7

Miniaturized Extracorporeal Circulation

Francesco Formica and Giovanni Paolini
Cardiac Surgery Clinic, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy

1. Introduction

Since the first cardiac surgical operations in the early '50s, the early and long-term outcomes have been dramatically improved also because of the refinement of technology regarding the extracorporeal circulation (ECC). It is recognized the ECC is associated with a systemic inflammatory response (SIRS), which is implicated in myocardial, renal, pulmonary and neurologic dysfunction. However, although the effects of ECC are very often subclinical, in some situations they can be responsible of worse outcome in the early post-operative period. In the early 1990s, many surgeons started to perform coronary revascularization without the use of ECC with the aim of strongly reducing the subclinical and clinical effects of the SIRS. Over the past fifteen years, the "off-pump" coronary artery bypass grafting (OPCABG) has demonstrated to have good results by reducing postoperative morbidity and mortality. On the other hand, the OPCABG presents some drawbacks such as the significant learning curve of the surgeon, the high rate of incomplete revascularization in dilated and hypokinetic heart due to very difficult exposure of obtuse coronary marginal branches and the lesser quality of the coronary anastomosis.
Over the past 10 years, concepts of miniaturized extracorporeal circulation (MECC) were developed with the aim of reducing the side effects of the standard ECC, strengthening the advantages of ECC and eliminate the limitations of OPCABG. In other words, the MECC joins the best of ECC with the best of "off-pump" surgery.

2. Anatomy of the miniaturized extracorporeal circulation system

Different types of MECC circuits are on the market and although they can have some differences among them in terms of characteristics of blood pump, oxygenator membrane, length of tubing, arterial and venous filters, the principle key is substantially equal for each system: closed circuit without a venous cardiotomy reservoir.
The MECC circuit consists of a closed loop, which includes the oxygenator and the pump. The circuit has not any open venous reservoir. All components of MECC circuit are pre-treated with heparin according to different techniques available on the market. The heparin pre-treatment of the circuit minimizes the systemic heparinization dose requirements (usually half dose of conventional ECC: 150IU/Kg instead of 300IU/Kg) (Curtis et al. 2010; Formica et al. 2009, Puheler et al. 2009; Beghi et. 2006) and provides biocompatibility for blood cells (Koivisto et al. 2010; Remadi et al. 2007; Remadi et al. 2004; Fromes et al 2002;)

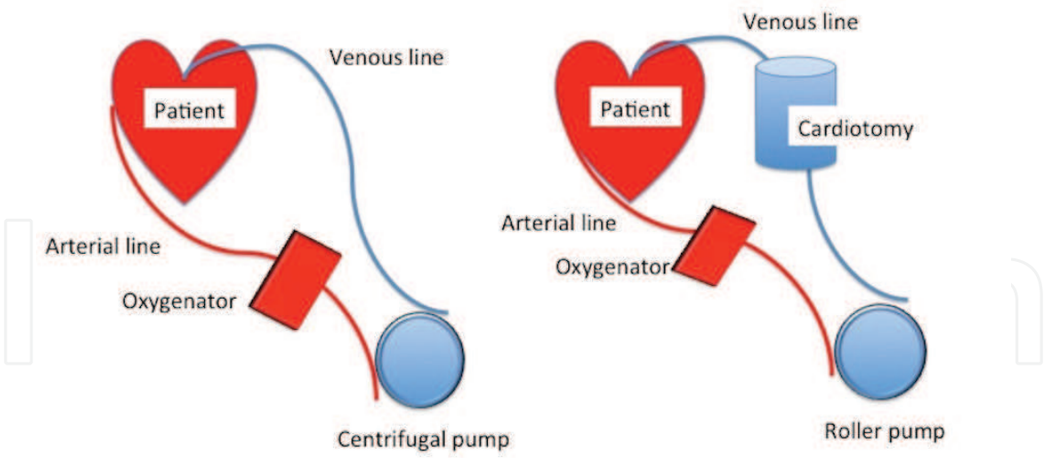

Fig. 1. Miniaturized extracorporeal circuit on the left and conventional extracorporeal circulation on the right

