore, in case of a critical preoperative condition, MECC can be used as an extracorporeal life support system (ECLS) to provide haemodynamic and respiratory support until the LVAD implantation [16].

MECC has also been proven valuable to cardiology in high-risk PCI procedures. High-risk PCI refers to patients with left ventricular ejection fraction less than 35 %, greater than 50 % of myocardium at risk, and PCI performed on the last remaining vessel [17]. A significant proportion of these patients are considered ineligible for coronary bypass grafting due to significant comorbidities or unfavourable coronary anatomy. Short-term cardiac support is applied in several clinical indications as postcardiotomy heart failure, acute cardiogenic shock or during high-risk PCI. Historically, mechanical circulatory support at the time of PCI has been instituted at one of the two settings: electively for presumed high-risk intervention and emergently for periprocedural haemodynamic instability [18]. Percutaneous left ventricular assist devices like the TandemHeart (CardiacAssist, Inc., Pittsburgh, PA) and the Impella (Abiomed, Inc., Danvers, MA) have been evaluated in clinical practice in such a setting [19–21]. MECC provides cardiopulmonary support by unloading the RV, while TandemHeart can only reach a maximum of 5 L/min and the Impella 2.5 L/min of flow. In severe cardiogenic shock, a high cardiac output is important for end-organ perfusion, while RV unloading and respiratory support is crucial for avoiding hypoxaemia due to pulmonary congestion. Reversal of overt pulmonary oedema could be further facilitated by incorporating haemofiltration during extracorporeal circulation with the MECC system. This allows for immediate stabilisation of haemodynamics and prompt correction of biochemical abnormalities [22].

There are several advantages of using MECC in high-risk PCI patients. Cannulation for MECC can be performed percutaneously in most circumstances under local anaesthesia while the patient is prepared for PCI. Venous cannulation uses a 21–23 Fr long venous cannula with multiple holes, and it is inserted through the femoral vein reaching the right atrium. The size of the cannula is similar to the inflow TandemHeart cannula which is advanced via transeptal puncture into the left atrium. The MECC arterial cannula is usually 17–19 Fr in size and returns blood through the femoral artery into the distal abdominal aorta. Correct positioning of the cannulae can be confirmed with fluoroscopy. This set-up may provide more than 6 L/min of support during the procedure. In comparison, the Impella 2.5 is advanced to the left ventricle through a 13 Fr femoral arterial sheath, while the Impella LP 5.0, which provides up to 5 L/min of flow, is inserted through a 19–21 Fr femoral arterial sheath and frequently requires surgical exposure and repair of the insertion site [23]. Vascular access complications with percutaneous LVAD range between 4 and 8 % [24]. This is similar to the rate observed in extracorporeal circulation-assisted PCI series [25]. In case of a failed PCI that requires immediate conversion to surgery, MECC enhances safety as the same circuit can be utilised during the operation. Furthermore, in patients who are haemodynamically severely compromised due to myocardial stunning and require longer mechanical support, MECC can be used as an extracorporeal membrane oxygenation (ECMO) circuit, which can provide cardiorespiratory support for an extended period. This requires exchanging of the hollow-fibre oxygenator of the MECC system, which can last for 6–10 h, with a long-lasting diffusion membrane oxygenator; such a set-up has been used for 28 days in our institution. MECC represents a short-lasting ECMO system with extra connections to the circuit which may be useful in cardiac surgery [22]. Compared to other devices, TandemHeart has been approved for 14 days, while Impella 2.5 received FDA approval for up to 6 h of continuous mechanical support [23]. Beyond prophylactic use of the system in the cath lab, MECC has been proved effective in supporting high-risk PCI on an emergency basis in a patient who suffered a cardiac arrest [26].

Furthermore, MECC systems could be extensively used in extracardiac pathologies for lesions that cannot be managed safely and effectively with conventional techniques, or conventional techniques carry significant risks to the patient, being most frequently employed by surgeons in advanced tumour removal and by emergency physicians or intensivists in resuscitation in or outside of the catheterization laboratory or operating room. Moreover, a few special fashions of CPB were also engaged in several specialties by noncardiac surgeons, such as ECMO, percutaneous cardiopulmonary support and venovenous bypass. CPB is a promising adjunct in thoracic surgery aiming to improve surgical technique and treatment in complex lung resection, combined lung cancer and heart operations, lung volume reduction surgery, lung transplantation, cases of tracheal surgery (malignant tracheal stenosis, congenital tracheal stenosis, traumatic tracheal injury, laryngotracheoesophageal cleft, etc.), mediastinal tumour resection, intrathoracic fistula repair, pulmonary artery surgery (endarterectomy, embolectomy, peripheral pulmonary artery aneurysm) and other procedures when safe organ perfusion must be ascertained [27]. Progression in transcutaneous cannulation technique facilitates application of MECC circuit [28]. MECC may be a useful alternative to CECC in such cases and may prove to be a valuable tool to thoracic surgery.

MECC can also be used in neurosurgery, and especially, cerebrovascular surgery. Giant cerebral aneurysms could be unresectable with the conventional neurosurgical techniques. Early attempts to use circulatory assistance and deep hypothermia were abandoned due to hemorrhagic complications. Recently, interest in circulatory support for complex neurosurgical procedures has been renewed after the successful application of MECC in such procedures [29]. Furthermore, MECC systems can be useful in specialties where CPB may be required, such as in anaesthesia or ENT surgery (difficult airway management), in general surgery (hepatic tumour resection), in urology (renal cell carcinoma resection with inferior vena cava invasion, adrenal tumour resection, testicular neoplasm removal), in gynaecology (intravenous leiomyoma excision), in vascular surgery (abdominal vascular fistula or aneurysm removal, massive haemangioma removal), in plastic surgery (preservation of free flap), in transplant surgery (multiple organ procurement), in oncology (isolated limb perfusion) and in the emergency department or in the ICU (use of emergent portable bypass systems is increasingly used for resuscitation, in patients who need short-term cardiopulmonary support after cardiac arrest or cardiogenic shock, massive drug overdose and severe accidental hypothermia, massive pulmonary emboli, extensive cardiopulmonary trauma or respiratory failure support) [27]. In all these cases, MECC could contribute in improving the results and expand the potential of these specialties.

