Review Article

MIECT: How did it start?

Yves Fromes[1,2], Olivier M. Bical[3,4]

[1]Institute of Myology, Sorbonne University, Paris, France; [2]Perfusion Unit, Groupe Hospitalier Paris St Joseph, Paris, France; [3]Hôpital Privé de Parly II, Le Chesnay, France; [4]Department of Cardiac Surgery, Groupe Hospitalier Paris St Joseph, Paris, France

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yves Fromes, MD, PhD. Institute of Myology, Sorbonne University, Paris, France; Former Head of the Perfusion Unit, Groupe Hospitalier Paris St Joseph, Paris, France. Email: yves.fromes@gmail.com.

Abstract: Transiently assuming the functions of both heart and lungs as surgeons repair critical valves and vessel lesions can be achieved by mechanical circulatory support has its origins in cardiopulmonary bypass (CPB). However, CPB technologies induce also some unintended adverse effects. During the 90s, a mayor trend pushed many physicians to reconsider the place of coronary artery bypass grafting (CABG) and challenged the surgical reference treatment by less invasive catheter-based angioplasties. Nevertheless, best long-term patient outcomes were related to surgery. Therefore, a small number of multidisciplinary teams in Regensburg and Paris started to develop a minimally invasive CPB system. The basic concept relied on a closed-loop perfusion circuit with a non-occlusive pump. Moreover, the team in Paris pushed the concept further and developed a complete fully integrated CPB system allowed first closed-heart and later open-heart surgery with aortic cross-clamping and efficient cardioprotection. Those were the initial steps towards the future developments of minimally invasive extracorporeal circulation technologies. Initial clinical results were clearly positive in terms of overall morbimortality. Moreover, several preliminary results pointed out the biological benefits that decreased hemodilution, improved preservation of the immune reactions and more stable anticoagulation could bring to the field of ECT.

Keywords: Extracorporeal circulation; cardiac surgery; minimally invasive; low-prime; inflammation; anticoagulation

Submitted Jan 23, 2019. Accepted for publication Feb 08, 2019.
doi: 10.21037/jtd.2019.02.19
View this article at: http://dx.doi.org/10.21037/jtd.2019.02.19

Whereas complete revascularization is necessary especially for high-risk patients, the surgical procedures, meaning coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB) technologies represented the reference treatment for this category of patients during the 90s (1,2). However, this therapeutic option also triggered severe adverse effects, like systemic inflammatory syndrome (SIRS) (3,4). Over the time increasing concerns raised about the postoperative side effects linked to CPB and cardiologists considered alternative approaches based on innovative catheter-based angioplasties. Such therapeutic strategies were not based on CPB assistance but operated on beating hearts. During the 90s significant improvements occurred in this field and coronary angioplasty became a key therapeutic strategy for patients with coronaropathies.

Independently of these technical evolutions, blood transfusion became a major issue in health care and more particularly in the context of cardiac surgery, where transfusion needs remained very high (ref. transfusion requirements in cardiac surgery). Side effects linked to blood transfusion have been identified more accurately and perioperative transfusion patterns might have led to inappropriate use of blood products. Therefore, medical strategies aiming at avoiding or at least reducing blood transfusion were developed. Over time the variability in transfusion practice has led to recommendations regarding

standardization within many countries (5).

The benefits of intraoperative autologous blood donation were not universally considered as a consistent and general strategy in order to reduce allogenic blood transfusion (6).

After the discovery of contamination of collected blood, the global management of blood collection and use of blood products was about to be deeply changed especially in France. Health care system integrated the notion that transfusion implies some intrinsic risk factors and a strong trend evolved towards reduction of the use of exogenous blood products during the perioperative periods (7-9). Cardiac surgery with CPB had high needs in transfusion of blood products and as such was considered to bear great risks for blood borne diseases.

Taken together a strong trend developed against the use of CPB, whenever possible. A large consensus among the community of cardiac surgeons appeared in favor of off-pump CABG (OPCABG) (10). New instruments were developed and rapidly, renewal of the old OBCABG techniques demonstrated positive results (11,12).

However, compared to standard CABG, OPCABG revealed that the number of grafts decreased, that some circumflex arteries were frequently more difficult to revascularize and that quite some procedure had to be converted to CPB assisted procedures. Coronary angioplasties underwent significant developments, but overall angioplasties remained less efficient than surgical procedures on the long-term.

