Diploma Thesis

P-MEC – Pediatric Minimal Extracorporeal Circulation

First clinical experience using a newly established closed miniaturized bypass circuit as a new perfusion technique for pediatric cardiac surgery

Submitted by

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Declaration in Lieu of an Oath

I, hereby, declare in lieu of an oath that I have produced the following thesis independently and without using any other than the aids listed. Any thoughts directly or indirectly taken from somebody else's sources are made discernible as such.

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Glossary

ACCP/SCCM	American College of Chest Physicans/Society of Critical Care Medicin
ACT	activated clotting time
AKI-CPB	acute kidney injury after cardiopulmonary bypass
AKIN	Acute Kidney Injury Network
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
ASD	atrial septal defect
ASP	acylation stimulating protein
AT III	antithrombin III
BSA	body surface area
CABG	coronary artery bypass graft
CECC	conventional ECC
CK-MB	creatine kinase-muscle brain type
CLS	capillary leak syndrome
CPB	cardiopulmonary bypass
CRP	C-reactive protein
ECC	extracorporeal circulation
ECMO	extracorporeal membrane oxygenation
ELAM	endothelial leukocytes adhesion molecule
GFR	glomerular filtration rate
GME	gaseous microembolism
HBC	heparin-bonded circuits
HLM	heart-lung machine
HRH	hypoplastic right heart
ICAM	intercellular adhesion molecule
ICU	intensive care unit
IVC	inferior vena cava
KAVD	kinetic-assisted venous drainage
MINI-ECC	miniaturized extracorporeal circulation
MOD/MOF	multiple organ dysfunction/failure
MRI	magnetic resonance imaging

MUF	modified ultrafiltration
NIRS	near-infrared spectroscopy
P-MEC	pediatric-miniaturized extracorporeal circulation
PaO2	partial pressure of oxygen in arterial blood
POCT	point-of-care testing
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
RHS®	Resting Heart System
RPM	revolutions per minute
RRT	requiring renal replacement therapy
RVOT	right ventricular outflow tract
SaO2	arterial oxygen saturation
SeptEctShunt	atrial septectomy and shunt ligation
SIRAB	systemic inflammatory response after bypass
SIRS	systemic inflammatory response syndrome
SVASD	sinus venosus atrial septal defect
SVC	superior vena cava
SvO2	mixed venous oxygen saturation
SVR	systemic vascular resistance
TAPVR	total anomalous pulmonary venous return
TCPC	total cavopulmonary connection
TGA	transposition of the great arteries
TNFα	tumor necrosis factor-α
UFH	unfractionated heparin
UVH	univentricular heart
VARD	vacuum air removal device
VCAM	vascular adhesion molecules
VSD	ventricular septal defect

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Zusammenfassung

GRUNDLAGEN: Geschlossene minimierte extrakorporale Zirkulationssysteme (mini-ECC) haben sich im Hinblick auf ihre schädlichen Wirkungen auf den Organismus des Patienten als vorteilhaft erwiesen. Das ist bedingt durch das verringerte Primingvolumen und der gedämpften Entzündungsreaktion im Vergleich zum konventionellen offenen kardiopulmonalen Bypass (CPB). Ausgehend von den überzeugenden Ergebnissen der mini-ECC Systeme, beschäftigt sich die aktuelle Forschung mit der Miniaturisierung des CPB-Aufbaus für den Einsatz in der Kinderherzchirurgie. Um die CPB-assoziierte Immunreaktion zu dämpfen und dem extremen Missverhältnis zwischen dem Füllvolumen und dem Gesamtblutvolumen der Kinder gerecht zu werden, ist eine spezielle Anpassung des CPB-Aufbaus notwendig. Wir berichten über die ersten klinischen Erfahrungen mit der Anwendung des neu eingeführten, geschlossenen Bypasssystems als neue Perfusionstechnik für die Kinderherzchirurgie.

METHODEN: Von August 2011 bis September 2013 wurden vierzehn Kinder mit einem Körpergewicht zwischen 6,3 und 18,7 Kilogramm und einem Durchschnittsalter von 2,9 ± 1,6 Jahren mit dem neuen pädiatrischen minimierten extrakorporalen Zirkulationssystem (P-MEC) operiert. Das neu entwickelte P-MEC ®-System zeichnet sich durch einen geschlossenen Kreislauf mit einem Low-Prime Oxygenator, einem durchschnittlichen Füllvolumen von 250 ml und der Möglichkeit einer notfallmäßigen Umstellung auf einen offenen Bypass aus. Um die Qualität der Perfusionsflussrate und den Grad der Blutverdünnung zu validieren, wurden die Laktat- und Hämatokritwerte prä-, intra- und postoperativ gemessen. Wir waren auch am Bedarf an homologen Bluttransfusionen, am alternativen Füllvolumen für den konventionellen Bypass und am klinischen Outcome inklusive chirurgischer oder embolischer Komplikationen sowie am Follow-up interessiert.

RESULTATE: Eine notfallmäßige Umstellung auf einen offenen herkömmlichen Bypass war nicht notwendig. Weder ein Todesfall noch andere postoperative Komplikationen wie Embolien, Sepsis oder Reoperation aufgrund von übermäßigen Blutungen traten bei einem der 14 Patienten auf. Die durchschnittliche Bypassdauer lag bei 72 Minuten mit einer mittleren Aortenklemm-Zeit von 13 Minuten. Die Hämatokritkonzentration betrug durchschnittlich 36 % vor dem Bypass, 28 % bzw. 26 % am Bypass und 28 % nach der extrakorporalen Zirkulation. Nur ein Kind erhielt 120 ml Erythrozytenkonzentrat nach Beendigung des Bypasses, die anderen Operationen wurden ohne Fremdblut durchgeführt. Alle Patienten hatten einen unauffälligen postoperativen Verlauf und ein

zufriedenstellendes Langzeit-Follow-up.

FAZIT: Höhere Hämatokritkonzentrationen und niedrigere Laktatwerte während des Bypasses, reduzierter Transfusionsbedarf und gute klinische Ergebnisse ohne den Verlust von Sicherheitsstandards sind die günstigen Eigenschaften des neuen P-MEC®-Systems.

Abstract

BACKGROUND: Closed miniaturized extracorporeal circulation (mini-ECC) systems proved to be beneficial in terms of the deleterious effects on the patient´s organism due to its reduced priming volume and lowered inflammatory response compared to conventional open cardiopulmonary bypass (CPB). Based on the convincing mini-ECC results current research deals with the miniaturization of the CPB setup for usage in pediatric cardiac surgery. To attenuate the CPB-associated systemic immune reaction and to cope with the extreme mismatch between the CPB priming volume and total blood volume of the children, a special adjustment of the CPB setup is required. Here we report on the first clinical experiences with the application of the newly established closed miniaturized bypass circuit as a new perfusion technique for pediatric cardiac surgery.

METHODS: From August 2011 to September 2013, fourteen children with a body weight between 6.3 and 18.7 kilograms and a mean age of 2.9 ± 1.6 years underwent congenital cardiac surgery using the new pediatric-miniaturized extracorporeal circulation (P-MEC) system. The recently developed P-MEC® system is characterized by a closed circuitry with a low-prime oxygenator, an averaged priming volume of 250 ml and the possibility of emergency conversion to open bypass. To validate the quality of the perfusion flow rate and the degree of hemodilution, lactate and hematocrit values were measured pre-, intra- and postoperatively. We were also interested in the demand of homologous blood transfusions, the alternative priming volumes for conventional bypass and the clinical outcome including surgical or embolic complications plus 6-months follow-up

RESULTS: An emergency conversion to an open conventional bypass was not necessitated. Neither death nor any other postoperative complications including embolism, sepsis or reoperation due to excessive bleeding, occurred in any of the 14 patients. The average CPB duration was 72 minutes, with a mean aortic cross clamp time of 13 minutes. The hematocrit concentration averaged 36 % before bypass, 28 % respectively 26 % on bypass and 28 % after extracorporeal circulation. Only one child received 120 ml pRBCs after cessation of bypass, the other surgeries were performed without foreign blood transfusions. All patients presented an uneventful postoperative course and a satisfying long-time follow-up.

CONCLUSIONS: Higher hematocrit concentrations and lower lactate levels on bypass, reduced transfusion requirements and good clinical outcome without the loss of safety standards are the favorable features of the novel P-MEC® system.

1. Introduction

The era of cardiac surgery started with the pioneering work of Dr. John Gibbon and his development of an heart-lung machine for extracorporeal cardiopulmonary bypass. This milestone in the history of medicine, enabled the surgeons to perform cardiac surgery on the open heart while total cardiac arrest. Since Dr. Gibbon´s first successful closure of an ostium secundum atrial septal defect by using CPB in 1953, the technical setup of the HLM as well as the surgical procedures have been enhanced enormously. By 1958, John Kirklin already had performed more than 240 cardiac surgeries with extracorporeal circulation and an advanced Gibbon-IBM heart-lung machine. Also the technical improvement of the various components of the HLM has been pushed forward during the following decades. The damaging impacts of extracorporeal circulation to the patient´s body were analyzed for better understanding. The membrane oxygenators fully replaced the bubble oxygenators in the 1990s. This change helped to perform CPB in a safer way without the imminent risk of bubbling and air embolism due to direct blood-to-gas interface. Massive hemodilution caused by large priming amounts has a negative influence on the patient, regarding his hematocrit values and blood coagulation. With constant enhancement of CPB techniques, deficits were eliminated and extracorporeal circulation by CPB is routinely used in today´s cardiac surgery worldwide. The standardized HLM circuit is suitable for most cardiac surgical interventions in adults. But certain procedures or pediatric patients often require a modification of the CPB circuitry, adapted to the specific surgical needs or to patient size. Especially the pediatric patient population needs special adjustment of the CPB setup, to cope with the extreme mismatch between the CPB priming volume and total blood volume of the neonate or premature baby. Therefore, current research deals with miniaturization of the CPB setup, to attenuate the deleterious effects of cardiopulmonary bypassing in pediatric cardiac surgery.