In conclusion, application of MECC system for haemodynamic support in several cardiac and extracardiac pathologies is feasible, and it comes with the philosophy that this system resembles more to a paracorporeal VAD rather than to a conventional CPB, as tubing length is minimal, the circuit is fully heparinized and biocompatible, and there is a centrifugal electromagnetic pump integrated into the system. Using the retrograde autologous priming (RAP) technique, haemodilution is minimal. An important feature of the proposed circuit is that both arterial and venous cannulation and decannulation can be performed in a minimally invasive way with the Seldinger technique and that the circuit can be used to reintroduce cell-saved blood rapidly into the circulation, if required. These advantages may render MECC a valuable tool to many medical specialties.

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Future Perspectives

10

Efforts have been made to miniaturize the conventional CPB circuit by incorporating a vacuum-assisted or a kinetic-assisted venous drainage system, downsizing venous cannulae [1] and placing pump heads closer to the patient [2] with the aim to improve clinical results from its use. The best product from such an effort is the MECC system which should be considered a multifactorial strategy, aimed to counteract the multiple deleterious effects of conventional extracorporeal circulation (CECC). It has adopted all modern technologies and translated the results from research in its structures, and thus, the beneficial effects of MECC systems derive from the implementation of all advances into one technology. MECC shows an acceptable safety profile with a reduction in the rate of postoperative complications and transfusion requirements [3]. Despite its low penetration in routine clinical practice, its future in cardiac surgery can be bright. Beyond the classic indications, MECC has the potential to expand the surgeons' practice beyond limitations.

Regarding off-pump coronary artery bypass (OPCAB) technique, the MECC system may be considered as a simplification of traditional CPB and may therefore represent an attractive compromise between CECC and OPCAB. The latter has been criticised for its technical difficulties and limitations predominantly due to haemodynamic instability, which may result in inefficacious coronary anastomoses [4]. When using MECC, distal anastomoses are performed on the arrested heart similarly as for the conventional CPB approach, and the technique is not compromised in the event of haemodynamic instability. Moreover, MECC is technically less demanding than OPCAB surgery and maintains a constant and stable global end-organ perfusion [5]. Even though the principle of MECC was initially developed to assist circulation in beating-heart procedures [6], it prevailed as an effective technique for performing CABG with cardioplegic arrest [7]. Beating-heart surgery on-MECC could provide an optimal operative exposure which allows for significantly more complete coronary revascularization when compared to OPCAB. Beating-heart CABG on-MECC is an acceptable trade-off and may represent the preferred procedure in the future when complete coronary revascularization is required and OPCAB is not technically feasible, especially in high-risk patients who may tolerate cardioplegic arrest poorly [8, 9].

Minimal invasive cardiac surgery (MICS) has been recently introduced as a valid concept that aims to simplify and promote a modern way of performing surgery. It is only after modifications in CPB, reductions in the size of incisions and alternate incision site usage, that the possibilities of MICS have been realised. Advances in cardiopulmonary perfusion, intracardiac visualisation, instrumentation and robotic telemanipulation have hastened a shift towards efficient and safe MICS [10]. Hence, it is legitimate to ask whether MECC is minimally invasive cardiac surgery. According to Vanermen, the degree of invasiveness of cardiac surgery depends on two factors:

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first is the surgical approach that refers to the length of the skin incision, the degree of retraction and aggression to the tissue and the loss of blood, and the second is the use of cardiopulmonary bypass. We try to distinguish between 'fashionable' strategies and those that are truly revolutionary and investments for the future [11]. Fernandes et al. stated that recent advances in minimally invasive surgical techniques and instrumentation, cardiac anaesthesia and perfusion technology have enabled MICS to be performed more efficiently. This translates into reduced wound pain, decreased incidence of wound infection, and reduced blood loss, less transfusion requirements, earlier discharge from hospital, faster recovery times and earlier return to normal activities [12]. It is obvious that MECC provides the perfusion technology to which MICS is referred, and it may enable heart surgery to expand its potential (Fig. 10.1).

A field where this concept has been translated in cardiac surgery is minimal access aortic valve replacement. Mini-AVR by partial J-shaped, V-shaped or transverse upper sternotomy as well as parasternal right mini-thoracotomy approaches has been described by several investigators with a few discrepancies in benefits over the years. Minimal access AVR using MECC shows excellent clinical results, including less postoperative mediastinal blood loss, ventilation time and quicker recovery, when compared to the median sternotomy technique [13]. It also results in less postoperative pain, which enables patients to mobilize earlier resulting in an improved resumption of daily activities and a better physical quality of life. This is of particular importance in the elderly, for whom it has been shown that mini-AVR shortens hospital stay and leads to a larger percentage of patients discharged home rather than to rehabilitation facilities [14].

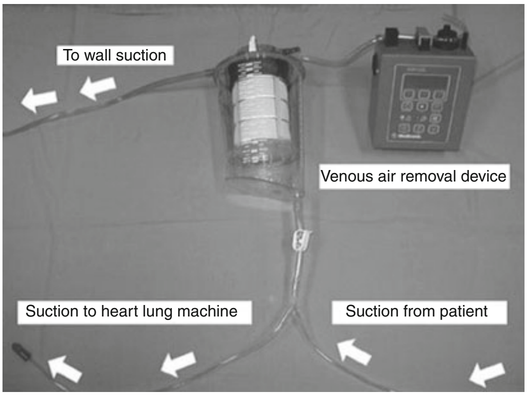

Fig. 10.1 MECC circuit modification for use in minimal invasive mitral valve surgery (Adapted from Fernandes et al. [12])

A major advantage of the MECC use translates into blood containment technique in heart surgery. Overall requirement for red blood cells and blood product transfusion in patients undergoing CABG was reduced with the use of MECC system in multiple series [7, 15–18]. Blood transfusion has been shown to be a major risk factor for multiorgan system failure, including transfusion-related acute lung injury (TRALI) [19]. Moreover, transfusion increases postoperative morbidity in patients having cardiac surgery, and its cost may be a major issue for health economics [20]. Current data demonstrate that use of MECC system provides an effective strategy towards a transfusion-free cardiovascular surgery. This may have serious implications for neonates and small infants. Colli et al. showed that the major advantages of the MECC system mainly in terms of decreasing blood transfusion requirements are more evident in patients with a body surface area >1.7 m^2, leaving open the choice for the surgeon in patients with low body surface area [21]. In addition, Vaislic et al. emphasised the clinical usability of MECC, as they used it successfully in 40 Jehovah's Witnesses, primarily to save blood [22, 23]. Furthermore, MECC could be an additional step towards reduction of surgical injury in selected patients with high risk of bleeding, for example, patients with cirrhosis, liver disease and thrombocytopenia [24].