The tubing length is described to be shorter than conventional ECC in different published reports. Tubing length of about 100 cm is frequently reported as well as a smaller tubing section than conventional ECC tubing (3/8″ size instead of 1/2″ size) (Formica et al 2009; Mazzei et al 2007). These characteristics lead to a circuit prime volume smaller than standard ECC, ranging between 200-650 ml for the MECC against 1200-1600 ml for the standard ECC (Formica et al 2009, Stalder et al. 2007; Remady et al. 2006). The combination of short length tubing, heparin pre-treatment, small size tubing and absence of a venous reservoir, leads to a significant reduction of hemodilution with as well as a reduction in clotting factor consumption ad triggering of SIRS (Vohra et al 2009; Ohata et al. 2007; Wippermann et al. 2005; Fromes et al. 2002). The blood pump included in the circuit is usually a centrifugal pump. The centrifugal pump is a very versatile pump, which reduces the cells trauma on the erythrocytes, and the platelets with possible lower effects on hemolysis. Moreover the centrifugal pump can generate up to 900 mmHg of forward pressure and only 400 mmHg of negative pressure with less cavitation and lower microemboli formation. The oxygenator of the MECC circuit is one of the most important components of the circuit itself. Oxygenators have the oxygenation membrane of either microporous polypropylene (El-Essawi et al. 2010; Wippermann et al. 2005) or polymethylpentene (Anastasiadis et al. 2011; Puehler et al. 2010; Formica et al. 2009; Remady et al 2006;). In the latter case the membrane is considered as a diffusion membrane Usually the oxygenator has an integrated heat exchanger and one of the largest gas exchange surface areas, reaching about 2.4 m^2. In this way the oxygenator can give a full oxygenation also with high blood flow pump up to 7 L/min.

Many MECC circuits include an arterial filter between the oxygenator and the aortic cannula. The filter has a prime ranging between 150-200 ml but its presence is of extreme importance because strongly reduce the risk of cerebral and systemic embolization or air, thrombus and calcium. Moreover some MECC circuits include a venous bubble trap or some similar device with the aim of reducing the big air entrainment in the circuit that could be one of the causes of accidental blockage of the MECC circuit. These devices are located between the venous cannula and the blood centrifugal pump.

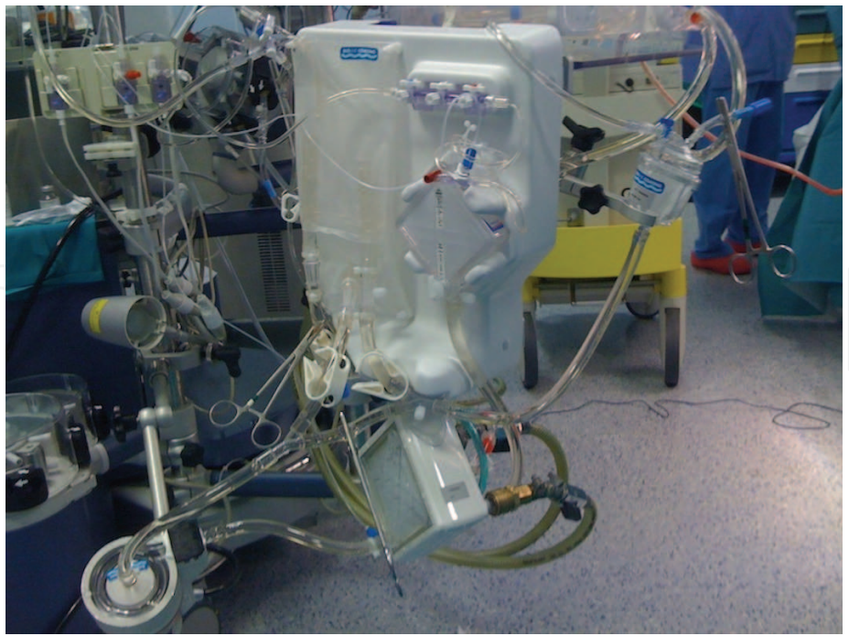

Fig. 2. MECC system.