1.1. Historical development of cardiopulmonary bypass

The idea of artificial perfusion of organs and tissues was not new at the time of Dr. John Gibbon. In 1812, Cesar-Julian-Jean LeGallois proposed, that parts of the body could be preserved by creating an artificial blood flow through the tissue with an external perfusion device [2]. In the middle of the 19th century, Charles Eduard Brown-Sequard demonstrated that oxygenated blood is needed for a successful perfusion [3], [4]. So the scientists

worked out several ways of oxygen supplement. But all failed as a result of gas embolism and too much damage to the blood cells. Only the filming method, first proclaimed by Max von Frey and Max Gruber 1885 in Leipzig, built the basis for today´s techniques. They established the hypothesis, that a thin film of blood exposed to oxygen would provide a good mechanism for gas exchange [5]. So, the basic ideas for extracorporeal circulation had their origin in the 19th and 20th century. In 1929 the Russian scientist Sergei Brukhonenko was the first to describe the idea, that artificial circulation of blood could be used to replace the human heart or to perform operations while the heart is temporarily arrested [6]. Charles Lindbergh and Alexis Carrel worked in the 1930s on a pumping apparatus for organ perfusion, but they had no solution for problems such as blood clotting, hemolysis and infection. They were more keen on building a mechanical heart pump and disregarded the need for mechanical oxygenation of the blood. And the demand for oxygenated blood should not stay the only obstacle on the way to a working cardiopulmonary bypass with a sufficient heart-lung machine. Important steps in the history of medicine had to be achieved before clinical implementation of cardiopulmonary bypass by extracorporeal circulation:

- mechanical ventilation
- discovery of the blood type system
- possibility of temporary interruption of venous return to the heart
- discovery of the correlation between body temperature and metabolic rate
- development of a reliable anticoagulant and its antagonist: heparin and protamine
- improvement of preoperative diagnostic technology including cardiac catheter, computer tomography, magnetic resonance imaging, 3D sonography
- profound knowledge of cardiac pathologies and intracardiac malformations
- adapted postoperative care on advanced intensive care units

Dr. John Gibbon started his research for a workable heart-lung machine in 1930, when he was forced to see a young woman dying of massive pulmonary embolism. He thought of a way to bypass the obstructive embolus by removing the venous blood, adding some oxygen to it, detracting carbon dioxide and putting the oxygenated blood back into the patient´s arteries [7]. Within a short time he enhanced this idea. He wanted to build a heart-lung machine, to replace the function of the heart and lungs entirely for a period of time [8]. In the first years of his research, Gibbon gained less support for his ambitious goal. But he and his associate Eugene Landis were convinced to succeed against all critics and obstacles. In the next years they reported successful experiments with cats, who survived a

period of total cardiopulmonary bypass with a clamped pulmonary artery. Relying upon this success, he predicted three possibilities for using extracorporeal circulation, including pulmonary embolectomy, temporary cardiorespiratory support till heart and lungs have recovered and mitral valve repair [9]. From 1945 on, Gibbon was supported by IBM engineers and the setup of the heart-lung machine became more professional. With a larger oxygenator, all dogs survived a bypass period of up to 4 hours [10]. Then Gibbon built a device suitable for human use. This heart-lung machine consisted of multiple stationary vertical screen oxygenators, where the blood flowed in an atmosphere of oxygen and carbon dioxide [11]. In February 1952, Gibbon used his heart-lung machine for the first time in an human being, to explore the atrium of a moribund child with an assumed diagnosis of an atrial septal defect. Unfortunately the preoperative diagnosis was wrong and the child died. Other surgeons like Mario Dogliotti, James Helmsworth and Clarence Dennis competitively tried to perform cardiac and open-heart surgery using pump or bubble oxygenators, but all failed.

It was on May 6, 1953, when Dr. John Gibbon reached the goal of his 20 years´ research. Cecelia Bavolek, an 18-year-old girl with an atrial septal defect and a large left-to-right shunt became his patient. The surgery was performed as follows: An intercostal incision enabled the exposure of the heart, the arterial cannula was placed into the left subclavian artery. The inferior vena cava was cannulated through the atrial appendage, the superior vena cava through atrial wall by two venous cannulas. After partial bypass was started, a vent was placed in the left ventricle to start the total bypass. The ostium secundum atrial septal defect had the size of a silver dollar and was closed with direct sutures. The patient had been on total bypass for 26 minutes and on extracorporeal circulation for 45 minutes. She recovered completely. This success approved the feasibility of cardiopulmonary bypass in humans [12].

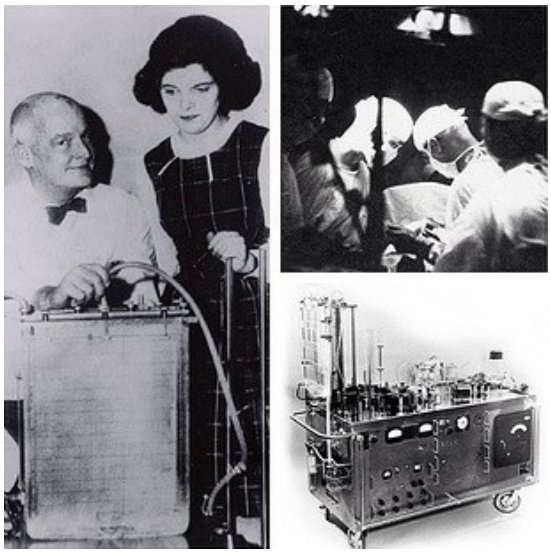

Figure 1: Gibbon's HLM

But Gibbon was not content with this success and the state of his heart-lung machine, because he never managed another successful surgery. He fathomed all deficiencies of his HLM and searched for a solution to overcome them. Gibbon included audible and visible safety devices to shut down the pump in case of too low blood level in the venous reservoir

or if the pressure becomes too high. He developed in-line ph meters, arterial filter systems, stainless steel cannulas and plastic tubing. He advocated to perform a rinsing of the circuit before CPB onset and to use colloid priming solution in low quantity to reduce hemodilution. Gibbon also advised to collect all the blood from inside the HLM and the blood from the chest drainage and reinfuse it to the patient, like modern Cell Saver devices do. The systemic blood pressure should be maintained at a level of 50 to 65 mmHg, which is still thought to be the optimal perfusion pressure [13]. And Gibbon was aware of the need for excellent assistance to perform CPB in a safe way, the precursor of today´s perfusionist. He not only invented a workable heart-lung machine and described nowadays well-established CPB practices, he also surveyed all CPB related problems meticulously and helped to solve them.

1.2. Cardiopulmonary bypass - equipment and function

To perform an open-heart surgery a cardiopulmonary bypass is needed. As the name implies, the heart-lung machine has two main functions to take on throughout the CPB: replacing the heart during complete diastolic cardiac arrest by maintaining the blood circulation and replacing the lung function for gas exchange. This bypassing of the heart allows surgical interventions in the blood-free chambers of the heart.

The traditional setup of an HLM contains an open circuitry for extracorporeal circulation, consisting of a venous hard-shell reservoir to collect the drained venous blood, an oxygenator and an heat exchanging device, all driven by a pumping system. All components are connected by tubing lines with integrated venous and arterial filter systems.

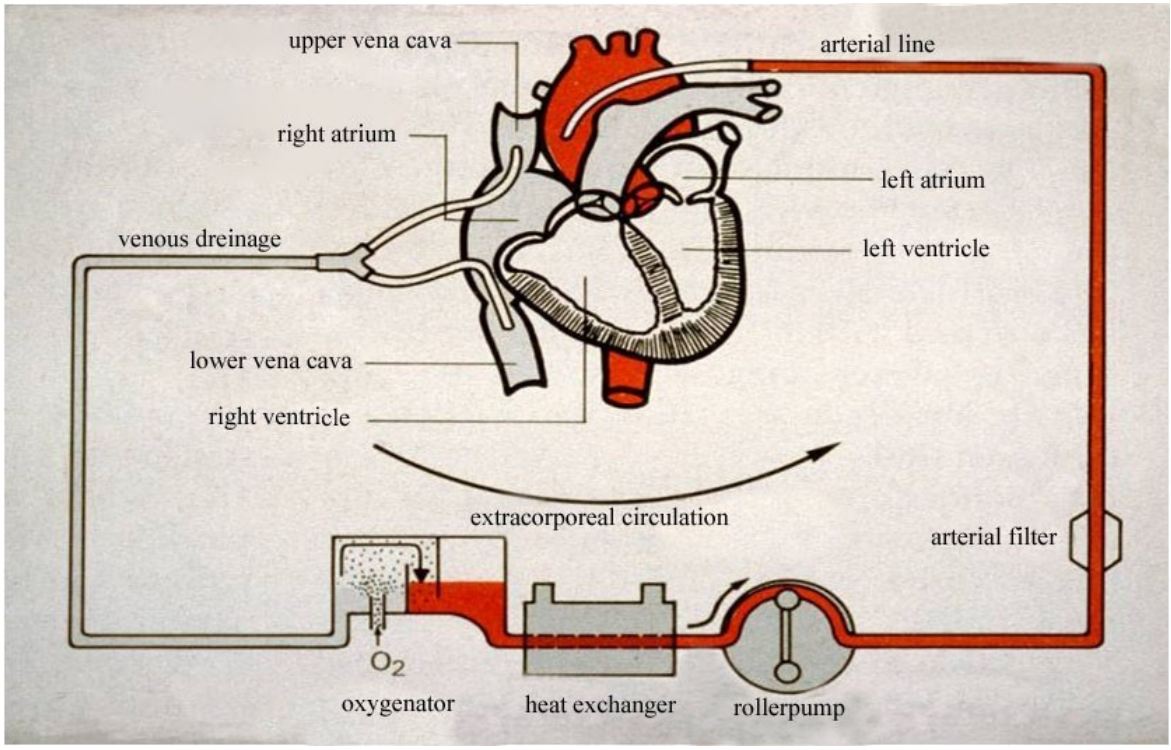

Figure 2: Scheme of cardiopulmonary bypass (by Prof. Rigler)

1.2.1. Conventional heart-lung machine

The conventional HLM is characterized by an open circuitry, with direct blood-air interface not only in the open venous reservoir, but also in the cardiotomy reservoir. The patient´s blood is typically drained by gravity through cannulas in cavoatrial position in the right atrium via the right atrial appendage or bicaval cannulas in the superior (SVC) and inferior vena cava (IVC) into the venous reservoir. From this reservoir, the blood is propelled either by a centrifugal or a roller pump. The dark venous blood flows out of the reservoir into the oxygenator, where it gets enriched with oxygen in exchange for carbon dioxide (CO_2). Simultaneously the blood passes the integrated heat exchanger, where it can be cooled for hypothermia and rewarmed. Then the oxygenated blood is reinfused into the patient through the arterial cannula placed in the ascending aorta. The femoral artery and vein in the inguinal region offer an alternative position for cannulation.

Oxygen-enrichment is not the only function of the oxygenator, it should be more likely called blood gas exchange device, because it also regulates the carbon dioxide and nitrogen exchange. There are two main types of oxygenators: bubble and membrane oxygenator. The bubble oxygenator is seldom in use nowadays because of its clear disadvantages like

foaming, bubble formation and embolic events due to its direct blood-to-gas interface in the mixing chamber. Modern oxygenators are usually of the membrane type, with a semipermeable membrane made of silicone or polypropylene. The blood flows along the microporous polypropylene membrane, which separates the fluid blood from gas phases and enables diffusion similar to the human lung. The diffusion rate is determined by the partial pressure gradient between the gas and fluid phases as well as the different diffusive characteristics. Membrane oxygenators with a silicone barrier are more suitable for long term support like ECMO (extracorporeal membrane oxygenation) because there is no loss of gas transfer capacity. Microporous polypropylene membranes develop a plasma leakage and membrane wet-out after employment periods longer than 24 hours. The physiological filling of the pores with plasma proteins starts immediately after initiation of the CPB and creates a protein coating on the membrane. There is no longer a direct blood-gas-contact and the surface tension of the blood is formed. This prevents leakage of plasma water into the gas phase and vice versa. Otherwise a gaseous microemboli and denaturation of the blood proteins would be triggered. But after several hours of use, evaporation and subsequent condensation of serum can occur and decrease the functional capacity of the microporous membrane. So the microporous polypropylene membrane oxygenators are used for a short-term conventional extracorporeal circulation with an HLM.