MECC system also allowed to perform open-heart surgery without blood transfusion in selected paediatric patients (small infants and children) [25, 26]. A major challenge still remains in neonatal open-heart surgery, for which blood prime is inevitable in order to maintain an optimal haematocrit level due to the considerable mismatch between the patient's body size and conventional CPB circuit volume [27, 28].

Inflammatory response and subsequent organ oedema increase in an exponential fashion as the amount of priming volume and blood transfusion increases [29, 30]. Stored blood products could also trigger an inflammatory response [31, 32]; therefore, reducing the amount of transfusions could potentially exert benefit in minimizing transfusion-related adverse effects in neonates. Current data demonstrate that with the use of MECC system, the goal of transfusion-free cardiovascular surgery can be accomplished, even in the smallest neonates undergoing complex CPB procedures (Fig. 10.2) [27, 33–36]. This particularly applies to patients undergoing corrective procedures, whereas patients with cyanotic malformations undergoing palliative procedures are more prone to receive blood transfusions [25]. Extended utilisation of MECC circuit in neonatal and small infant cardiac surgery within the next few years could provide the basis for reducing post-CPB organ dysfunction and improving clinical outcomes in this population [37, 38].

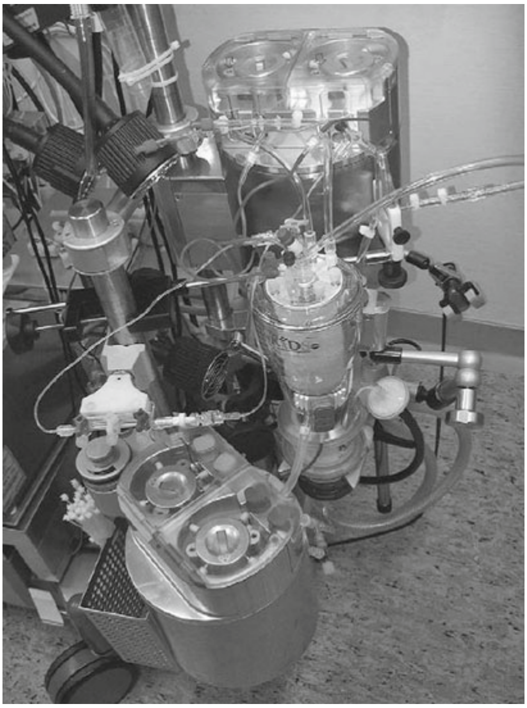

Fig. 10.2 A miniaturised neonatal system. It resembles an adult MECC circuit, but utilises two remote roller pumps (Adapted from Koster et al. [33])

Advances in equipment design allowed for percutaneous application of the MECC system in a minimal invasive setting (plug and play – ready to use sets). A compact portable system can be readily available in the catheterization laboratory or in the Accident and Emergency Department for trauma patients, as well as in noncardiac surgery. So far, MECC has been successfully implemented in supporting the circulation during complex neurosurgical procedures, such as giant cerebral aneurysm repair [39]. Similar to this concept, there is a variety of pathologies and surgical procedures where MECC could be applied and contribute to improved results in high-risk patients.

The summation of the advantages that MECC offers is responsible for the earlier recovery observed in patients as confirmed by the reduced ICU and hospital length of stay. This strategy combined with fast-track surgery may account for financial implications to the affiliated organisation. A detailed cost analysis will identify the real position of this technology in the contemporary cardiac surgical setting.

So far, there is a low penetration of MECC worldwide. In a recent survey, 20 % of the perfusion departments within the UK and Ireland are using MECC interestingly, this use is claimed to be in certain clinical scenarios [40]. Further data regarding this technology may increase its popularity and expand its use. Up to date, all available studies provide evidence regarding short-term clinical outcomes using the MECC system. In order to draw definite conclusions, large, multicenter, well-designed randomized controlled trials focusing on long-term outcome data are considered mandatory.

A semi-closed system is already under clinical evaluation with implementation of an optoelectrical suction device designed for operations with predicted massive blood loss to mediastinum intraoperatively, such as redo surgery, acute aortic dissection or intracardiac surgery. Immer et al. have successfully tested such a system. A contemporary suction device, the SmartSuction (Cardiosmart AG, Muri, Switzerland), was integrated into the MECC system (Fig. 10.3). Aspiration is controlled by an optoelectrical sensor placed at the tip of the suction cannula and is activated only when in direct contact with a

Fig. 10.3 The Cardiosmart suction device (Maquet, Hirrlingen, Germany) with the integrated optical sensor

liquid interface. Aspirated blood is automatically retransfused into the venous line of the circuit, and therefore, no additional suction pump or reservoir is required [5, 41]. With the use of an aortic or pulmonary artery vent, the system is described from some surgeons as ‘semi-closed’. However, we do not consider this set-up as a semi-closed system since no blood–air interaction results from the use of the pulmonary artery vent, and the aortic root vent is used intermittently, while continuously monitoring the aortic root pressure, in order to create a bloodless field, especially during coronary surgery.

Moreover, main concerns regarding safety of MECC systems have been raised mainly addressing air entrainment into the circuit [42]. Despite these theoretical concerns, no fatal or major episodes have been described by any author [43]. Furthermore, Gunaydin et al. compared conventional CPB to the MECC circuit and found no significant difference in gas microemboli within the circuits as well as no difference in air handling between the two systems [44]. Integration of a venous bubble trap into the circuit literally minimized this problem and enhanced safety. The novel modular systems which refer to an additionally mounted, clamped-off venous reservoir for transforming the system to an open circuit if required, offer great promise (Fig. 10.4). Generally, it is widely accepted that MECC systems require a specific expertise, have a prolonged learning curve and need dedicated team effort [45]. Without the venous reservoir, the perfusionist may not compensate for insufficient venous return with additional volume. Thus, minimized systems require a particular differentiated volume management and bring up new challenges in the clinical application of CPB [46]. On the other hand, bloodless and non-inotropic cardiac surgery can be feasible with MECC by the aid of cell-saver and closed-circuit anaesthesia [47].