Aortic and atrial cannulation are equal to conventional ECC. Usually an aortic vent is positioned in ascending aorta and a further vent is inserted in the pulmonary main trunk during aortic valve surgery.
A cell-saver device can be associated with the MECC with the aim to sucked all the pericardial and bloodshed.
The very strong difference between the MECC and the standard ECC circuit is the absence of a venous reservoir. In the MECC, the patient is the own venous reservoir and for this reason the straight collaboration among the cardiac surgeon, the anaesthesiologist and the perfusionist is extremely important to guarantee the best outcome. Use of vasodilator and vasoconstrictor drugs, Trendelemburg or anti-Trendelemburg position of the patient, reducing or increasing the centrifugal pump flow are all fundamental keys to manage a MECC system with the aim to avoiding malperfusion syndrome, systemic embolization, failure of the MECC and rapid conversion to standard ECC.

3. Systemic inflammatory response

The Systemic Inflammatory Response Syndrome (SIRS) is a complex plurifactorial syndrome often associated with the ECC. The SIRS to ECC is initiated by many aggressive factors including surgical trauma, blood contact with nonendothelial sufaces, cardioplegia, ischemia-reperfusion injury (Raja & Berg, 2007; Larmann & Theilmerr, 2004; Royston, 1997). Several blood elements such as neutrophils, monocytes, endothelial cells, platelets and complement proteins are involved in the SIRS. These blood components when activates, release of cytotoxic and vasoactive substances, produce inflammatory and inhibitory cytokine, express cell receptors interacting with specific cellular substance (Royston 1997). Therefore when SIRS is initiated, several inflammatory mediators, including anti-inflammatory and pro-inflammatory cytokines could be associated with a worse postoperative course.

3.1 Activated blood cells

3.1.1 Neutrophils

Neutrophils are strongly activated during ECC. When activated, the neutrophils are recruited to inflammation site by inflammatory cytokines (IL-1β, TNF-α, IL-8), complement proteins and adhesion molecules (Royston 1997). The activated neutrophils can contribute to myocardial damage by infiltrating the myocardium and worsening the mechanism of ischemia-reperfusion damage that initiates after aortic cross clamp removal (Paparella et al 2002). Moreover the neutrophils can infiltrate not only the myocardium but also the lungs and the brain (Lagan et al. 2008). Usually the neutrophils blood count and the total white blood cell count increase during ECC and over the first 48 hours after the operation (Fromes et al 2002)

3.1.2 Monocytes

Monocytes are activated during ECC and play a role in thrombin formation, but also they can produce a potent arsenal of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-8, MCP-1 and CD40 ligand), reactive oxygen substances and prostaglandin (Borregaard & Cowland 1997). Monocytes also release different types of enzymes (elastase, collagenases, lipooxygenase), interferons, growth factors, matrix proteins. Moreover, monocytes produce nitric oxide (Paparella et al. 2002)

3.1.3 Endothelial cells

The vascular endothelium is actively involved during the pathologic processes of the SIRS by means of endothelial cells activation. During the SIRS the several endothelium control mechanisms of the vascular tone and permeability can modify. A large variety of agonist plays an important role in endothelial cells activation. Among them cytokines such as IL-1β, TNF-α, thrombin and complement C5 are the most important (Beghetti et al. 1998). In particular, IL-1β, TNF-α may induce the expression of P-Selectin and of E-Selectin by the endothelium. The P-Selectin is a glycoprotein that is stored in platelets and in the body of endothelial cells. P-Selectin participates in myocardial injury caused by myocardial ischemia-reperfusion mechanism (Robertson & Coopersmith 2006; Royston 1997). E-Selectin is minimally expressed on activated endothelium and for this reason this glycoprotein and its soluble form are considered a very strong marker of endothelial damage and activation (Asimakopoulous & Taylor 1998). Moreover E-Selectine is elevated in congestive heart failure (Chong et al. 2003). The activated endothelium induces also the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-2 (VCAM-2). These two molecules bind monocytes and neutrophils to the endothelium (Asimakopoulous & Taylor 1998).

3.1.4 Platelets

Platelets are directly involved during the SIRS and several potent platelet agonists activate them. Thrombin is probably the most important of platelet agonist. Other platelet agonist activators are epinephrine, vasopressin, platelet-activating factor (PAF), serotonin and thromboxane A2 (Downing & Edmunds. 1992). Activation of platelets during and after ECC leads to platelet aggregation and aggregates with monocytes and neutrophils.