The heat exchanger is a device for temperature control and is either integrated into the oxygenator or an external component, mostly used for ECMO. Blood and water are pumped against each other in separate chambers and, following the convection principle, heat is transferred. During the extracorporeal circulation some organic regions are undersupplied with blood and oxygen because of low perfusion. Therefore a mild hypothermia of 32° C is used in most cardiac procedures. The patient gets cooled down to protect the minder-perfused tissues from hypoxic ischemia by reducing their metabolism rate and oxygen consumption. Hypothermia also allows lower pump flows to decrease the shear stress and trauma on the blood cells. After the surgical intervention, the aortic cross-clamping is removed and the heart starts beating again. The patient´s circulation is still supported by the HLM for volume replacement and to rewarm his blood with the heat exchanger. The oxygen-enriched and warmed-up blood is pumped back into the patient via the arterial cannula placed in the ascending aorta.

In order to maintain the blood flow through the patient´s body and to keep the perfusion pressure at the right level, a sufficient pumping system is required. Two different systems are in use in modern heart-lung machines: the roller pump and the centrifugal pump. The

roller pump has a long history and is still employed in most conventional HLM systems because of its simple principle of displacement. Two rollers are placed in opposite to each other and roll the blood through a piece of tube. The roller pump is able to generate positive and negative pressures, so it can be used as suction device too. Furthermore the roller pump is mostly independent of resistance and hydrostatic pressure. Its output depends on both the number of rotations of the pump head, called revolutions per minute (RPM), and the internal diameter of the tubing. The roller pump is the better choice for low volume flows and high pressures. But it also has some disadvantages like the mechanical material fatigue, spalliation of tubing and higher grade of hemolysis caused by shear stress on the blood cells. Whereas rotary pumps like the centrifugal pump are more suitable for large volume flows and low pressures and cause less blood damage. A centrifugal pump moves the blood from inlet to outlet by using rotation of an impeller in a rigid housing. This creates a pressure gradient between regions of low pressure in the centre and high pressure on the sides. The output of the centrifugal pump is afterload dependent. The blood flow is influenced by changes in patient´s systemic vascular resistance (SVR) and in resistance of the CPB circuit. The circuit resistance depends on the HLM components like oxygenator, filters, tubing size and the size of the venous and arterial cannulas. In combination with a centrifugal pump an in-line flowmeter has to be used, because of their nonocclusive characteristics.

During cardiac surgery and CPB it is essential to aspirate the blood from the heart chambers and the surgical field like the pericardium, pleural cavities and the sternal wound. If the amount of blood loss is large, there is no time to reinfuse the blood via the Cell Saver. Another way to collect the blood and return it to the ECC is needed immediately. This is the remit of the cardiotomy suction and reservoir. It receives the blood and pumps it through a defoaming chamber into a storage chamber and through several included macro- and microfilters. When the blood is cleaned from all particulate residues it gets joined the venous reservoir of the HLM.

The microfiltration of the cardiotomy blood is not the only filtering system of the extracorporeal circuit. There are several filters interposed in various locations of the HLM. The venous reservoir has a built-in filtering system anyway. Just before the blood is given back to the patient, a filter is placed into the arterial line. Filters are made of microporous membranes in order to avoid gas, micro particles or fat embolism entering the patient´s arterial system.

1.2.2. MINI-ECC miniaturized extracorporeal circulation

With growing knowledge about the adverse effects of cardiopulmonary bypass, two different strategies arose to overcome those side effects. Especially for patients with a simple atherosclerotic heart disease without the need for an aortic valve repair, the off-pump coronary artery bypass, called OPCAB, is a perfect solution. The surgeon is able to perform coronary artery bypass grafting on the beating heart without using an heart-lung machine. So the deleterious impact of extracorporeal circulation could be eliminated for these patients. But other surgical interventions such as cardiac valve repair, thoracic aortic surgery or any form of open-heart surgery for congenital heart defects invariably require the use of cardiopulmonary bypass circuits. That´s the reason why current CPB research tends to the development and clinical implementation of minimized heart-lung machines. But the term minimized cardiopulmonary bypass is not precisely defined and trademarked. So the setup of these mini-HLMs ranges from open systems with a reduced surface area, to semi-closed CPB systems, to total closed circuits with complete avoidance of venous reservoirs and cardiotomy suction. Some companies, such as Terumo Inc. Japan, Sorin Group Italy, and Eurosets Italy, provide mini-CPB systems with main focus on reduced priming volume. This is achieved by using very low-prime oxygenators and reservoirs, as well as bringing the roller pumps closer to the patient and shortening all tubing lines. The CPB circuitry is still open and blood-air interface still exists.

Figure 3: Medtronic Resting Heart System

Other miniaturized extracorporeal circulation (mini-ECC) systems, including the Jostra MECC system (Jostra AG, Hirlingen, Germany) or the Medtronic Resting Heart System® (RHS, Medtronic Inc., Minneapolis, USA) contain a minimized HLM with closed circuitry, centrifugal pumps, special coating and abandonment of the venous reservoir and cardiotomy suction. These closed mini-CPB systems are characterized by the absence of direct blood-air contact, good biocompatibility, reduced priming volume due to decreased hemodilution and less demand for homologous blood products [14], [15], [16], [17].

By abolishing the blood-air interface, shortening the tubing length, omitting the venous reservoir and creating a closed circuit system, large efforts were taken to reduce the CPB-

related morbidities. These morbidities are: hemodilution by large priming volumes causing anemia and increased consumption of blood products, blood cell damage, complement activation and systemic inflammatory response.

The new mini-ECC systems all utilize traditional and approved bypass components, that have been modified for closed CPB systems. Here, the vascular system of the patient serves as the venous reservoir. The venous cannula drains the blood out of the right atrium via the atrial appendage or through insertion into the superior and inferior vena cava. A kinetic-assisted venous drainage (KAVD), driven by a centrifugal pump, is needed to achieve active drainage of the patient´s blood into the mini-HLM. This centrifugal pump is the only pump and has to manage both the venous return via KAVD and a sufficient systemic perfusion pressure, without any venous reservoir [18].

Before the initiation of the cardiopulmonary bypass, the heart-lung machine needs to be filled with priming solution. This can either be based on blood or on asanguineous prime made of crystalloid or colloidal solutions. There is a minimum priming volume to initiate the CPB in a safe way without the risk of inadequate flow rates and air embolism. This minimum amount of prime depends on the patient´s body surface area (BSA) and the calculated target flow rate.

In order to reduce the priming volume and decrease the negative effects of hemodilution, the CPB surface area has to be minimized. One important step is to shorten the tubing length. This could be reached by getting the CPB circuit closer to the patient and by decreasing the internal diameter of the tubing. As proclaimed in Poiseuille's law, the flow is proportional to the fourth power of the radius. Therefore a smaller tube saves on priming volume. It is also possible to reduce the size of the membrane oxygenator and its membrane surface area and still guarantee a sufficient gas exchange.

As mentioned before, neither a venous reservoir nor a cardiotomy suction are used in the closed minimized heart-lung machines. This is another way to reduce the prime solution and avoid unnecessary blood-air contact plus the contact with foreign surfaces. The blood from the operation field is aspirated with a cell-processing device, called Cell Saver. Heparinized saline or citrate is added simultaneously. The red blood cells (RBCs) are washed with saline, centrifuged to separate from the fluid and reinfused into the patient via the ECC or intravenously.

Another progress in development of the minimized HLM was the insertion of biocompatible heparin coatings in all components of the CPB. By coating the synthetic nonendothelial surfaces with heparin, the vascular endothelium is imitated. This improves

the biocompatibility of the HLM. Also the defense reaction with complement activation and inflammatory response, which is initiated by the interaction of blood cells with foreign surfaces, is reduced. All these achievements in construction have been made to make the clinical use of the minimized HLM for cardiopulmonary bypass as easy and safe as possible.

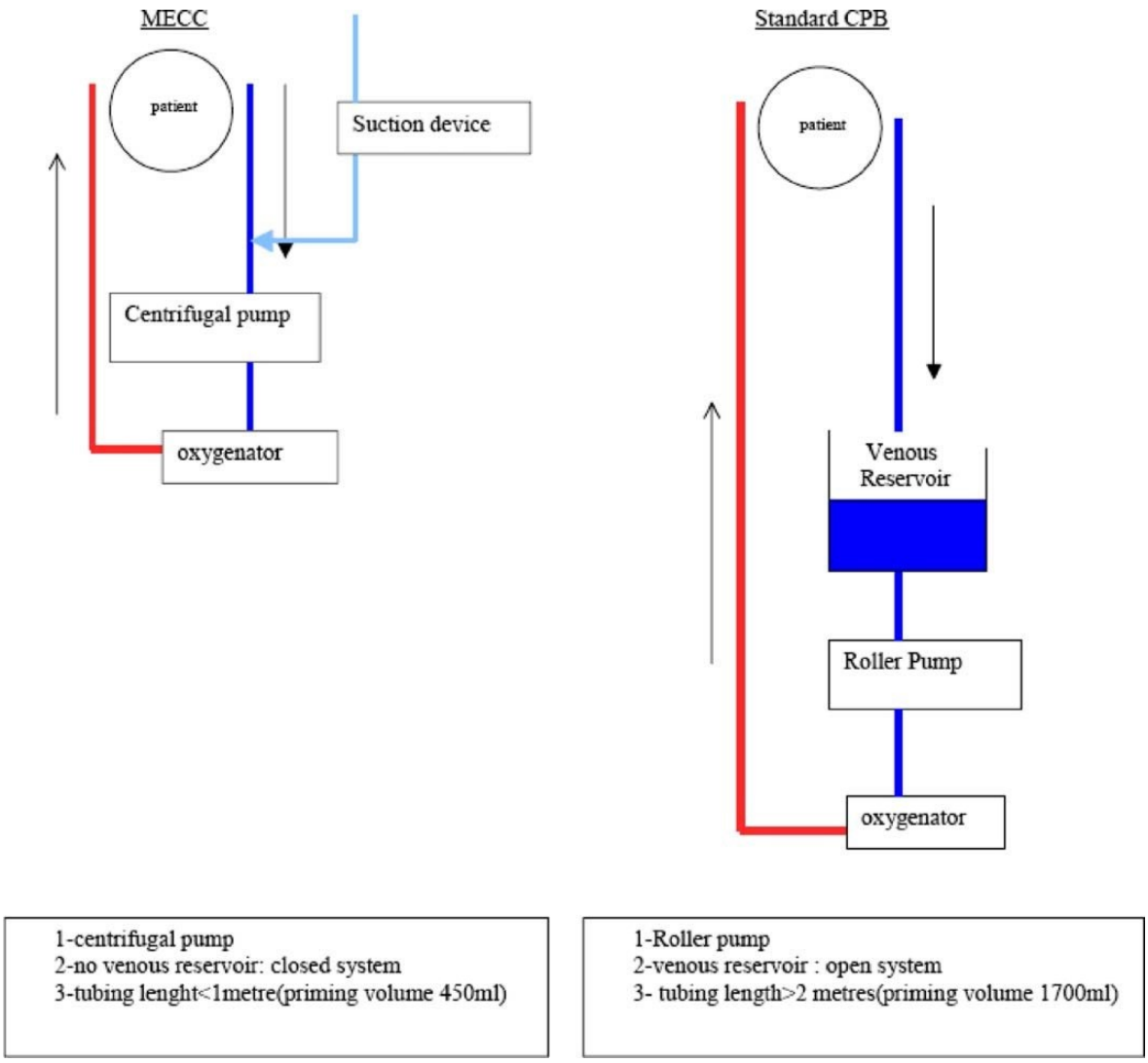

Figure 4: Scheme of mini-ECC vs. conventional CPB

1.3. CPB in pediatric cardiac surgery

Despite the immense technical improvements of CPB systems over the past decades, the pediatric cardiac surgery using cardiopulmonary bypass in newborns and infants is associated with higher morbidity and mortality than in older children or in adults. The incidence of complications such as low cardiac output syndrome, atrial fibrillation, reperfusion injury, renal and pulmonary dysfunction, neurologic deficits, general edema and capillary leak syndrome is increased. The young patients are more susceptible to

injuries of immature organ systems and their immune response is different, depending on their age. But the ratio of extracorporeal circuit size to patient size and blood volume has the largest impact. The smaller the patient, the more vulnerable he is to the damaging effects of the CPB [19].