Van Boven et al. supported in 2004 that reduced volume shifts, a traumatic blood treatment and conservation, together with advanced myocardial protection techniques and lower heparinisation levels, are expected to reduce side effects and have positive impact on patient outcomes [48]. At the same year, Remadi wondered whether MECC represents an evolution or a revolution in cardiac surgery [49]. Eight years later, answers to these questions emerged from multiple clinical results published from different centres. It is obvious that cardiac surgery with the use of the mini-extracorporeal circulation systems is heading a step forward. Modern times need modern ideas and modern way of dealing with things. MECC stands as the only modern contemporary tool in heart surgery, which is established, that reduces short-term morbidity as well as perioperative mortality. Long-term data regarding survival and adverse events are required to draw further conclusions. Meanwhile, provided that MECC system proves to be cost-effective compared to conventional CPB, it will ultimately replace conventional CPB.

CPB has successfully completed more than a half of a century after its introduction into the clinical practice. MECC should be considered as the ideal technique to perform cardiac surgery. Nevertheless, MECC philosophy demands a strong multidisciplinary effort from all the parts of the surgical team (surgeon, anaesthesiologist, perfusionist), technical skills to perform focused manoeuvres and a close cooperation in order to recognise and respond promptly and accurately to any haemodynamic derangement during the procedure. Based on available clinical and labo-

Fig. 10.4 Hybrid perfusion setting incorporating a hard-shell reservoir (**a**) parallel to MECC system (**b**) for immediate conversion from closed to open circuit

ratory evidence, we strongly consider that in the future, this technology will expand its use and increase its potential so as to be established as the gold standard technique for performing heart surgery.

MECC is the descendant of ECMO. Modern portable ECLS systems have already penetrated the contemporary practice (Fig. 10.5). These systems can be considered as simplified MECC circuits and hence operating on them is literally surgery on-MECC. This perspective opens the horizon for practising cardiac surgery in any environment (i.e. non-tertiary hospital without cardiac surgery facilities, military or out-of-hospital conditions).

Fig. 10.5 CARDIOHELP portable ECMO system developed by Maquet

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11

MECC—The Perfusionist's Point of View. One Decade MECC: From a Pioneering to Standard Procedure

Currently, cardiac surgery offers four options to treat coronary artery disease (CAD): conventional extracorporeal circulation (CECC), minimized extracorporeal circulation (MECC), pump-assisted beating heart (PACAB) and off-pump coronary artery bypass (OPCAB). Coronary artery bypass grafting using CECC is still the most accepted and applied technique for the surgical treatment of CAD today. It is a safe and well-established technique with a low mortality rate [1–3]. Although morbidity caused by CECC is still significant [4, 5], the vast majority of CABG procedures using CECC are without any complications. Nevertheless, 35% of all perioperative complications are reported to be related to the use of the heart–lung machine [6].

For this reason, since the evolving of cardiac surgery, researchers wanted to minimize the side effects of extracorporeal circulation (ECC). Most of these improvements can be seen in the context of evolution, which means the continuously improving of existing components of cardiopulmonary bypass (CPB). During the first half of the twentieth century, scientists and engineers refined their methods in the development of ECC to overcome its limitations and laid the path for final application in humans [7]. In 1937, Gibbon reported the first successful use of ECC in animals (in this case, cats). On May 6, 1953, Gibbon performed his first successful operation. It was Lillehei who, one year later, introduced the bubble oxygenator, simple and inexpensive, opening the doors of open-heart surgery to all surgeons around the world [8]. Since this time, the development of extracorporeal circulation made great progress.

Developments in Perfusion

The Oxygenator

The spinning disc oxygenator, introduced by Gibbon in 1949, had enough capacity to perfuse only a dog and the potential to increase the oxygenation capacity through the addition of more discs. When cardiac surgeons started to perform three to four open-heart operations per day, the disposable bubble oxygenator turned out to be more practical [9]. Over a long period of more than 30 years, the bubble and film oxygenators were the gold standard for ECC in cardiac surgery. However, in 1956, engineers and physicians had already developed a new type of oxygenator using nonporous silicone as well as modified silicone membranes. These devices were characterised by high priming volumes, high pressure drops and marginal gas transfer efficiency. Recent advances in membrane technology spawned a new generation of membrane oxygenators using microporous polypropylene in the 1980s [9]. This type of oxygenator has been the gold standard in ECC up to present days. Nowadays, the size can be reduced due to more effective gas transfer rates.

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Drives and Pumps

Although the roller pump is the most used and accepted pump in cardiovascular technology, it is suspected of causing harmful side effects. Damage to blood particles (erythrocytes, platelets, etc.) might be caused by mechanical occlusion using the roller pump and could potentially lead to haemolysis. Therefore, researchers have been looking for new technologies in order to reduce injury to blood and blood particles.

In comparison to the standard roller pump, the centrifugal pump largely reduced the negative side effects of blood injury. While the first model had already been developed in 1900, it was not until 1960 that Saxton and Andrews designed a centrifugal pump which could be deployed in humans as a circulatory support device [10]. Nevertheless, this was still part of an experimental setting. It took another 20 years before McGovern used a centrifugal pump in a clinical setting as a circulatory support, which could later be incorporated in ECC: the Bio-Pump® (the first commercially available centrifugal pump, Medtronic®). Current inquiries show higher acceptance for centrifugal pumps among perfusionists during their daily routine [11].