Considering the complexity of the coronary pathology, a small number of cardiac surgeons, anesthesiologists, perfusionists and physiologists tried to reevaluate in depth the needs of circulatory assistance and cardioprotection during cardiac surgery.

Initial aims for new CPB techniques

The leading concept for improved CPB was decreased invasiveness, and more specifically low systemic inflammation after a surgical procedure involving CPB. A more conservative blood product management was an important part of the concept, partly based on low hemodilution. Improved anticoagulation management appeared as another key feature during the use of CPB. The balance between systemic anticoagulation and clotting is a major biological challenge. The physiological interphase the contact between blood and the vessel wall relies heavily on the integrity of the endothelial layer. Unlike these biological conditions, CPB introduces direct contact of non-biological materials to the blood and triggers thereby the coagulation cascade. This intrinsic adverse effect had been recognize since the early days and almost ever since treated by massive doses of heparin (13,14). Various coatings options were available aiming at improved management of the systemic anticoagulation strategies during CPB. Heparin-bonded coatings represented an important step in that direction (15,16). Moreover, we aimed at a patient-oriented anticoagulation strategy including on-site point-of-care technologies, even if still based on unfractionated heparin (UFH) (14).

Stable and efficient operative conditions for the surgeons were obviously a major issue in favor of the use of CPB *vs.* OPCABG.

Rapidly it appeared important to us that the option of aortic cross-clamping and cardiac arrest was a key step in developing an optimal CPB system. Therefore, the use of a simple and efficient cardioprotection was mandatory.

Initial attempts to set up a new CPB technique

During the mid-90s a multidisciplinary team headed by Olivier Bical in Paris started to develop a minimally invasive CPB system focusing on coronary surgery. The use of an assist device with a centrifugal pump served as the basis for the circulatory support. The idea to add circulatory support to OBCABG surgery was discussed at several meetings on cardiac surgery. The team at the University of Regensburg in Germany probably led the most active promoters of the concept of simple circulatory assistance during CABG. On the other hand, the Parisian team promoted since its origins the notion that cardiac arrest would allow best surgical conditions for optimal revascularization. Therefore, our strategy included the option for aortic cross clamping. After evaluation of several cardioplegic solutions, cardioprotection was mainly based on a blood cardioplegia solution (17-19). Common to other teams the circuit was based on short AV lines and no cardiotomy reservoir in order to reduce as much as possible hemodilution and thereby early transfusion requirements. Kinetic venous drainage with arterial pump flow allowed developing a compact closed circuit that could be installed close to the patient's chest. In order to improved biocompatibility all lines and oxygenator were coated. At these times mainly two types of coatings were commercially available. Heparin-coatings seemed to be more attractive with regards to anticoagulation strategies. However, technically speaking these coatings required several steps in order to caver the plastic support and

complex surfaces could not really be coated efficiently. On the other hand, inert coatings either lipid- or amphiphilic polymer-based had appeared. Such coatings allowed more extensive coatings, including complex surfaces. Our team in Paris favored the later solutions and as much as possible went for tip-to-tip coating, including the cannulae. Basically, our main aim was to decrease the activation of the intrinsic (contact phase) pathway of the coagulation cascade. Pharmacologically no specific drugs exist that could achieve this goal *per se*, but improving biocompatibility might help to achieve the goal.

To some extend the simplification of the circuit allowed some simplification of the monitoring. The fact that the concept was based on a closed veno-arterial loop, we considered that filters could be suppressed. A double sling purse secured a double-staged venous cannula in order to avoid blood leakage and air aspiration. Therefore, a rather simple way to de-air was included in the closed-loop circuit. Fundamentally, we did not include a venous reservoir into the main loop, considering that the best blood reservoir would be the venous capacitance of the patient.

Finally, one important evolution was to generalize separate management of shed blood by cell saving/washing device and retransfusion. From the perspective of coagulation, this approach was designed to reduce the blood concentrations of tissue factors that activate the extrinsic pathways of the coagulation cascade.

After multiple discussion about the surgical rationale and the physiological requirements a first circuit was designed around a low-prime centrifugal pump and a membrane oxygenator, no venous reservoir, with short 3/8" venous line and a short 3/8" arterial line. The circuit was placed closed to the shoulder of the patient. Initial prime volume was less than 500 mL.