Massive hemodilution due to the mismatch between CPB priming and patient´s blood volume, results in lowered hemoglobin concentration and hematocrit values. To maintain a sufficient oxygen delivery to all organs and to manage dilution of coagulation factors, homologous blood products are administered to the patient. Especially the pediatric cardiac surgery of complex congenital heart defects in newborns is associated with the use of homologous blood transfusions. Consequently the risk of perioperative complications and transfusion accidents is increased. But not only the small patient size poses a challenge, also the higher metabolic demand and the altered homeostasis of the immature organ system require a specific adaptation of the cardiopulmonary bypass circuit. The pediatric patients need smaller CPB circuits with less priming volumes and a reduced blood-artificial surface interaction, but simultaneously ensuring higher pump flow rates to serve the altered metabolism. There are different approaches to overcome this discrepancy: On the one hand minimized, but still open CPB systems with main focus on reduced priming volumes and on the other hand miniaturized closed circuits to avoid the deleterious effect of blood-air contact. Another benefit of the miniaturized CPB circuits is the possibility to perform transfusion-free surgeries as a result of less hemodilution.

A reduced priming volume is gained by using very low-prime oxygenators and blood reservoirs as well as bringing the roller pumps closer to the patient and shortening all tubing lines. This kind of minimized setup with a Terumo Inc. Baby RX Oxygenator and Tonokura Compo III roller pump, is used in a study published by Miyaji et al. in 2007 [20]. Also the KIDS D100 oxygenator from the Italian company Sorin (Sorin group, Mirandola, Modena, Italy) represents a low-prime oxygenator. De Rita et al. describe their clinical experience with the Dideco KIDS D100 Oxygenator and a miniaturized bypass circuit in a study from 2013 [21]. Kulat et al. report on their remote-mounted perfusion system using the Terumo System 1 Advanced heart-lung machine, which is characterized by minimized tubing length, reduced prime volume and less need for blood by bringing all components closer together and closer to the patient [22]. Also the team of the German Heart Institute in Berlin uses the low-prime KIDS D100 Oxygenator by the Sorin Group. The D100 oxygenator is incorporated into the Stöckert S3 mast mounted pediatric console, a neonate CPB system (by Stöckert Instrumente GmbH, Munich, Germany). This CPB

system has been modified by shortening all tubing connections, by reducing the tubings´ internal diameter and using the Sorin D130 arterial filter. Despite still having venous and cardiotomy reservoirs, Koster et al. managed to reduce the priming volume down to 110 ml for cardiac surgeries in neonates [23], [24], [25].

The other sort of miniaturized bypass systems totally disposed the venous reservoir to create a closed circuitry without direct blood-air interaction and to decrease hemodilution. The Jostra MECC system (Jostra AG, Hirlingen, Germany) and the Medtronic Resting Heart System® (RHS, Medtronic Inc., Minneapolis, USA) represent such a miniaturized extracorporeal circulation system.

With intent to use the assumed positive impact of minimized and particularly closed CPB circuits, a new setup of a miniaturized extracorporeal circulation system has been designed by the team of Prof. Dr. Knez at the Clinical Department for Cardiac Surgery, Department of Surgery at the University Hospital of the Medical University of Graz, Austria. With collaboration of Medtronic, the new developed P-MEC® system is engineered for use in pediatric cardiac surgery in infants weighing from 5 to 20 kilograms and a target flow rate of up to 2 L/min. The modified P-MEC® setup is built upon the advancement of the Medtronic Resting Heart® System. The RHS® is used for adult cardiac surgery and contains a low-prime and a closed circuitry. The miniaturized P-MEC® system is driven by the Medtronic® BioPump centrifugal blood pump, which provides the kinetic-assisted venous drainage (KAVD) as well as the systemic perfusion. There is neither a venous reservoir nor a conventional cardiotomy suction. A suction drain plus a left heart vent cannula are used to collect the pericardial blood from the operating field and to drain the left atrium. The drained blood is accumulated in a modified cardiotomy reservoir, that is totally separated from the closed circuitry. If the blood volume decreases or an emergency conversion to open bypass is needed, this cardiotomy reservoir is added to the venous line. Furthermore, a Medtronic Cell Saver® device is used to collect blood from the surgical field. This autoLog® Autotransfusion system salvages the red blood cells to reinfuse them into the patient. Because of the absence of a venous reservoir, the Affinity® arterial filter placed in venous position serves as an air trap. The Affinity® Pixie membrane oxygenator with an integrated heat exchanger provides the gas exchange. All components of the P-MEC® circuit are covered with a special Medtronic Carmeda® BioActive Surface coating to increase the biocompatibility and to avoid cell adhesion and thrombotic processes.

Before clinical implementation, the P-MEC® system has been tested in two earlier experimental animal models at the animal laboratory of the Section for Surgical Research,

Department of Surgery, Medical University of Graz. Based on these experimental experiences and on the analysis of the clinical results of the first patients, Prof. Dr. Knez and his team demonstrated the favorable setup of the P-MEC® system.

1.4. Physiology and pathology of the CPB – conventional HLM versus mini-ECC

The development of the heart-lung machine as a tool for extracorporeal circulation during complete cardiac arrest has changed the cardiac surgery entirely. The HLM allows open-heart surgeries of the most complex heart diseases and increases the life expectancy of cardiac patients [26].

Although heart-lung machines are routinely used today, there are some adverse effects to mention. With initiation of the cardiopulmonary bypass, a complex setting of non-physiological interactions and impacts is induced to the patient´s body. The pathophysiological aspects of the HLM include systemic inflammatory response, myocardial damage, massive hemodilution, coagulation disorders, embolic events, neurocognitive decline, hypoperfusion as well as renal and pulmonary dysfunction. The miniaturized heart-lung machine was developed to overcome these CPB associated complications. The mini-ECC system is either an open or a closed circuit, that is usually heparin-coated to reduce the blood-foreign surface interface. By omitting the venous reservoir and the cardiotomy suction device, the blood-air contact is avoided. This modification results in clear benefits, all proved by numerous studies. The clinical advantages of using the minimized HLM are:

- lower systemic inflammatory response [27]
- reduced hemodilution [15]
- less activation of coagulation cascades [28]
- less peri- and postoperative bleeding and decreased need for blood transfusions [29]
- reduced postoperative morbidity [16]
- lower incidence of myocardial damage, atrial fibrillation, low cardiac output syndrome, neurological complications and respiratory insufficiency [30]
- shorter duration of ventilation and reduced length of stay on ICU [31]

1.4.1. Systemic inflammatory response to CPB

During CPB the blood circulates through the nonendothelial system of hoses, tubes and other HLM components like the microporous membrane of the oxygenator and several filter systems. With this contact to artificial surfaces the humoral and cellular blood cells are exposed to malicious processes, which initiate a noninfectious systemic inflammatory response.

For the diagnosis of the "systemic inflammatory response syndrome" (SIRS) two or more clinical symptoms must be fulfilled:

- body temperature higher than 38°C or lower than 36°C
- heart rate more than 90 beats/min
- respiratory rate > 20/min or a P_aCO_2 less than 32 mmHg
- leukocyte count > 12000 cells/mm^3 or < 4000 cells/mm^3 or the presence of more than 10% immature neutrophils

These requirements were published 1992 by the American College of Chest Physicans/Society of Critical Care Medicine (ACCP/SCCM) consensus conference [32]. Most of the patients with cardiopulmonary bypass suffering from a mild form of "whole-body" inflammatory response, called "postbypass syndrome". In 2-10% the postbypass syndrome changes into a systemic inflammatory response after bypass (SIRAB) [33]. This is a noninfectious clinical picture with a wide range from less critical inflammation with leukocytosis and pyrexia to severe illness with pulmonary, renal, intestinal and myocardial dysfunction and with increased susceptibility to infections [34]. An early diagnosis of SIRAB is very difficult because of its variability of clinical manifestations. Its hard to say whether the symptoms are caused by inefficient perfusion during CPB or by the inflammatory response itself [34].

The onset of CPB by connecting the HLM to the patient is associated with a generalized activation of the innate immune system. Neutrophils, monocytes (macrophages), natural killer cells, endothelial cells and soluble (humoral) factors such as cytokines, acute phase proteins, coagulation cascade, bradykinin and the complement system are part of this innate immune system [35]. The inflammatory immune reaction is not only based on humoral but also on cellular defense. All starts with the interaction of blood, air and the synthetic components of the HLM. The contact with the nonendothelial surfaces as well as the surgical trauma and the reperfusion injury induce the sequence of cytokine-mediated processes and the activation of the vascular endothelium [36].

Pumping the blood through the heart-lung machine, shear stress forces cause damage to the membrane integrity of the red blood cells (RBCs). This changes the function of the Na^+/K^+ ionic pump at the cell surface and induces an abnormal accumulation of intracellular cations [37]. So the RBC deformability is hampered, which influences the microcirculation negatively. The complement activation generates a membrane attack complex (MAC), which attacks the deformed RBCs and causes an haemoglobin leakage [34]. By red cell lysis potassium, haemoglobin and adenosine diphosphate (ADP) are released. Free haemoglobin in plasma alters the plasma oncotic pressure and viscosity of the blood, whereas ADP changes the platelet function and their hemostasis ability. Potassium release may result in arrhythmias. Furthermore, the red cell membrane ghosts occlude the microcirculation in the capillaries [37], [38]. This ischemia triggers a release of cytokines like interleukin-1, IL-6, IL-8 and activates the vascular endothelium [35].

The endothelial cells are extremely sensitive to changes in the vascular integrity but also to cytokine-mediated stimulation. They start with the expression of E-selectin, endothelial leukocytes adhesion molecule (ELAM), intercellular adhesion molecule (ICAM) and vascular adhesion molecules (VCAM), which mediate leukocytes recruitment [39], [40]. Circulating neutrophils get activated through interaction with activated endothelial cells and then adhere on the adhesion molecules, particularly on ICAM, which are expressed on the endothelium surface. The activated wall-adherent neutrophils pervade into the tissue interstitial space, where they cause even more inflammatory reactions. Another mechanism of neutrophil activation is via the complement system. Giving protamine to antagonize heparinization also generates neutrophil activation [41], [42]. The loss of L-selectin and the up-regulation of CD11b/CD18 (membrane-activated complex MAC-1) shows the grade of activation of neutrophils during CPB [43]. So the neutrophil cells are the predominant cell type in the mediation of this „whole-body“ inflammation.

Another process during CPB is the bacterial secretion of endotoxin caused by transient hypoxia of the gastrointestinal mucosa. Endotoxin is found in high concentration after CPB and stimulates complement activation and endothelial cell activation by release of cytokines and TNFα [44].