Artificial Surfaces-Coatings

Blood contact with artificial surfaces activates the coagulation system, the fibrinolytic system and cellular and humeral immunity. For this reason, haemocompatible surface coatings for the synthetic surfaces of extracorporeal circuits were designed. The most popular coatings in cardiovascular technology are the heparin- and albumin-bonded coatings. Primarily, these coatings were developed aiming to reduce platelet drop and to further increase the biocompatibility of ECC systems [12, 13]. Early animal experiments with sheep in the late 1980s by Mottaghy et al. demonstrated event-free ECC over 5 days in terms of clotting and coagulation with coated surfaces compared to non-coated circuits [14]. Other authors reported less haemolysis and reduced inflammatory response in clinical trials [15].

Furthermore, even after modification of the oxygenator and the reduction of its surface area below 2 m^2, some authors saw an increasing amount of transient high-pressure drops across the oxygenators in approximately 5% of the patients [16]. After the use of coated oxygenators (e.g. Trillium® Medtronic, Safeline® Maquet) found its way into clinical practice, this phenomenon almost completely disappeared.

Modified ECC Systems

Closed Systems

The idea behind closed CPB systems, at best in conjunction with tip-to-tip coated bioactive circuits, is to avoid the contact between blood and air in order to minimize the detrimental effects of coagulation and inflammation responses caused by ECC. First reports were published in the early 1960s; that is, Yamada et al. published a study in which they highlighted the advantages of this method [17].

Small Adult Systems

A very simple method to improve ECC systems is to minimize the set-up as small as possible and thereby to reduce artificial foreign surface and priming volume. This must be done without any restrictions with regard to patient safety. A further positive influence of small adult systems is to be found in the decreased need for blood transfusions. Using this method is very simple to implement in clinical practice and could depict a first step towards patient-orientated care, especially for clinical practitioners who need to be further encouraged regarding the evident advantages of using minimized closed systems.

Unfortunately, until present, there is still a lack of solid data in this specific area of clinical practice [18–20]. Nowadays, more and more fellow clinicians are aware of their responsibility and their personal liability towards patients' care in their specific field and thus push the limits beyond previously accepted standards. One example here is the huge effort made with regard to blood conservation over the last years, and in this context, aiming at designing smaller CPB sets demonstrates the growing consciousness among clinicians, perfusion scientists and research-based colleagues.

Shed Blood Separation

Shed mediastinal blood collected by cardiotomy suction has been shown to be a large contributor to lipid microemboli ending up in different organs [21]. The aim of shed blood separation is to reduce these side effects and to avoid the transfusion of activated factors (i.e. from the coagulation cascade) contained at sucked mediastinal blood. The avoidance of shed blood recirculation maintains physiological coagulation levels and reduces red blood cell trauma in ECC procedures remarkably [22].

Minimised Bypass: Revolution or Evolution?

Since the beginning of clinical perfusion, all new developments and improvements in perfusion science were mainly focusing at one objective: the reduction of the observed deleterious effects of extracorporeal circulation [23]. At the end of the 1990s, many perfusionists and scientists devised a system combining the whole knowledge of perfusion science. The modifications to the new system were much more revolutionary than the individual improvements to the existing conventional CPB systems. The idea behind was to create a system including all known and evident benefits in one combined CPB set-up: The minimized extracorporeal circulation system was born.

Regardless of the manufacturer, minimized cardiopulmonary bypass comprises the following characteristics: (1) low priming volume, (2) active venous drainage (smaller tubing lines), (3) centrifugal pumps, (4) biocompatible surfaces, (5) separation of suction blood and (6) closed systems in order to avoid blood–air contact.

One of the first commercially available minimized systems was the CORx® from CardioVention®. This system included an integrated centrifugal pump, a polypropylene oxygenator, a complete heparin-coated surface and a low priming volume [24, 25]. The most known and distributed minisystem, the MECC® system from Maquet Cardiopulmonary, was introduced almost at the same time [26].

Some of the most prominent advocates of miniaturized CPB systems and its clinical introduction were Liebold and Philipp et al. at the University Hospital of Regensburg, Germany. Their insistent pioneering works in this new field of research led to the development and introduction of this technology in Europe. At the early twenty-first century, more and more institutions started projects with minimized systems and made a lot of contributions to this specific field of cardiac surgery and perfusion science. More and more technical improvements and further developments such as the venous bubble trap were introduced and improved the MECC system considerably. Among many other groups of researchers, the following stand out through their extensive contributions in this field: Remadi et al. [27–29] (France); van Boven et al. [30] (Netherlands); Carrel et al. [31, 32] (Switzerland); Castiglioni et al. and Mazzei et al. [33–35] (Italy); Biancari et al. (Finland) [36]; Curtis et al. [37] (United Kingdom); El Essawi et al., Perthel et al. and Bauer et al. [38–41] (Germany) and Anastasiadis et al. [42–45] (Greece).

Today, there are several meta-analyses and reviews [37, 42, 46, 47] available showing the effectiveness and also safety of the procedure [47, 48]. A multicentre trial shows that the incidence of major adverse events can be decreased by using minimized ECC (9.1 vs. 16.5%; $p = 0.02$) [38]. The benefits of using this type of ECC are well known. One of the major findings in all studies is the lower consumption of blood and blood products, observed in the peri- and postoperative period. Therefore, the 'Society of Thoracic Surgeons Blood Conservation Guideline Task Force' at the last update of the guideline in 2011 awarded a class 1 (level of evidence: A) recommendation for minimized systems due to contribution to the reduction of red blood cell transfusions [49]. In the published literature, there is evidence for less frequent occurrence of postoperative low cardiac output syndrome, need for inotropic support and a lower early peak of creatinine levels in patients treated with MECC systems [40, 42, 50].

Furthermore, minisystems are referred to several advantages, that is, lower inflammatory response [29, 36, 40, 51, 52]. The presence of atrial fibrillation and neurologic events postoperatively is reduced with MECC [31, 38, 41, 42, 47, 53, 54]. MECC is also associated with reduced levels of peak troponin release, one potential indicator for low cardiac output syndrome and the lesser need for inotropic support [40, 42].

In summary, it can be stated that the use of miniaturized ECC systems in cardiac surgery resulted in improved outcome accompanied by reduced mortality and morbidity compared with conventional extracorporeal circulation.

Despite these facts, up to now, the technology is still not fully established as a standard procedure in cardiac surgery across Europe.