First clinical experience was gained during the late 90s and progressively we could demonstrate not only the feasibility of CABG with such a minimal circuit and cardiac arrest, but more importantly the safety and absence of significant adverse effects. First presentation of the clinical results of the Parisian team was reported to the international community at the BelSect meeting in 2000 (20). Later presentations at the FECECT, the CREF, the EACTS and the AHA meetings confirmed the initial experience of the team in Paris (21-24). The Regensburg team reported similar experience in 2001 and thereby confirmed the general strategy based on a minimal CPB circuit (25). Clinical results were promising, and several other teams adhered to the concept. While the Regensburg team focused on CABG and developed their practice mainly in order to optimally reach this goal, the team in Paris was aiming at an extension of the notion of minimally invasive CPB. Several technical variations were implemented over time in order to allow open-heart surgery:

- A cardiotomy reservoir, with a Y connection to the main circuit, keeping a closed main loop and a side line converting to a partially open circuit.
- A venous line filter, with bubble detector and automated clamp, leading to improved air handling.
- The oxygenator design, hollow fiber design *vs.* membrane oxygenator; were modified at least in some clinical settings. Silicone membrane oxygenators have been the standard at the beginning of our developments, as they have excellent biocompatibility. They provide good gas-exchange characteristics, and they are relatively non-thrombogenic, but and cannot be coated with heparin. However, they have a high resistance to blood flow, so global efficiency remains modest. Moreover, they are difficult and time-consuming to prime. On the other hand, new generation of polymethylpentene hollow-fiber oxygenators do not develop significant plasma leak, have lower platelet consumption, and require limited blood product support. Hollow-fiber membrane oxygenators produce lower membrane pressure drops and pre- and post-oxygenator ECC pressures during normothermic CPB.
- Newer generation oxygenators with integrated arterial line filters might further improve the efficiency of CPB.
- Over time different centrifugal pump heads with various impeller designs were tested and concept of minimal invasive CPB design reveal to be robust and safe independently from any given material.

In a rather systematic fashion, we investigated not only the clinical benefits, but also some biological effects of the new way to proceed with minimal CPBs. From a clinical perspective, the use of such minimal circuit improved teamwork in the operation room. Hemodilution was reduced drastically and intra- as post-operative transfusion could be reduced significantly. Even if it was difficult to predict the management of the intra-operative hemodynamics, we did not observe increased use of vasoactive drugs. Specific management of shed blood by means of a cell collecting/washing device did not deeply change the usual way to proceed by our surgical team. Use

of blood cardioplegia had been implemented prior to the switch to minimal circuits but contributed largely to the reduced hemodilution. Nevertheless, the main arguments in favor of the blood cardioplegia were mainly its good efficiency, before considering reduced hemodilution. Port-operative management confirmed the good tolerance and improved hemodynamic stability in patients who underwent CABG with minimal CPB. Therefore, at least the team in Paris was confident to extend the experience to high-risk patients. Meanwhile our investigations of the biological effects of minimal CPB compared to standard CPB revealed some interesting features (23).

Reduced circuit length and suppression of the air-blood interface were implemented by design in order to obtain better biocompatibility. To further improve interaction between blood and non-biological surfaces we generalized the use of coatings. However, monitoring systemic inflammation at an early stage was not trivial at those times. Acute phase reaction could of course be monitored in a clinical setting by dosing C-reactive protein, but this represents mainly a delayed indicator and its biosynthesis can be triggered by many stimuli during a surgical procedure as complex as CABG, so it remains difficult to conclude on specific effects of the CPB circuit per se. Few pro-inflammatory biomarkers could be used in a non-research setting, but some allowed us to gain some insight on the biological effects of the new designed way to conduct extra circulatory support during cardiac surgery.

Another initial assumption was that improved blood management should lead to more stable anticoagulation profiles. Since the early days of the new minimal CPB, we paid quite some attention to optimize the anticoagulation profile. Our strategy was based on a patient-targeted dosing of UFH, with reversal of its effects by protamine at the end of surgical procedure. Even if UFH is far from having the optimal pharmacokinetic profile, it was the drug of reference in the context of cardiac surgery.