The contact with foreign surfaces induces C3a secretion, which marks the beginning of the alternative pathway of complement cascade. C3a is the precursor of an important cytokine called acylation stimulating protein (ASP). C3a also has anaphylatoxin activity to degranulate mast cells and increase vascular permeability [45]. The antagonisation of heparin forces basophile granulocytes to release histamine, which causes a local

inflammatory reaction as well as a release of C3a and leukotrien. This leads to more vascular permeability, platelet aggregation and activation of leukocytes. A raised permeability of the vascular system produces edema in peripheral tissue and in the lungs [34]. So the patients suffer from hypotension, an hypovolemic shock, higher hemoconcentrations and hypoalbuminemia as a result of the fluid shift from the circulatory system to the interstitial space.

In a nutshell, the immune reaction is extremely complex. None of the individual steps occurs isolated, they are all interdependent. Therefore a prediction of the intensity and severity of the inflammatory response to CPB is impossible. The clinical manifestation varies from patient to patient and can never be foreseen. Of course the duration of extracorporeal circulation is one risk factor, just as the patient himself with his pre-existing conditions and comorbidity. But also the various components of the HLM with their inflammation-triggering impact play an important role. By minimizing the HLM the adverse side effects of the extracorporeal circulation can be reduced. Numerous studies verified that the mini-ECC is superior to conventional bypass regarding the reduction in the incidence of SIRAB.

Immer et al. ran a large study with 1053 patients undergoing coronary artery bypass graft (CABG) operated with a mini-ECC system. Out of this 1053 patients they analyzed the inflammatory markers of 60 patients, divided into a conventional and a minimal ECC-group (CECC/mini-ECC). Interleukin-6 (IL-6) belongs to the pleiotropic group of cytokines, activates the acute phase proteins such as C-reactive protein (CRP) and complement protein 3 and is a lymphocyte-stimulating factor. SC5b-9 is a terminal complement complex and a sensitive marker in assessing the grade of complement activation [46]. The serum levels of SC5b-9 and IL-6 were significantly reduced in mini-ECC patients. This is an evidence that mini-ECC is less proinflammatory than conventional CPB [31].

In a study including 400 CABG patients, Remadi et al. also reported significantly lower CRP levels in patients treated with mini-ECC than patients receiving CECC 24h and 48h postoperatively [15]. Fromes et al. found a reduced release of the proinflammatory cytokine IL-6. Also the plasma levels of tumor necrosis factor (TNFα) and neutrophil elastase did not rise as high as in the standard CPB group. TNFα is a potent proinflammatory cytokine with a negative inotropic effect, which decreases the contractility and therefore the efficiency of the myocardium [47]. Neutrophil elastase (ELA2) is a serine protease, which is released by activated neutrophils and promotes the

inflammatory process [27]. Ohata et al. published a study in 2007 on their measurements of inflammatory markers as IL-6, IL-8, neutrophil elastase and CRP. The measured levels of these biomarkers were all significantly lower in the mini-ECC group than in patients operated with CECC [48]. And in one of the recent studies from 2012, Kiaii et al. tested the miniaturized CPB system by Medtronic Resting Heart System (RHS®) on 60 patients undergoing CABG. The degree of inflammatory response was analyzed by changes in levels of cytokines (IL-6, IL-10 and TNFα), acute phase proteins (CRP, complement protein 3) and cell numbers of neutrophils and thrombocytes. The RHS® showed a decreased secretion of IL-6, IL-10, complement protein 3 and TNFα [49].
These study results demonstrate the superiority of the miniaturized ECC systems to conventional CPB concerning the initiation of systemic inflammatory response syndrome. This superiority gains even more importance when the surgical intervention gets more complex or the patient´s age decreases.

1.4.2. Myocardial protection

Two key principles have to be followed to protect the myocardium from harm: reduction of metabolic activity by hypothermia and pause of electrical and mechanical heart activity. The so-called complete diastolic cardiac arrest is induced via direct infusion of cardioplegia, an hyperkalemic solution. It is assumed that damage to the myocardium during cardiopulmonary bypass is multifactorial. Ischemia and reperfusion injury related to the cross-clamping of the aorta, as well as the direct surgical trauma are responsible for the postoperative rise of cardiac-specific enzymes. And the CPB machine itself triggers inflammatory processes, which are again associated with increased cardiac specific markers [50]. These biomarkers for myocardial damage are cardiac troponin T and I (cTnI) and creatine kinase-muscle brain type (CK-MB). In case of myocardial ischemia, for example caused by coronary stenosis or occlusion, the serum level of Troponin T, cTnI and CK-MB rises in relation to the degree of myocardial cell destruction. This increase is also seen after termination of cardiopulmonary bypass. Especially cardiac troponin I is a sensitive marker for myocardial damage after open-heart surgeries [51]. In a large study, Immer et al. collected the data from 1257 patients, who all had a CABG operation either with standard CPB (n=326) or a miniaturized ECC system (n=931). The mini-ECC group showed significantly lower serum levels of cardiac troponin I 24 hours postoperatively [31]. Skrabal et al. ran another randomized study of 60 patients and reported that the

patients with mini-ECC had significantly lower levels of serum troponin T and CK-MB [50]. These results indicate that the use of mini-ECC systems reduces the degree of myocardial injury more than a conventional CPB.

1.4.3. Hemodilution and need for blood transfusions

With the first successful use of a cardiopulmonary bypass maintained by an heart-lung machine in 1953, Dr. John Gibbon already postulated to fill up the HLM with blood-based prime before connection to the patient. But using whole blood to prime the CPB circuit entails the risk of anaphylactoid transfusion reactions and infection as well as a lot of logistic problems. It was not easy to have all blood types in adequate quantities available in the blood banks. At least two units of whole blood were needed to prime the extracorporeal circuit and even more to perform the surgical intervention. In 1960 surgeons started to use an asanguineous prime with crystalloid or colloid solutions. The clinical application of crystalloid priming gained popularity because of its clear benefits: it helped to save homologous blood products, to launch CPB as an emergency procedure and improved the oxygenation of the blood in the bubble oxygenators.

With the onset of cardiopulmonary bypass, the blood volume of the patient gets diluted. This happens with whole blood prime as well as with crystalloids. But the hemodilution also has desired effects on blood viscosity and the rheologic characteristics of blood. The technique of hemodilution has become current practice in cardiac surgery, although it provides pros and cons.

Being a non-newtonian fluid, blood behaves differently when it is set in motion. Unlike water, a newtonian fluid, the viscosity of blood is not constant and changes with altered blood flow. Blood viscosity is related inversely to the shear rate. That means, if the blood flow decreases, the blood viscosity rises. This leads to an increased peripheral resistance in the patient´s vascular system. In order to achieve sufficient tissue perfusion, a higher perfusion pressure is needed, but this results in an higher blood cell damage and hemolysis. Thus, hemodilution is used to reduce blood viscosity and to enable lower perfusion pressures during bypass. Hemodilution allows better tissue perfusion plus improved oxygen delivery to all organs. Additionally, a mild hypothermia is used in most cardiac surgeries to protect the organs and in particularly the myocardium from harm due to the lowered hemoglobin concentration and the slowed blood flow.

After termination of conventional cardiopulmonary bypass it is necessary, especially in newborns and infants, to remove the additional fluids from the blood while the patient is still attached to the HLM. This technique is called modified ultrafiltration (MUF). The mixture of diluted blood, priming solution and remaining contents from inside the circuit, is drained through the aortic cannula. Then the mixture gets concentrated and filtrated by a membraneous hemoconcentrator, also referred as ultrafiltration device. After the filtration the concentrated blood including albumin, platelets and coagulation factors, is reinfused into the patient via the venous cannula. Using the MUF decreases the postoperative blood loss and thus the consumption of blood products by raising the hematocrit level and oxygen delivery [52], [53]. With removing the excess fluid, the arterial blood pressure gets raised and the gain on body weight due to total body water is reduced. Furthermore, the MUF technique is assumed to attenuate the systemic inflammatory response after bypass (SIRAB) by detaching inflammatory mediators [54], but reliable studies are still lacking. The conventional ultrafiltration during the rewarming phase on CPB is an alternative to MUF, but numerous studies reported on MUF to be advantageously regarding hemodynamics and transfusion requirements [55].

As moderate hemodilution decreases the bypass-related neurological, renal and pulmonary complications, which would occur as a result of inadequate perfusion, most centers aspire an hematocrit level below 30% during cardiopulmonary bypass [56]. Yet too low hematocrit values also go along with an increased risk of intra- and postoperative complications. Excessive hemodilution and a too abrupt drop of the hematocrit result in hemodynamic instability and high blood transfusion requirements. The incidence of coagulopathies, hemodilutional anemia, hemorrhagic bleedings, insufficient oxygen delivery and ischemic organ injury followed by low cardiac output syndrome or renal dysfunction increases with hematocrit values below 20%. In a retrospective data analysis of 5000 cardiac operations in adults, Habib et al. referred the decrease of hematocrit below 22% to the increased incidence of stroke, myocardial infarction, low cardiac output, pulmonary edema, reoperation due to bleeding and multiorgan failure [57]. By reducing the oxygen carrying capacity of blood, massive hemodilution may also be responsible for adverse neurologic outcome due to cerebral hypoxia [58]. In a systematic review of literature, Hirsch et al. identified the avoidance of severe hemodilution and maintenance of an hematocrit level higher than 24% being the only effective strategy to protect the brain [59]. Also the risk of acute renal failure requiring dialysis (ARF-D) is reduced, when the

nadir hematocrit is kept between 21% and 25% by moderate hemodilution during bypass [60].

Miniaturized bypass circuits enable the achievement of a moderate degree of hemodilution by requiring less priming volumes as a result of their reduced setup. Despite their low-flow perfusion rates, mini-ECC systems provide an increased oxygen delivery due to higher hematocrit and hemoglobin levels [61]. This also affects the consumption of homologous blood favorably and allows to reduce the transfusion requirements [62], [63].

1.4.4. Optimal pump flow

During cardiopulmonary bypass the pulsatile pump function of the heart is replaced by the nonpulsatile blood flow provided by a roller or centrifugal pump. A nonpulsatile extracorporeal circulation causes less shear stress and damage to the blood cells and is easier to obtain. An artificially produced pulsatile blood flow would require higher flow rates to overcome the compliance and resistance of the CPB components placed behind the pump [64]. Especially the oxygenator with its large membrane surface area represents the greatest obstacle.