Open Questions

1. *Why do we still see no major impact of MECC in cardiac surgery?*
2. *Is it due to the different practical approach – because of the difficulties to adapt to a 'new procedure'?*
3. *Are we afraid of an assumed lack of safety?*

The Differences of Closed Minisystems Compared with CECC

Two things in the use of MECC systems differ fundamentally from conventional CPB: firstly, the handling of air, also referred to as air management, and, secondly, the management of patient haemodynamics (volume management). One particular key aspect is the handling of changes between intracorporeal and extracorporeal blood volumes, which means closed minisystems are more similar to the use of extracorporeal life support systems (ECLS, ECMO) in terms of the obligation to run the system completely free of air and the integral part of an active venous drainage.

Air Management

As pointed out earlier, the most vital part for all clinical practitioners involved in using miniaturized closed CPB systems is the intraoperative air management. Bringing this issue up to mind, it becomes evident that this key aspect potentially contributes largely to the remaining scepticism about the safety of minisystems. It also leads us to the point of teamwork which is more dwelled on comprehensively later in a separate section and involves all clinical practitioners, the cardiac surgeon, the anaesthetist and, of course, the perfusionist.

Right from the beginning of the operation, the surgeon must be aware of his part in preventing air from entering the system, that is, fixing of the cannulae and vents with additional sutures, airless connection of the cannulae to the tubing set, etc.

The anaesthesiologist must take care of avoiding air entrance leaks, that is, preventing air entering via central venous line due to the negative vacuum pressure in the right atrium.

The perfusionist also contributes inevitably to the reduction of the risk from air entering the extracorporeal circuit. This incidence of microbubbles can be minimized through a series of actions.

Firstly, one important point is the elimination of air within the venous line. The air must be eliminated prior to entry into the centrifugal pump, thus preventing the 'shredding' of larger bubbles into microbubbles by the forces acting within the pump head. Once these small microbubbles are generated and due to their size which is supposed to be much smaller than most of the commercially available arterial line filters (40 μm), they can no longer be prevented from entering the body. For this purpose, there are specially built bubble-removing devices (bubble traps) for all systems available on the market.

Almost all of them are operated dynamically with regard to their ability to remove accumulating air bubbles either automatically or manually.

Secondly, the control of the venous line pressure is of great importance; ideally, the negative pressure measurement is coupled to the arterial pump, and therefore, the system is able to adjust the systemic flow smoothly and even stops the pump in case of excessive negative pressures in the venous system. This control feature helps to avoid negative suction spikes because, especially during phases with high negative suction pressures, the risk of sucking air into the CPB system is increased.

Thirdly, the perfusionist must make sure in his patient care to act 'air-free' all the time, especially when injecting medications or during drawing of blood samples. Additionally, the use of flexible infusion bags is helpful in avoiding air embolism.

Once these policies have been considered carefully by all involved clinical practitioners, the issue of air management is well to handle, and therefore, the use of minimized closed systems does not constitute a higher risk than conventionally performed perfusions with an open circuit and the use of an integrated cardiotomy reservoir.

Volume and Blood Management

Minimized closed systems usually do not have a venous reservoir integrated within the circuit, and for this reason, it is not possible to reduce the intracorporeal blood volume in common ways in favour of unloading of the pulmonary circulation and to empty the heart finally. Nevertheless, it is possible to drain the patient's blood into flexible reservoirs, but as this static blood remains uncirculated and restrained from being part of the blood circulation, it may contribute to complement activation. Due to this reason, it may be more appropriate to use the patient's own venous vascular system for pooling (physiological reservoir) in terms of preventing blood damage and activation processes.

One way for the anaesthesiologist to fill or empty the heart is to adjust the position of the OR table as required either in 'Trendelenburg position' with the patient's head down (filling of the heart) or the opposite position with lowered legs and head elevated (emptying of the heart). In this position, the patient's own physiological venous pooling capacity is increased. Simultaneously, the perfusionist increases the flow of the MECC in order to draw more blood from the right atrium which then will be shifted through the ECC and the arterial system into the enlarged venous pool of the patient. This leads to a decreased pulmonary circulation. Should this action not result in adequate unloading of the heart, the anaesthesiologist and/or perfusionist can still generate further venous pooling by administration of vasodilators, for example, nitroglycerin. All these measures take time to be effective compared with the conventional approach using an open CPB system with an integrated venous hard-shell reservoir, and of course, this should be considered by the whole team.

Another key aspect with regard to the volume management is the importance of haemostasis. While in conventional CPB, the direct returning of the suction blood into the cardiotomy reservoir is widely accepted, massive blood loss due to intraoperative bleeding included, the same approach is obsolete in using a minimized closed system. Here, in favour of complete sucker blood separation, a significant volume deficiency can occur, which of course can be treated by volume administration. This inevitably leads to an increased haemodilution. Additionally, by use of a cell saver, the patient loses coagulation factors and blood plasma. The well-documented advantages of a suction blood separation (elimination of harmful components such as activated coagulation factors and enzymes) could be counteracted, further increasing blood loss [55]. This potentially leads to an increased demand for transfusion of blood and blood products.

Teamwork and Concerted Introduction

Because of these evident differences between conventional CPB and minimized closed systems, more comprehensive and new interfaces between perfusionists, anaesthesiologists and surgeons have been implemented. This inevitably leads to the aspect of the team approach. Teamwork is the major requirement and the most important factor for a successful implementation of a MECC programme.

Perhaps we are still facing a lack of widespread consciousness and acceptance that the team approach is of such a tremendous importance, and this could be the reason why this method has not been fully established in cardiac surgery yet.

When only one 'piece of the puzzle' is not fully involved in the process by heart and possibly bears an inner reluctance towards this method, a clinical implementation cannot be entirely successful. Finally, the results may not match the expectations, and the step back into the routine application of CECC does not seem to be unlikely.

In particular, the teamwork and in-depth training with an appropriate time frame are mandatory and thus can guarantee a successful implementation of the method.

Safety: Do We Need a Modular System?

Time and time again in the past, the possibility of a lower safety standard of closed minisystems was discussed [56]. The closed design and the absence of the cardiotomy reservoir may increase the risk of air entrainment into the circuit. Subsequently, this would potentially result in the production of gaseous microemboli and higher rates of neurologic injury in the MECC group [54, 57].