3.2 Other inflammation mediators

3.2.1 Cytokines

Cytokines are small pro-inflammatory peptides produced and released by tissue and blood cells. Cytokines influence hemodynamic mechanism and regulation and negatively affect

renal function and lung function (Royston 1997). Cytokines are strongly involved in myocardial stunning process and in multiorgan failure syndrome (Larmann & Theilmeier 2004) Important cytokines involved in the SIRS are the interleukin 1β (IL-1β), the interleukin 6 (IL-6), the tumor necrosis factor α (TNF-α), soluble CD 40 ligand (sCD40L).
IL-1β is produced mainly by monocytes. This cytokine derives from IL-1 by the action of the IL-1β converting enzyme. An increase of IL-1β was found after ECC with a peak concentration after 24 hours (Fromes et al 2002).
IL-6 is produced and released by the monocytes and endothelial cells following a stimulus by the IL-1 and TNF-α The IL-6 has the peak concentration few hours after the end of ECC and gradual decrease within the following 24 hours (Beghi et al 2006; Whipperman et al 2005; Fromes et al 2002). The IL-6 concentration increase also after major noncardiac operation and the peak concentration occur after 6-24 hours the end of operation.
TNF-α is a cytokine produced by neutrophils and monocytes. This cytokine stimulates the surrounding stromal and parenchymal cells to produce more cytokines and chemokines. A significant increase of TNF-α was shown after removal of the cross-clamp and a peak concentration is reached after 24 hours the end of ECC. The TNF-α has an inotropic negative effect and the myocardium is a major source after ischemia reperfusion injury.
sCD40L is produced by activated platelets and upregulates the expression of inflammatory adhesion receptors including E-selectin, VCAM-1, tissue factor and matrix mettalloproteinases (Nannizzi-Alaimo et al 2002). Furthermore, sCD40L was described has a major mediator of vascular inflammation (Antoniades et al 2009a). Plasma levels of CD40L increase within 1 hour on ECC and increased further to almost 4 fold hours after 2 hours. (Nannizzi-Alaimo et al 2002). High preoperative level of CD40L were associated with an high risk of postoperative atrial fibrillation in patients underwent off-pump myocardial revascularization (Antoniades et al 2009b)

3.2.2 Chemotactic proteins

Chemotactic proteins play an important role in inflammatory response to ECC. Monocyte chemotactic protein 1 (MCP-1) is implicated in transendothelian monocyte recruitment to inflammatory site (Luster 1998). Various stimuli in the heart cause the production and releasing of MCP-1, leading to recruitment of monocytes that causes a stress response in the heart. There is strong evidence that MCP-1 plays a role in atherosclerosis, myocarditis, ischemia/reperfusion injury and transplant rejection.

3.2.3 Mettalloproteinases

Metalloproteinases are proteolityc enzymes that have a role in degradation of proteins and collagens of extracellular matrix and vascular basement membrane. MMP-8 and MMP-13 increase at the end of ECC and 30 minutes later (Joffs et al. 2001). MMP-9 increases after the removal of aortic cross-clamp and the reaches the peak concentration after 24 hours

3.2.4 Oxidative stress

Oxidative stress describes an increased bioactivity of reactive oxidant substances (ROS) that can participate to endothelial and myocardial damage. The ROS are produced and released by neutrophils, monocytes and macrophages when they are activated. The ROS are a potent arsenal of cytotoxic mediators of acute inflammation response (Babior 2000). There are four enzymes that generate a various amount of ROS. They are represented by nicotamide

adenine dinucleotide phosphate (NADPH), oxidase, superoxide dismutase and nitric oxide dismutase. When the aortic cross clamp is removed, myocardial ischemia is followed by reperfusion, which generates oxidative stress with production of reactive oxidants (O_2^-, H_2O_2, NO and HOCl) by the action of the four enzymes.

4. Clinical application of miniaturized extracorporeal circulation

Clinical experience with the MECC is rapidly increasing over the last 10 years. Several reports describe the application of MECC in isolated CABG operation; however some reports describe the use of this strategy during aortic valve replacement operation, mitral valve surgery, ascending aorta operation.