Although the HLM is used for over fifty years now, there are no international standards defined for optimal pump flow during CPB. The perfusionist has to develop his own perfusion strategy on a fundament of large experience and measurements of oxygen saturation. The few existing guidelines for adequate perfusion flow are based on clinical and experimental data:

- total flow of 2.0 L/min/m^2 or < 50 ml/kg/min in normothermic adults
- total flow of 2.2 L/min/m^2 in adults for 28°C or warmer [65]
- in patients with BSA > 2 m^2 a total flow of 1.8 to 2 L/min/m^2
- 2.5 L/min/m^2 flow in infants and children
- minimum flow rates of 30 mL/kg/min at 18°C and 30 to 35 mL/kg/min at 27° to 28°C in pediatric patients [66]

Optimal pump flow rates for children, the so-called target flow rates, are calculated using the body surface area (BSA) and the Cardiac Index. The adequate flow on the ECC bypass is determined by arterial blood gases, whole body O_2 consumption and acid-base balance. Monitoring the levels of S_vO_2, pH, hemoglobin, oxygen saturation and lactate concentration enables an evaluation of the adequacy of O_2 transport and quality of tissue oxygenation. S_vO_2 is not only the percentage of mixed venous oxygen saturation in

pulmonary arterial blood, it also represents an average of venous oxygen saturation of all organs and tissues [67]. A low S_vO_2 during CPB shows inadequate perfusion caused by an insufficient blood flow. But there are several other factors which increase the disparity between oxygen demand (= VO_2) and oxygen delivery (DO_2). These are: a reduced hemoglobin function or concentration, decreased arterial oxygen saturation (S_aO_2), low cardiac output or an excessive oxygen consumption (VO_2). S_vO_2 levels under 60% (standard values between 60% and 80%) indicate either inadequate oxygen delivery or increased O_2 consumption. This reflects a dangerous change in organic perfusion or a deterioration of the cardiopulmonary situation [68].

Lactate is also a sensitive marker for cellular perfusion, oxygen delivery and cardiac output. An anaerobic metabolism due to tissue hypoperfusion results in a raise of whole blood lactate level [69], [70]. Inadequate systemic perfusion leads to cellular dysfunction and to an accumulation of waste products such as lactate, adenosine and adenosine diphosphate [71]. Postoperatively measured serum lactate levels are commonly used for detecting low cardiac output and assessing the mortality risk to predict the clinical outcome of patients after cardiac surgery [72]. But intraoperatively measured lactate also has an high predictive power and could be used as an early indicator of adverse outcome. This might be helpful to detect the high-risk patient already in the operation room [73]. Only a few studies deal with the intraoperative change of lactate levels during cardiopulmonary bypass. Munoz et al. proclaimed that the initial stimulus for lactate production already occurs during CPB. They pointed out several potential factors for the generation of hypoperfusion while extracorporeal circulation: duration of CPB and circulatory arrest, the degree of hypothermia, duration of cooling and rewarming, pH management strategy, and hematocrit value [74]. In another study, Basaran et al. named duration of aortic cross-clamping and lowest hematocrit as lactate increasing factors [75]. Munoz et al. explored the intraoperative change of lactate levels in 174 children undergoing pediatric cardiac surgery with CPB. They wanted to show that hyperlactatemia during CPB could be used as an early indicator to identify patients with high risk for postoperative morbidity and mortality. As expected, the increase of lactate levels was associated with surgical complexity. Munoz et al. found out that a change in lactate level of more than 3 mmol/L has a sensitivity of 82% and a specificity of 80% for mortality, as well as a positive predictive value of 45% for complications. The non-survivors had consistently higher lactate levels at all time points. But Munoz et al. could not define an absolute lactate level which correlates with morbidity and mortality [74]. In a study of Basaran et al. with 60

pediatric patients, a serum lactate level of 4.8 mmol/L was taken as a line to divide the patients into two groups. In group I with lactate levels of 4.8 mmol/L or more, the postoperative mortality was significantly higher. Also postoperative complications and length of stay on ICU and hospital were increased in this group. Therefore Basaran et al. defined a blood lactate level of 4.8 mmol/L or higher during the first postoperative period to be a reliable predictor of mortality and morbidity [75].

As previously mentioned, using the minimized HLM results in higher hematocrit levels and higher hemoglobin concentration due to moderate hemodilution. Excessive hemodilution leads to organic hypoperfusion and thus to an anaerobic metabolism with lactate production caused by inadequate oxygen delivery. Pump flow rates during CPB and hemoglobin concentration affect the volume of oxygen delivered to tissues = DO_2. This correlation is shown in the following formula:

$$DO_2 = \text{pump flow} \times (Hb \times 1.36 \times S_aO_2 + 0.003 \times P_aO_2)$$

In a recent study with 160 patients undergoing CABG intervention operated with miniaturized CPB, Bennett et al. examined the combined influence of blood flow rates and hemodilution on oxygen delivery during bypass. They showed that the average CPB pump flow was lower in mini-CPB than in conventional CPB. But despite the lower flow rate, the amount of DO_2 was the same as in cCPB, due to a higher hemoglobin level, P_aO_2 and arterial oxygen saturation (S_aO_2) during miniaturized CPB. Less hemodilution with mini-CPB results in preservation of oxygen delivery [61]. This hypothesis is confirmed by other studies. For example, Yuruk et al. proclaimed in a 2012 study that using a minimized ECC system is associated with a reduction in hemodilution and microcirculatory hypoperfusion [76]. In another study, Mandak et al. assumed that a decrease in blood flow is well tolerated by the organism due to an increased hematocrit and higher concentration of hemoglobin during mini-CPB [77].

1.4.5. Embolic events and brain protection

Brain injury and neurocognitive deficiency are the common and most dreaded complications after cardiopulmonary bypass. According to the guidelines of American College of Cardiology/American Heart Association post-CPB neurological events can be divided into two categories. Type 1 deficits are major focal neurological events such as focal stroke, transient ischemic attack and fatal cerebral injuries. These are caused by cerebral hypoxia due to low cerebral perfusion or embolic events. Type 2 deficits represent

a more global and diffuse injury, known as postperfusion syndrome with deterioration in intellectual function, memory and disorientation, but without evidence of focal injury [78], [79]. It is of unclear etiology, but is supposed to be multifactorial. Cerebral hypoperfusion, duration of CPB, type of procedure, age and perioperative inflammatory response are thought to be such factors [80].

Embolic events associated with CPB are classified into three types of etiology: gaseous emboli, foreign material and bloodborne emboli. With displacing the bubble oxygenators by modern membrane oxygenators, the high risk of gaseous embolism exists no longer. But gaseous microembolism (GME) can still occur during extracorporeal circulation. GME originates from the membranes of oxygenator or filter systems, the cardiotomy suction or from aspirated air through the venous drainage. The surgical intervention also represents a source for air embolism. By opening the heart chambers for reconstruction or even by cannulating the great vessels, air can enter the arterial circulation. The cannulation for antegrade cardioplegia leaves a small hole in the aortic root, where again, air could be aspirated if the heart contracts before intracardiac de-airing is completed [81]. Foreign materials such as cotton fibers, bone wax, microfibrillar collagen, plastic or metal particles and filter or tubing elements are possible sources of embolism too. But not only artificial materials could be found, also organic material including bone and muscle fragments, fat cells and fragments of an atherosclerotic plaque are aspirated from the surgical field [82]. Proximal aortic atherosclerosis is supposed to have the highest potential for a stroke during CABG intervention [83]. With increased average age of the patients undergoing coronary bypass, the incidence of intraoperative atheroembolism detached from an aortic arch atherom has raised as well [84]. Bloodborne emboli consist of cell aggregates built from platelets, neutrophils, fibrin and red blood cells. Fibrin formation and platelet aggregation occur when the coagulation cascade is initiated by blood contact with foreign surfaces of the HLM components. But bloodborne emboli and platelet aggregation can also be observed in stored whole blood transfusions or packed red cells as well in stored platelet concentrates. The so-called “storage lesion” increases proportionally to duration of storage [85]. In some parts of the CPB circuit, such as the venous reservoir, the oxygenator or the centrifugal pump, areas of potential stasis and stagnant blood flow exist. This may also result in an activation of platelets and red blood cells [86].

Roach et al. examined the incidence of stroke (type 1 deficit) and encephalopathy (type 2 deficit) after CABG in a large study with 2108 patients. Adverse cerebral outcomes were observed in 6.1 %, with same distribution between type 1 (3.1%) and type 2 (3.0%)

deficits. There was a 21% mortality rate for patients suffering from type 1 deficits and 10% mortality due to type 2 events [87]. Other reports suggest an incidence of clinically detectable stroke after CPB ranging from 1% to 5%. In studies with magnetic resonance imaging (MRI) the occurrence of a new cerebral infarct is estimated for 30% of the patients undergoing CPB [88], [89]. Encephalopathy as a type 2 deficit is variously described, ranging from confusion, delirium, coma, agitation to prolonged alteration in mental status. The reported incidence of postoperative delirium goes up to 32% [90].

The avoidance of embolic events regardless of their origin is one main goal in development of new technologies. The current technical devices, including Cell Saver, membrane oxygenator, arterial filters, surface coatings, bubble traps and emboli detection systems, help decreasing the incidence of emboli during CPB. Furthermore, several recent studies confirmed that the use of miniaturized ECC systems as well as the use of heparin-bonded CPB circuits result in an improved protection of the brain. Hirsch et al. ran a systematic review of literature with 162 papers concerning neuromonitoring and neuroprotection strategies during CPB in children younger than one year. They found only one strategy with clear evidence for effectiveness: the avoidance of severe hemodilution and maintenance of an hematocrit level higher than 24% [59]. Wipij and Jonas from the Boston children´s hospital evaluated the influence of hemodilution on neurodevelopmental outcome in children younger than one year undergoing pediatric cardiac surgery. They showed that extreme hemodilution and hematocrit values under 24% are associated with an increased risk of developmental impairment [58], [91].

With initiation of the extracorporeal circulation a systemic inflammatory response is started. Especially the contact of blood to the artificial circuit system activates the humoral and cellular immune defense as well as the vascular endothelium. This generates not only an acute cytokine-mediated inflammatory response, but also massive thrombotic processes. Before starting the extracorporeal circulation, the anesthesiologist applies heparin to the patient´s body. Unfractionated heparin (UFH) is an anticoagulant to prevent thrombotic clot formation. Heparin binds to the enzyme inhibitor antithrombin III (AT III) and activates it by conformational change of its reactive site loop. Then, the activated antithrombin III inactivates blood-coagulation factor IIa, also known as thrombin. AT III also inhibits factor Xa, which plays a relevant role in the blood clotting cascade. Therefore, heparin is standardly used to avoid clot formation in the circuit system and in the patient´s vascular system. Supplementary to the intravenously applied heparin, UFH is added to the crystalloid solution for priming the heart-lung machine. Another strategy for a prevention

of brain injury during CPB is the use of heparin-bonded circuits (HBC). Heparinized coatings improve the biocompatibility of the cardiopulmonary bypass system. An intact cell membrane is simulated by coating the hoses and other components with heparin. With its anti-thrombotic property, heparin reduces the contact and complement activation and absorbs lipoproteins to create a biocompatible surface similar to the natural cell membrane [92]. This attenuates the inflammatory immune reaction and decreases the activation of the coagulation cascade [93]. Mangoush et al. published a large meta-analysis in 2007 where they evaluated the effect of heparin-bonded circuits on clinical outcome. According to their analysis of 41 trials with 3434 patients, heparin-bonded circuits reduce the postoperative blood loss, the need for transfusions of red blood cells and other blood products, as well as the necessity for resternotomy. The average duration of ventilation, just as the averaged length of stay on ICU and in hospital were shortened in a significant manner [94].
With less activation of the coagulation system due to heparin-coated circuits, the extracorporeal circulation is better tolerated by the patient´s body. And in combination with a miniaturized CPB system it is even more gentle for the patient, because of the reduced inflammatory response.