In contrast, Biancari et al. and Zangrillo et al. have shown in their meta-analyses considerable and significant reductions of emboli as well as significant reductions of neurologic damage (4/548 [0.7%] vs. 19/555 [3.4%]; odds ratio = 0.30 [0.12–0.73]; $p = 0.008$), while other reviews did not confirm these findings, although the lower microembolic load is meanwhile detectable by retinal photographic imaging [42, 47, 58–60]. Probably three reasons could account for these findings: (1) A reduced embolic load would not be surprising because today all modern closed minisystems are adapted to the requirements of de-airing and are mostly equipped with venous bubble traps or air removal devices. (2) One should also be aware of the mandatory air-free connection of MECC systems to the patient. (3) Last but not least, the absence of exposure to lipid microbubbles and microparticles from the cardiotomy suction and vent suckers as used in CECC due to suction blood separation and application of cell savers.

To improve the flexibility and safety of the procedure, more and more manufacturers are offering modular systems, which find many advocates within the perfusion community. The term modular refers to an additionally mounted, clamped-off venous reservoir which allows the perfusionist to run the system as an open circuit if required. This measure follows the proverb 'always expect the unexpected' and offers the clinical practitioner an additional safety margin in case of unexpected intraoperative events. Three potential indications for the immediate need to switch to conventional bypass are conceivable: (1) uncontrollable air intakes in the venous line, (2) the total inability to unload the heart and (3) intraoperative expansion of surgical indication due to the ongoing improvements in the use of transoesophageal echocardiography.

With a modular system, these requirements, without changing the CPB system intraoperatively, are finally possible and safe.

Conclusion

The development of perfusion and the accompanying scientific field always evolved in both, periods of innovation and stagnation. More than 10 years ago, the surge of innovation was again initiated by the introduction of minimized CPB. A lot of concerns and open questions regarding minimized bypass systems are answered today. Manufacturers and users have responded to initial concerns and problems, and today's systems are comfortable to handle and safer than ever.

Further considering the results of some studies on the quality of the operated bypass grafts comparing CECC with OPCAB technique, they clearly indicated that patients operated on CPB received more grafts and had a comparable outcome. Operating under the support of CPB leads to less re-occlusion rates and a higher patency of the grafts [61, 62].

The operation on an arrested heart using MECC offers the surgeon the same beneficial conditions as with CECC, while the learning curve, especially for the surgeon, is significantly steeper in comparison to OPCAB in particular if one considers all points of a concerted implementation.

Further considering that the reduction of side effects by using MECC showed similar results compared with OPCAB, a further expansion of this technology in the field of perfusion and cardiac surgery seems to be very useful [41].

The future of closed minimized systems now lies in the hands of clinical practitioners – cardiac surgeons, anaesthesiologists and perfusionists – to offer this well-researched and advantageous method to their patients. For the perfusionist in particular, this process bears an extraordinary chance to take a positive influence on the patient outcome.

In addition, this field offers the chance for the perfusion community to expand its effort in the field of research of MECC systems and thus its opportunities to integrate this young perfusion-related scientific field as an integral part of medical science.

In conclusion and with regard to the measures mentioned before, the wider implementation and application of closed minimized CPB systems is a fundamental step towards patient-guided care and consequently strengthens its role as a routine method within the field of extracorporeal circulation.

Comment

MECC became the standard technique for performing coronary artery bypass grafting (CABG) in Antonius Hospital, Nieuwegein since many years. Many other centres followed that approach. However, there are not many cardiac centres in Europe that use MECC. There are several reasons for this: (a) It needs a skilled perfusionist, and unfortunately, there is a lot of difference in education level between perfusionists; (b) there is lack of training on MECC technology, and (c) there is no financial proof of benefit. Although there is scientific evidence, this is not so robust so everybody changes practice. Moreover, custom-made MECC sets and techniques are different; everybody performs MECC in a different way. This creates difficulty to compare results between centres.

We use MECC for AVR (mini) or AVR/CABG in our institution since 2005. We have also used it for complex surgery like MVR/MAZE, even though an advanced cardiotomy reservoir (lipid-/leuco-treated filter) may be required in this setting. We have recently started using the portable ECLS system CARDIOHELP as MECC for CABG procedures.

Regarding the low penetration of MECC in the USA, the main reason for this is more likely a lack of proven cost-effectiveness. Generally, MECC is considered more expensive than the conventional ECC set. However, the fact that MECC is a cost-containment practice which comes from the reduced transfusions and shorter ICU and hospital stays may eventually result in financial benefit. A detailed cost analysis is required.

I will not give up, because I believe in this technique!

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Epilogue

12

In an attempt to attenuate the pathologic effects of cardiopulmonary bypass (CPB), miniaturized extracorporeal circulation (MECC) systems have been developed to allow the ease of on-pump heart surgery while tempering the disadvantages from the CPB use. The idea of MECC systems has initiated important new efforts within science and industry to improve the biocompatibility of CPB systems and hence minimize their side effects as well as offer better global organ protection. To meet this goal, MECC has integrated in the system a centrifugal blood pump with optimal biocompatibility, especially low thrombogenicity, reduced haemolysis and activation of leukocytes as well as mediators; minimized components to reduce the priming volume, thus haemodilution and less need for donor blood. The system was designed to provide access to all coronary regions as well as to intracardiac structures; temperature management of the different forms of normothermia or hypothermia depending on the need is possible; safe de-airing procedures for open-heart surgery are possible. Finally, it is of paramount importance that MECC supports modern concept of fast-track anaesthesia.

Overall, MECC represents a new philosophy in applying cardiac surgery, and the system may be considered more an extracorporeal cardiac assist device (comprising a rotary blood pump, an oxygenator and a closed loop of short tubing) rather than a CPB. Even though avoidance of any kind of CPB is an attractive concept, many open-heart procedures simply cannot be performed off-pump; interestingly, the total amount of valve, multivalve and redo procedures is still increasing. Generally, MECC offers a new way of practising cardiac surgery.