4.1 Miniaturized extracorporeal circulation and isolated CABG operation

Different studies have reported the use of MECC compared to conventional ECC strategy in isolated CABG to demonstrate a clinical superiority of the MECC versus ECC. Actually no clinical benefits of MECC were reported in terms of early mortality and in terms of neurological or renal impairment. The most important differences between MECC and standard ECC that were reported regard the impact of SIRS, the myocardial protection and hemodilution.

Many Authors have conducted randomized studies to compare MECC system with conventional ECC in patients undergoing isolated CABG operations. Fromes et al. (Fromes 2002) reported a series of 60 patients divided into two groups. They demonstrated that in both MECC and standard ECC groups the monocyte count drops following the initiation of bypass and then increases again during the next 24 hours. The drop in monocyte count was greater in standard ECC group probably as a consequent major hemodilution Moreover the MECC group had reduced release of IL-6, TNF-α, neutrophil elastase and S100B. No differences were found in IL-1β or β-thromboglobulin in both groups. In this study Fromes et al measured the release of cytokines at six interval points during and after extracorporeal circulation up to 24 hours postoperatively. Van Boven et al. (Van Boven et al. 2004) measured the levels of malondialdehyde (MDA) and allantoin/urate ratio in 184 patients divided in MECC and standard ECC. They can demonstrate a reduced release of MDA and allantoin/urate ratio in MECC patients. Moreover a significant blood transfusion rate was described in the MECC group. They found also reduced levels of oxidative stress in the MECC patients following the release of the aortic cross clamp. In a cohort of 400 patients, Remady et al. (Remady 2007) demonstrated a higher CRP levels in the standard ECC patients, at 24 and 48 hours, a less hemodilution and a reduced need for blood product transfusion in MECC patients, a higher evidence of focal neurological and renal impairment in standard ECC and a lower release of troponine in MECC groups. In another randomized trial, Skrabal et al (Skrabal et al. 2007) reported lower myocardial damage with lower levels of creatine-kinase MB and troponine T in patients operated on with MECC system. In a prospective randomized multicenter study (El-Essawi et al. 2010), comparing MECC system with conventional ECC, the Authors found statistical differences in need of total transfusion and blood product transfusion. Moreover a lower incidence rate of postoperative atrial fibrillation was detected in MECC group. In a big series of 1.053 patients operated on with the MECC system, Immer et al (Immer et al. 2007) reported a reduced troponine level release, a

reduced postoperative release of IL-6 and also a low incidence of postoperative atrial fibrillation and an early extubation time. Similar results were already reported by others (Wiesenack 2004). In some prospective randomized trials comparing MECC and OPCAB, some Authors did not find dramatic difference between the two techniques. In particular Mazzei et al. (Mazzei et al. 2007) comparing 150 MECC patients with 150 OPCAB patients, found that the mortality and morbidity had not significant difference and the release of IL-6 and S-100 protein were similar in both groups as wel as the length of stay and the use of blood product. In a recent prospective randomized study (Formica et al.2009) we wanted to study the inflammatory response and the myocardial damage in two groups of patients operated either with MECC or with OPCAB technique. We can demonstrate that the releases of cardiac TNF-α and IL-6 from coronary sinus were similar in both groups during the operative period and that the hemoglobin levels were higher in MECC GROUP than in OPCAB after 24 hours. Moreover the production of blood lactate from coronary sinus did not reach statistical difference in both groups. Other Authors (Reber et al. 2010) have observed in a retrospective study that MECC system can guarantee a more complete revascularization compared to OPCAB. In a recent publication (Puelher et al 2011), the outcome of 2243 patients underwent CABG operation with MECC were reported. They found a 30-mortality of 2.3%, and a very low incidence of blood transfusion, need for inotropic support, renal substitute therapy, release of myocardial necrosis enzymes and neurological dysfunction. The rate of conversion from the MECC was extremely low (0.4%).
Other Autrhors (Anastasiadis et al 2011a) have reported better neurocognitive outcome in MECC system compared to conventional ECC on the day of discharge and at 3 months.