1.4.6. CPB-related renal and pulmonary effects

As previously described, a complex systemic immune reaction is triggered with the application of conventional extracorporeal circulation. Inflammatory mediators including cytokines as interleukin and tumor necrosis factor-α (TNFα), complement anaphylatoxins and histamine are liberated. These factors raise the capillary permeability, which causes a shift of fluid and proteins from the intravascular to interstitial space [95]. A change in water balance hormones and in control factors of endothelial integrity, such as atrial natriuretic peptide (ANP), also boost protein-rich edema and water accumulation in the interstitial space [96]. This CPB-related fluid and protein shift may cause pleural effusion, liver enlargement and other severe complications including hypovolemia, massive generalized edema, capillary leak syndrome (CLS), acute respiratory distress syndrome (ARDS) and even multiple organ dysfunction/failure (MOD/MOF).
The entire respiratory system including the lungs, bronchial system, the thoracic wall and diaphragm is influenced by open-heart surgery and the application of extracorporeal circulation. Various factors as massive hemodilution, microembolism, reduced oncotic pressure and impaired lung compliance due to sternotomy, can alter the pulmonary

function. Also the release of vasoactive substances due to CPB-related systemic inflammatory response, has a negative effect on the alveolar capillary permeability [97]. The immune reaction is mediated by complement activation, neutrophil migration, cytokine production and arachidonic metabolites, causing noncardiogenic pulmonary edema and capillary leak syndrome. This results in acute respiratory failure, being morphologically identical to the acute respiratory distress syndrome (ARDS). By using heparin-bonded circuits for CPB and membrane instead of bubble oxygenators, the rate of occurrence of ARDS after CPB has declined in the last years[98], [97], [99].

The capillary leak syndrome not only occurs in the lungs, the whole vascular system could be affected. CLS is defined as noncardiogenic generalized edema including pleural effusion or ascites or blood pressure instability requiring volume substitution [100]. It is caused by fluid and protein shift from the intravascular to interstitial space due to increased capillary permeability [101]. CLS alters the hemoconcentration, leading to hypoalbuminemia and hypotension. The resulting complications include acute renal failure with oliguria or anuria based on hypovolemia or tubular necrosis as a result of rhabdomyolysis. Also hypoperfusion of tissues caused by less oxygen delivery in case of pleural edema or compartment syndrome due to massive swelling of the extremities is a possible complication [102].

Intraoperative oliguria and postoperative renal dysfunction are very common in cardiac surgery using cardiopulmonary bypass systems. According to the AKIN classification (Acute Kidney Injury Network)[103], stated in 2007, the development of a new-onset acute kidney injury after cardiopulmonary bypass (AKI-CPB) could be defined by these criteria:

- rapid time course, less than 48 hours
- reduction of kidney function either with rise in serum creatinine (absolute increase of > 0,3 mg/dl or percentage increase of > 50%) or with reduction in urine output, defined as < 0.5 ml/kg/h for more than 6 hours

Depending on the diagnosis criteria for acute kidney injury or renal failure, the incidence of AKI after CPB varies from 5% up to 30% [104]. About 1-3% of these patients develop acute renal failure (ARF) requiring renal replacement therapy (RRT), in the forms of dialysis or hemofiltration. AKI after CPB not only increases the mortality rate, but also the count of patients who remain dependent on dialysis for the rest of their life. Receiving a renal replacement therapy also elongates the length of stay on intensive care unit and consequently raises the medical costs.

During the extracorporeal circulation, the renal perfusion and the glomerular filtration rate (GFR) decline about 25 to 75%, depending on the systemic blood pressure and the optimal pump flow [105]. The alteration of GFR is only partially reversible in the first postoperative days. Renal dysfunction due to CPB is promoted by several mechanisms:

- low blood pressure and hypoperfusion during extracorporeal circulation and postoperatively
- activation of RAAS due to renal hypoperfusion causes production and liberation of renin and angiotensin II, leading to aldosterone release and fluid retention as well as decreased perfusion of renal parenchyma
- postoperative low cardiac output
- development of SIRS
- thromboembolic events causing damage on renal parenchyma

Other risk factors for ARF are prolonged duration of CPB, advanced age, atherosclerosis of the ascending aorta, a preexisting abnormal renal function with increased creatinine levels, a preoperatively low glomerular filtration rate, diabetes mellitus and low hematocrit during or after extracorporeal circulation [104]. The incidence of an oliguric kidney failure results in an 8-fold increase of lethality and morbidity risk.

Several clinical trials and published studies give a definite evidence, that using miniaturized extracorporeal circulation systems results in decreased incidence of acute kidney injury [106], less need for hemofiltration and lower postoperative levels of blood creatinine [15] plus reduced postoperative systemic edema and shorter postoperative mechanical ventilation time [107]. Hence, mini-ECC systems enable an attenuation of the undesirable CPB-related renal and pulmonary effects.

1.5 Aim of the submitted thesis

The following thesis examines the clinical application of a closed, miniaturized extracorporeal circulation system as a new perfusion technique in pediatric cardiac surgery. The newly developed setup of the pediatric-miniaturized extracorporeal circulation (P-MEC®) system enables cardiopulmonary bypass with a reduced priming volume and avoidance of blood-air interaction as a result of the omitted venous reservoir. These savings are supposed to affect the consumption of blood products, the accumulation of acidic metabolic products as well as the severity of post-bypass inflammatory response syndrome. Based on the description of the analysis of the first fourteen patients´ clinical

results, this thesis shall demonstrate that the closed P-MEC® system features an high-quality performance pursuant to current security standards and facilitates transfusion-free congenital cardiac surgery.

2. Material and Methods

2.1. From animal model to clinical application

Before clinical usage in children, the setup of a miniaturized extracorporeal circulation (mini-ECC) system had to be tested in an experimental animal model. The animal model had to fulfill special requirements, including feasibility of standard cannulation techniques used in adult or pediatric cardiac surgery, as well as comparability and transferability to clinical practice and human physiology.

This study was performed from 2008 to 2009 with 14 domestic pigs at the animal laboratory of the Section for Surgical Research, Department of Surgery, Medical University of Graz, Austria. The 14 pigs were prospectively and randomly assigned to two groups, group A (n=7) and group B conventional CPB (n=7). Another 14 pigs were used as blood donors if a transfusion would have been required. All pigs, with a mean weight of 30.7 ± 2.5 kg, were operated in the same way, including anesthesia, sternotomy, arterial and venous cannulation, aortic cross-clamping for 60 minutes, reperfusion on CPB for 30 minutes and post-bypass observation for another 30 minutes. At previously defined points, blood samples and hemodynamic parameters were collected. The measured data included arterial and venous blood gases (pH, pO_2, pCO_2, SaO2, lactate), hematocrit, erythrocytes cell count, hemoglobin and temperature. Furthermore, online-measurements of the O_2 and CO_2 distribution in the parieto-temporal lobe of cerebrum, the myocardium and the right lobe of the liver were collected with special opto-chemical probes. To determine the developing of inflammatory markers, blood samples of arterial blood were taken from every animal at the initiation and at the end of CPB. TNF-α, IL-1β, IL-6 and IL-10 should be assayed in a quantitative sandwich ELISA at the Institute of Nuclear Medicine at the University of Medicine, Graz.

The conventional CPB group was operated with a standard HLM with an integrated roller pump (Stöckert™ HLM) and a membrane oxygenator (Dideco® D 905 oxygenator). The averaged priming volume was 1928 ± 188 ml and no heparin-coatings were used. The CPB circuit had a venous and a cardiotomy reservoir as well as a intrapericardial suction. Whereas the circulation of the animals in the mini-ECC group was performed with the Resting Heart System (RHS®; Medtronic™ Performer CPB® console). This Resting Heart System® is a closed-loop circulation tool with a centrifugal pump and a priming

volume lower than 1000 ml. Furthermore, the RHS® includes a second circuit for venting the heart and a Cell Saver device (Cell Saver®, Medtronic™) instead of the cardiotomy suction. The oxygenator has a membrane surface area of 2.5 m^2 and the centrifugal pump can provide a blood flow from 1 to 6 liters per minute. Surfaces in contact with blood are coated with a biocompatible heparin coating (Carmeda® Bioactive Surface).

The evaluation of the measuring results distinctly showed that this mini-ECC system is superior to conventional CPB systems. The animals in the mini-ECC group needed less blood transfusions due to less hemodilution as a result of the reduced priming volume. The averaged prime in mini-ECC group was 964 ± 94 ml. Furthermore, the brain derived pO_2 levels were higher in the mini-ECC group, whereas the arterial and bulbovenous lactate level, as an indicator of anaerobic metabolism, was reduced. Unfortunately the inflammatory markers could not be evaluated, because they got too much diluted within the laboratory serial dilution [1].

In a second experimental animal model from 2009 to 2011, 24 newborn domestic pigs were prospectively and randomly assigned to two groups, the conventional CPB group (n=12) and the P-MEC group (n=12). In the congenital setup, the pigs had a mean weight of 10.53 ± 2.7 kg in the conventional CPB group and 10.63 ±2.9 kg in the P-MEC group. All pigs were operated in the same manner, including pre- and postoperative management, anesthesia, sternotomy, arterial and venous cannulation and positioning of the fibre-optical sensors. After anesthetization, two photochemical sensors for pO_2 and pCO_2 measurement were placed into the parietal and temporal lobe of the brain. Another sensor was set into the myocardium of the left ventricle and another one into the right lobe of the liver. Hemodynamic and respiratory variables, as well as arterial, central-venous and intracranial metabolic values were measured at twelve points during operation. The newborn pigs in the P-MEC group were operated with a miniaturized HLM, using the Medtronic® Performer CPB®, the Congenital Resting Heart™ Set, Medtronic® bio-pump Centrifugal blood pump, Medtronic® Affinity arterial filter in venous position serving as vacuum air removal device (VARD) and the new marketable Medtronic® Pixie baby-oxygenator. With these components, a closed circuit for extracorporeal perfusion has been setup. The miniaturized CPB circuit was filled with an averaged priming volume of 202 ± 37 ml. To simulate a cardiac surgical procedure, the pigs were operated in accordance to a study protocol. After baseline measurements (T1) for 15 minutes, the cardiopulmonary bypass was started (T2), then cross-clamping of the aorta for 90 minutes (T3-T8), after opening the aortic clamp reperfusion of the pigs for 30 minutes (T9-T10) and postoperative

observation for another 30 minutes (T11-T12). In the conventional CPB group the Stöckert^{TM} HLM and the Terumo FX 05 baby oxygenator were used for extracorporeal circulation.

The measured data of this second trial showed significantly higher need for blood transfusion (395.7 ± 47.2 ml vs. 28.5 ± 4.8 ml) and higher lactate levels in the conventional CPB group. The measurements of the opto-chemical sensors revealed significantly higher cerebral pO_2 levels in the P-MEC® group, while pCO_2 levels appeared similar. In contrast, both hepatic and myocardial pCO_2 levels were higher in the cCPB group, while pO_2 levels were similar. This second experiment proved our expected advantageous results of the P-MEC system in reference to reduced priming volume and transfusion requirements, less lactate production and more physiological O_2/CO_2 metabolism [108], [109].

Because of these results and good experiences with the safe application of the P-MEC system in both animal experiments the clinical trial with pediatric patients could be started.

2.2. Patient demographics

Since August 2011, fourteen pediatric patients with a body weight between 5 to 20 kilograms underwent cardiac surgery with the new pediatric-miniaturized extracorporeal circulation system (P-MEC) at the Clinical Department for Cardiac Surgery, Department of Surgery at the University Hospital of the Medical University of Graz, Austria.