Despite its obvious advantages that are extensively discussed in this book, the low penetration of MECC in contemporary practice may be attributed mainly to the fact that it initially offered less safety than the conventional extracorporeal circulation (CECC). This is due to the absence of venous reservoir and several other upcoming issues from its design such as venous decompression, venting possibilities, air (entrapment, embolization and handling), volume management in the presence of massive bleeding and advanced perfusion technique for obtaining the optimal result even in complex cases. However, recent improvements in the systems introduced innovative de-airing and safety features to remove these potential concerns. Complexity of modern MECC circuits lost their initial beauty of simplicity (Fig. 12.1) but they offered the novel modular systems which refer to an additionally mounted, clamped-off venous reservoir for transforming the system to an open circuit if required. This design may represent a hybrid circuit (a MECC plus a CECC in parallel) with the option to use MECC as the standard circuit and the conventional as the alternate.

In summary, MECC is technically less demanding than off-pump surgery and allows maintaining safe organ perfusion though it demands a strong multidisciplinary effort from

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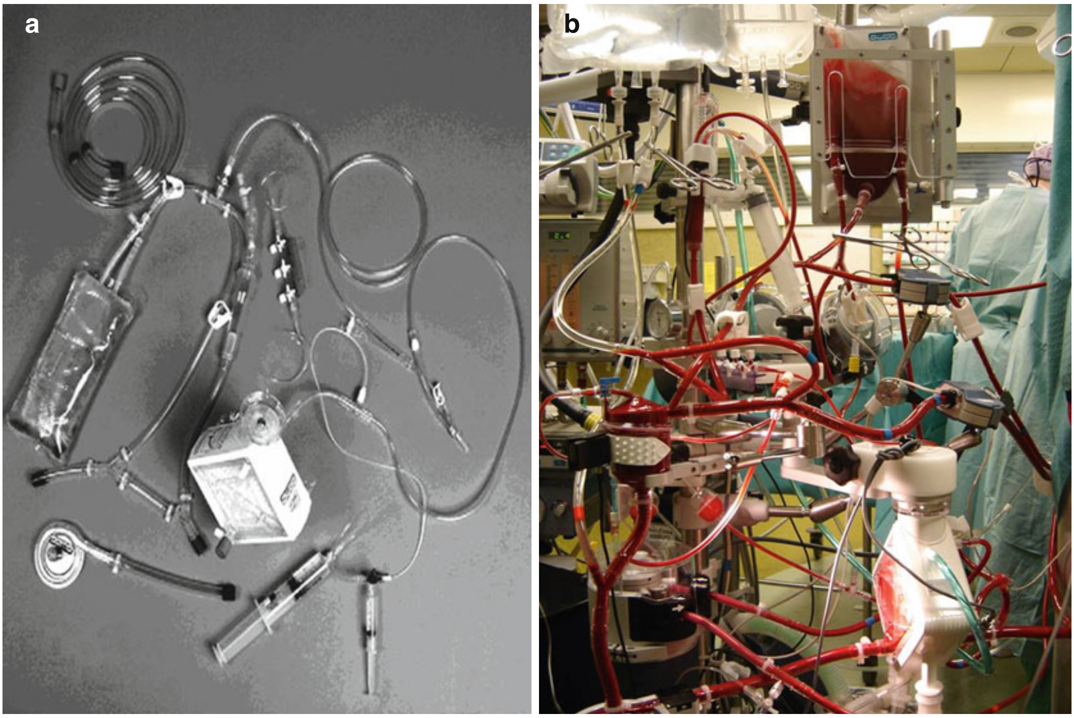

Fig. 12.1 Two MECC circuits, from simple to composite. (**a**) From Alois Philipp (Regensburg) – the beauty of simplicity. (**b**) From Frans Waanders (Nieuwegein) – the art of complexity

all the parts of the surgical team (surgeon, anaesthesiologist, perfusionist), technical skills to perform focused manoeuvres and a close cooperation in order to recognise and respond promptly as well as accurately to any haemodynamic or physiological derangement during the procedure. This book aims to teach MECC to the surgical team.

Having read this book, we hope the answer to the open question in the literature whether MECC is an evolution or revolution in cardiac surgery is already obvious.

Erratum

Principles of Miniaturized ExtraCorporeal Circulation

From Science and Technology to Clinical Practice

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Glossary

ACT	Active clotting time
AF	Atrial fibrillation
AKI	Acute kidney injury
ALI	Acute lung injury
AVR	Aortic valve replacement
BP	Blood pressure
BIS	Bispectral (index)
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CECC	Conventional extracorporeal circulation
CK	Creatinine kinase
CO	Cardiac output
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
CVP	Central venous pressure
ECC	Extracorporeal circulation
ECLS	Extracorporeal life support
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
FFP	Fresh frozen plasma
GFR	Glomerular filtration rate
GME	Gaseous microemboli
Hb	Haemoglobin
Ht	Haematocrit
ICU	Intensive care unit
IFABP	Intestinal fatty acid binding protein
IL	Interleukin
IV	Intravenous
IVC	Inferior vena cava
LHB	Left heart bypass
LV	Left ventricle
LVAD	Left ventricular assist device
MAP	Mean arterial pressure
MDA	Malondialdehyde
MECC	Minimised extracorporeal circulation
MICS	Minimal invasive cardiac surgery
MVR	Mitral valve replacement
NAG	*N*-Acetyl-glucosaminidase
NCD	Neurocognitive decline
NIRS	Near-infrared spectroscopy
OPCAB	Off-pump coronary artery bypass
PA	Pulmonary artery
PAP	Plasmin–antiplasmin complex
PAWP	Pulmonary artery wedge pressure
PCI	Percutaneous coronary intervention
PEEP	Positive end-expiratory pressure
PLT	Platelets
PMN	Polymorphonuclear neutrophils
PVR	Pulmonary vascular resistance
RAP	Retrograde autologous priming
RBC	Red blood cells
RMs	Recruitment manoeuvres
rSO2	Regional cerebral tissue oxygenation
SIRS	Systemic inflammatory response syndrome
SR	Sinus rate
SVR	Systemic vascular resistance
TCI	Target-controlled infusion
TCD	Transcranial Doppler
Tn	Troponin
TNF	Tumour necrosis factor
tPA	Tissue plasminogen activator
TRALI	Transfusion-related acute lung injury
VARD	Venous air removal device
VBT	Venous bubble trap

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