4.2 Miniaturized extracorporeal circulation and aortic valve replacement

The first application of MECC for aortic valve replacement (AVR) was reported by Remady et al (Remady et al. 2004). They applied the MECC system in 45 patients requiring isolated AVR or associated with CABG. The Authors reported a very low 30-day mortality and morbidity incidence rate and considered the MECC system a new cardiopulmonary concept safe and reliable in aortic valve surgery too. Since than few Authors reported the use of MECC for AVR. In a prospective randomized study Remady et al (Remady 2004) reported better clinical results with reduced myocardial damage, good preservation of renal function and better platelets count in MECC group compared than standard ECC group. In another prospective randomized study conducted on a total of 40 patients, Castiglioni et al (Castiglioni et al. 2007) reported better clinical data with lower hemodilution, lower intraoperative blood transfusion and lower postoperative bleeding in the MECC group compared to standard ECC. Furthermore they reported a lower release of troponine in MECC patients than standard ECC groups.

4.3 Miniaturized extracorporeal circulation and other surgical applications

At the best of our knowledge no other surgical application of MECC are schematically reported in the literature. Some reports (Anastasiadis et al 2011b; Palombo et al. 2004) described the use of MECC in elective thoracoabdominal aortic surgery. They described only 7 cases without any complications. We used the MECC system in few case of CABG associated with mitral valve annuloplasty and in 5 cases of kidney cancer and inferior vena

cava metastathic thrombosis. In this operation, we used the MECC system to cool the patients during the isolation of renal tumor mass. The two surgical equips could work contemporaneously. Once the patients reaches the body temperature of 20 °C, the MECC system was converted in a standard ECC to drained all the blood and arrested the systemic circulation. Once the thrombus was from the inferior vena cava and the vessel was sutured, we restarted the systemic circulation and the standard ECC was converted in MECC system. We preferred to use this strategy to reduce the risk of bleeding from the abdomen, which is very high in such tumoral pathologies.

5. Conclusion

We did not find in the literature significant differences in terms of clinical results regarding post-operative mortality. One of the reasons is because the MECC strategy is widely applied in low risk populations and only few Authors describe the use of MECC in high-risk patients (Puehler 2011, Koivisto 2010). At the moment, most of the clinical benefits with the use of MECC were seen in the SIRS, hemodilution, platelet function protection.

The good amount of data described in favor of MECC could induce to apply this strategy in more cardiac surgical operations. However, the MECC system presents some limitations that create some concern about a wider use of this technique. One important limitation is high risk of air entrapment along the venous line that could suddenly stop the cardiopulmonary bypass. Another limitation is the need of learning curve because, as well as in the OPCAB, the MECC technique requires an experienced team (surgeon, anesthesiologist and perfusion) before to be applied routinely in all CABG patients and by all surgical staff.

We feel that the MECC technology gives better advantages than standard ECC and we feel that MECC could be applied to other surgical procedures. Of course more randomized, large, multicenter studies are mandatory to verify the safety of this technology in such cardiac complex surgical operation (aortic dissection, congenital disease).

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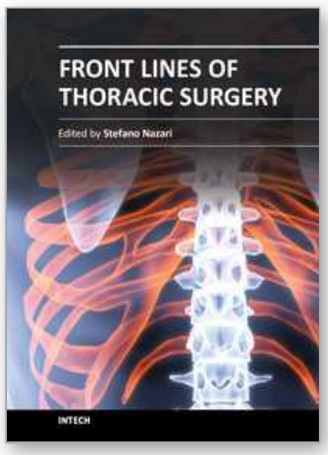

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Front Lines of Thoracic Surgery collects up-to-date contributions on some of the most debated topics in today's clinical practice of cardiac, aortic, and general thoracic surgery,and anesthesia as viewed by authors personally involved in their evolution. The strong and genuine enthusiasm of the authors was clearly perceptible in all their contributions and I'm sure that will further stimulate the reader to understand their messages. Moreover, the strict adhesion of the authors' original observations and findings to the evidence base proves that facts are the best guarantee of scientific value. This is not a standard textbook where the whole discipline is organically presented, but authors' contributions are simply listed in their pertaining subclasses of Thoracic Surgery. I'm sure that this original and very promising editorial format which has and free availability at its core further increases this book's value and it will be of interest to healthcare professionals and scientists dedicated to this field.

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University Campus STeP Ri
Slavka Krautzeka 83/A
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
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