Limitations and developments

Several limitations have to be recognized linked to the initial design of the circuit. One has to acknowledge that increased pressure was put on the perfusion team as a short circuit implies also shorter reaction times towards changes in the hemodynamic conditions. This allows improved reaction times but needs closer collaboration between members of a multidisciplinary team around the patient. The absence of a venous reservoir implies that the venous capacitance represents a physiological reservoir of blood, thus the perfusion reserve is no longer extracorporeal. Some adjustments with reference to the classical management of the CPB had to be implemented. Given the excellent collaboration within the team in Paris, development went steadily. Sophistication of the circuit in order to extend the field of applications was implemented soon, i.e., blood volume displacement out of the main circulating loop (adding a reservoir). Similarly, we improved monitoring capacities (26) and continued to refine the anticoagulation strategies (27).

Conclusions

Data still highlight the deficiencies of the current knowledge base that physicians rely on to guide patient care during CPB, but in the 90s medical evidence based on clinical experience considered that CPB had multiple adverse effects that could be avoided by non-surgical treatments.

At the same time a few multidisciplinary teams in the cardiac surgery departments in Paris and Regensburg, started to develop an innovative new design of CPB circuits and the way to use them during surgical procedures in order to make them minimally invasive and provide optimal surgical support.

Whereas the team in Regensburg aimed at circulatory assistance during CABG procedures, the team in Paris intended to develop a full CPB system that allowed cardiac arrest. The conduct of adult CPB to achieve optimal perfusion was key in the new design of a minimal CPB circuit. The design of components of a CPB circuit may influence tissue perfusion and clinical outcomes. Given the theoretical advantages to centrifugal blood pumps over roller pumps the initial design included a compact centrifugal pump head. The kinetic venous drainage by arterial pump flow and short venous and arterial lines contributed to significant reduction of the priming volume and thus the intraoperative hemodilution. Our minimal circuit was based on a closed-loop perfusion system, without cardiotomy reservoir. Significant controversy related to appropriate management of physiologic variables during CPB remains and are not specific to minimal CPB circuits. No distinct clinical benefits have been observed when open venous reservoirs have been compared to closed systems. Nevertheless, multiple clinical trials have established the non-inferiority of minimal CPB circuit over conventional circuits. Moreover, systematic coating of the CPB circuit

may attenuate inflammation and coagulation pathways as minimal circuit have contributed to demonstrate.

Those were the early days of minimally invasive extracorporeal technologies (MiECT), and even if much has to be done to further improve the concept, one has to acknowledge that at least partly several of the basics of this innovative way to perform CPB have been integrated in a large proportion of more conventional CPB circuits.

Acknowledgments

The authors acknowledge the major contributions of Didier Gaillard, MD and Pablo Bua Novo to the initial development of the minimal circuit.

The authors are grateful to all the perfusionists of the department of cardiac surgery at the Groupe Hospitalier Paris St Joseph for their various contributions.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bical O, Braunberger E, Fischer M, et al. Bilateral skeletonized mammary artery grafting: Experience with 560 consecutive patients. Eur J Cardio-thoracic Surg 1996;10:971-5; discussion 976.
2. Uva MS, Braunberger E, Fisher M, et al. Does bilateral internal thoracic artery grafting increase surgical risk in diabetic patients? Ann Thorac Surg 1998;66:2051-5.
3. Taggart DP. Respiratory dysfunction after cardiac surgery: effects of avoiding cardiopulmonary bypass and the use of bilateral internal mammary arteries. Eur J Cardiothorac Surg 2000;18:31-7.
4. Kraft F, Schmidt C, Van Aken H, et al. Inflammatory response and extracorporeal circulation. Best Pract Res Clin Anaesthesiol 2015;29:113-23.
5. Stover EP, Siegel LC, Parks R, et al. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. Anesthesiology 1998;88:327-33.
6. Helm RE, Klemperer JD, Rosengart TK, et al. Intraoperative autologous blood donation preserves red cell mass but does not decrease postoperative bleeding. Ann Thorac Surg 1996;62:1431-41.
7. Perioperative red cell transfusion. National Institutes of Health Consensus Development Conference. Transfus Med Rev 1989;3:63-8.
8. Fresh frozen plasma: indications and risks. National Institutes of Health Consensus Conference. Transfus Med Rev 1987;1:201-4.
9. Consensus conference. Fresh-frozen plasma. Indications and risks. JAMA 1985;253:551-3.
10. Işik O, Ipek G, Daglar B, et al. Complete myocardial revascularization with left heart bypass without oxygenator on the beating heart. Eur J Cardiothorac Surg 1997;12:516-8.
11. Rivetti LA, Gandra SM. An intraluminal shunt for off-pump coronary artery bypass grafting. Report of 501 consecutive cases and review of the technique. Heart Surg Forum 1998;1:30-6.
12. Pym J. Off-pump arterial grafting: 125 cases using the Medtronic-Utrecht Octopus. Eur J Cardiothorac Surg 1999;16 Suppl 1:S88-94.
13. Despotis GJ, Joist JH, Goodnough LT. Monitoring of hemostasis in cardiac surgical patients: impact of point-of-care testing on blood loss and transfusion outcomes. Clin Chem 1997;43:1684-96.
14. Rosenberg RD. Biologic actions of heparin. Semin Hematol 1977;14:427-40.
15. Wildevuur CR, Jansen PG, Bezemer PD, et al. Clinical evaluation of Duraflo® II heparin treated extracorporeal circulation circuits (2nd version) The European working group on heparin coated extracorporeal circulation circuits. Eur J Cardiothorac Surg 1997;11:616-23.
16. Fosse E, Thelin S, Svennevig JL, et al. Duraflo II coating of cardiopulmonary bypass circuits reduces complement activation, but does not affect the release of granulocyte enzymes : a European multicentre study. Eur J Cardiothorac Surg 1997;11:320-7.
17. Bical OM, Gerhardt MF, Paumier D, et al. Effects of two different crystalloid cardioplegic solutions assessed by myocardial pH, tissue lactate content and energy metabolism. Eur J Cardiothorac Surg 1996;10:417-21.
18. Gaillard D, Bical O, Paumier D, et al. A review of myocardial normothermia: its theoretical basis and the potential clinical benefits in cardiac surgery. Cardiovasc Surg 2000;8:198-203.
19. Bical OM, Fromes Y, Paumier D, et al. Does warm antegrade intermittent blood cardioplegia really protect the heart during coronary surgery? Cardiovasc Surg 2001;9:188-93.

20. Gaillard D, Bical O, Deleuze P, et al. Alternative aux pontages aorto-coronaire sans CEC « La totale MECC ». In: BelSECT, editor. BelSECT. Brussels: BelSECT; 2000.
21. Fromes Y, Gaillard D, Ponzio O, et al. MECC. In: FECECT. Killarney, Ireland; 2001.
22. Fromes Y, Gaillard D, Ponzio O, et al. Minimal extra corporeal circulation (MECCTM) triggers reduced inflammatory response following coronary bypass grafting. In: AHA. Anaheim, CA, USA: American Heart Association, Inc.; 2001.
23. Fromes Y, Gaillard D, Ponzio O, et al. Reduction of the inflammatory response following coronary bypass grafting with total minimal extracorporeal circulation. Eur J Cardiothorac Surg 2002;22:527-33.
24. Gaillard D, Fromes Y, Ponzio O, et al. Clinical experience with total minimal extracorporeal circulation for coronary grafting. In: 22 nd Annual San Diego Cardiothoracic Surgery Symposium. San Diego, CA, USA: CREF; 2002.
25. Philipp A, Foltan M, Thrum A, et al. MECC - Ein minimiertes EKZ-system für ACB-operationen. Kardiotechnik 2001;10:14-9.
26. Bical OM, Fromes Y, Gaillard D, et al. Comparison of the inflammatory response between miniaturized and standard CPB circuits in aortic valve surgery. Eur J Cardiothorac Surg 2006;29:699-702.
27. Fromes Y, Daghildjian K, Caumartin L, et al. A comparison of low vs conventional-dose heparin for minimal cardiopulmonary bypass in coronary artery bypass grafting surgery. Anaesthesia 2011;66:488-92.

Cite this article as: Fromes Y, Bical OM. MIECT: How did it start? J Thorac Dis 2019;11(Suppl 10):S1492-S1497. doi: 10.21037/jtd.2019.02.19