The inclusion criteria involve the patient´s body surface area and calculated target flow rate, because the Medtronic Affinity Pixie® membrane oxygenator is suitable for infants with a body weight ranging from 5 to 20 kilograms who require a maximum flow rate of 2.0 L/min. Also the complexity of the surgical intervention was a leading criterion for inclusion.

All patients, respectively their legal guardian, were informed about the proceeding, the implications and possible complications of the procedure, especially in regard to the new P-MEC setup. They gave their informed written consent for the surgical, anesthesiology and monitoring procedures, according to the guidelines of medical and research ethics. The retrospective data analysis was approved by the institutional review board of the Medical University of Graz (26-206 ex 13/14).

2.3. Study end points

Primary study end points contain pre-, intra- and postoperatively measured lactate and hematocrit values to identify the validity of the perfusion flow rate and the degree of hemodilution. This measured data is collected routinely during cardiac surgery and do not stress the patient additionally. Secondary study end points were transfusion requirements, use of homologous blood, calculated transfusion requirements in case of conventional CPB circuits, in-hospital results including surgical or embolic complications plus clinical outcome at 6-months follow-up.

2.4. Preoperative evaluation

Anamnesis, physical examination and status reports, otorhinolaryngological check-up, chest radiography, transthoracic and transesophageal echocardiography and, if needed, cardiac catheterization plus preoperative blood analysis were performed in all patients before surgery.

2.5. P-MEC setup and surgical strategy

After finishing phase I and II with development of an animal model and minimization of the extracorporeal circuit, phase III including clinical application started in 2011.
For usage in pediatric cardiac surgery the P-MEC® system has to fulfill the following requirements:

- improved perfusion quality with high reliability and predictability
- safe and easy application
- easy setup with sufficient number of ports for infusions, additional suction devices and measurement equipment
- efficient gas and heat exchange
- smallest possible foreign surface area for blood contact
- no blood-air contact with closed circuit design
- minimal amount of priming volume to reduce hemodilution
- avoidance of microbubbles and air embolism despite the absence of a venous reservoir

In cooperation with Medtronic™, the team around Prof. Dr. Igor Knez adapted the Medtronic Resting Heart® System (for adult use) and advanced it with the special design

of the pediatric miniaturized extracorporeal circulation system (P-MEC®) at the Clinical Department for Cardiac Surgery, Department of Surgery at the University Hospital of the Medical University of Graz, Austria.

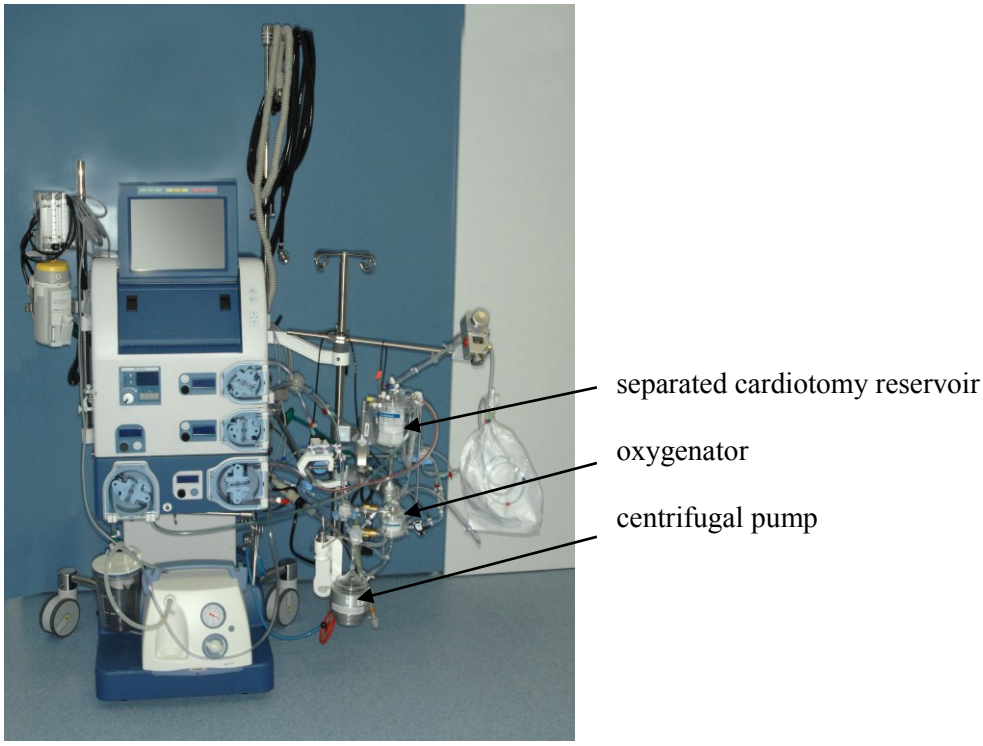

Figure 5: P-MEC

The CPB circuit was modified by shortening the tubing length, by reducing the internal diameter of all tubings, omitting the venous reservoir and using a smaller membrane oxygenator, powered by a centrifugal pump. For all 14 patients asanguineous priming was used, consisting of a mix of Elomel isoton® infusion solution (Fresenius Kabi Austria) and 600 to 800 IU unfractionated heparin (UFH). Table 1 lists the priming volumes required by each component of the P-MEC.

	priming volume (ml)
blood pump	50
VARD	39
Oxygenator	48
art. filter	39
1 meter tube	32

Table 1: Priming volume of each P-MEC component

For all 14 pediatric patients the same surgical approach was obtained. Preoperative and anesthesiologic management was routinely performed by the anesthesiologist Dr. Krumnikl and his team. After general anesthetization and intubation, the surgical preparation with disinfection and bedding in dorsal position took place. Exposure of the heart was achieved by a median sternotomy in typical manner. After heparinization and accomplishing of an activated clotting time (ACT) over 400 seconds, the connection to the HLM was performed. The aortic cannula was placed into the ascending aorta, the venous cannulation was in most cases connected via the superior and inferior vena cava.

The various anatomic aberrations, including partial cavopulmonary connection, sinus venous defects with partial anomalous pulmonary venous return or doubled insertion of the inferior vena cava, required different approaches of the venous cannulation. But in all cases a total bypass via bicaval cannulation was performed.

The P-MEC® is a closed, fully heparin-coated circuit without a venous reservoir to eliminate the blood-air contact. All components of the P-MEC® circuit are covered with a special Medtronic Carmeda® BioActive Surface heparin coating to increase the biocompatibility and to avoid cell adhesion and thrombotic processes.

The patient´s vascular system replaces the venous reservoir, which is usually used in conventional heart-lung machines. The venous blood is removed from the patient via bicaval cannulation of both the superior and the inferior vena cava. Instead of siphoning by gravity, the blood is actively drained by a kinetic-assisted venous drainage (KAVD) system, which is driven by the Medtronic® BP-50 BioPump centrifugal blood pump. Because of the absence of a venous reservoir, another device for detecting and removing air and bubbles is needed. The Medtronic Affinity® vacuum air removal device (VARD) is placed into the venous line of the Medtronic Resting Heart® System. If air enters the VARD and the liquid level drops below the sensor level, the sensor evokes an acoustic signal to warn the perfusionist. A safety valve gets opened automatically to abandon the bubbles via vacuum suction. But unfortunately this VARD is only available for adult miniaturized bypass systems. In the setup of the P-MEC circuit, the Affinity® arterial filter is placed in venous position and serves as an improvised air trap. The perfusionist has to keep the arterial filter under strict surveillance to detect air bubbles and to eliminate them by opening a valve manually.

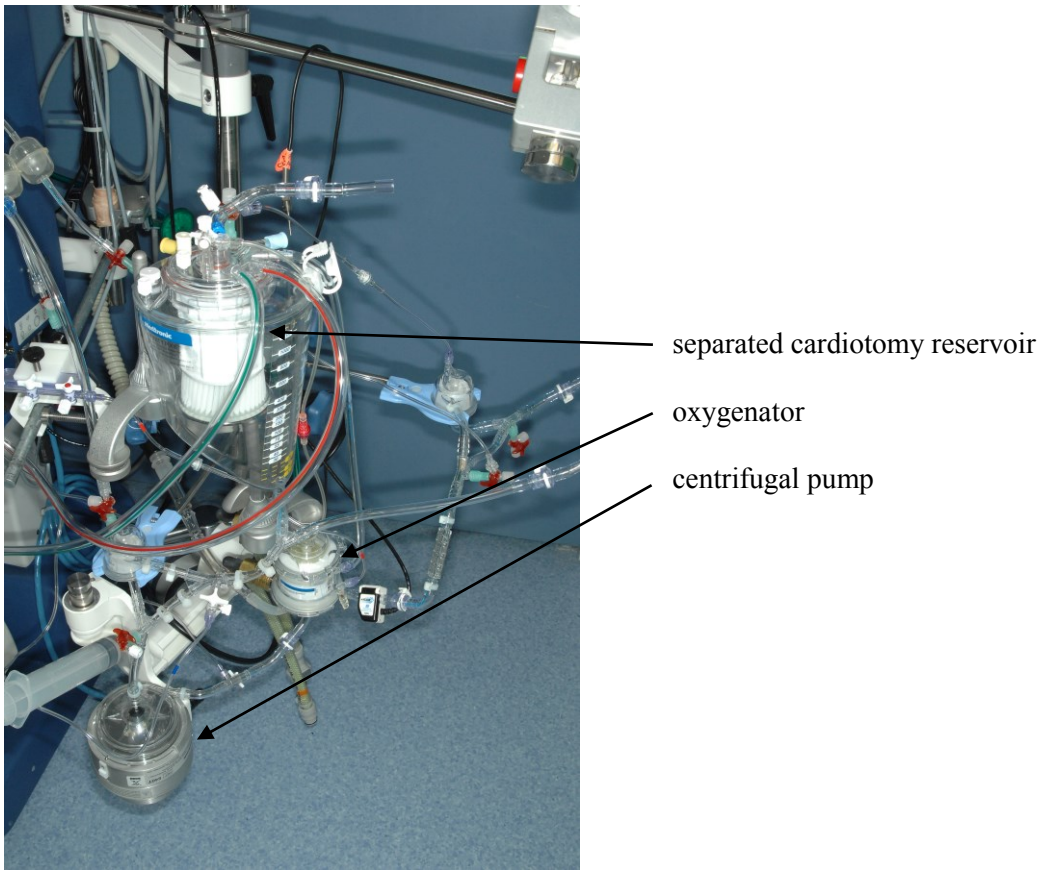

Figure 6: P-MEC components close-up

After the air trap, the blood flows through the centrifugal pump and enters the membrane oxygenator. According to manufacturer´s data, the Medtronic BP-50 BioPump centrifugal blood pump is able to provide a blood flow rate from 0 to 1.5 liters per minute. But our perfusionist´s experiences show that a flow rate of 2 L/min can be achieved easily without any lack of safety. The Medtronic Affinity® Pixie oxygenator has a flow rate up to 2.0 liters per minute. The microporous polypropylene hollow fiber membrane of the oxygenator has a surface area of 0.67 m^2 for diffusion to exchange carbon dioxide with oxygen (technical information from www.medtronic.com, ©2014 Medtronic Inc., seen on the 15th of March, 2014). Also, the anesthetic gas is added while the blood passes the oxygenator.

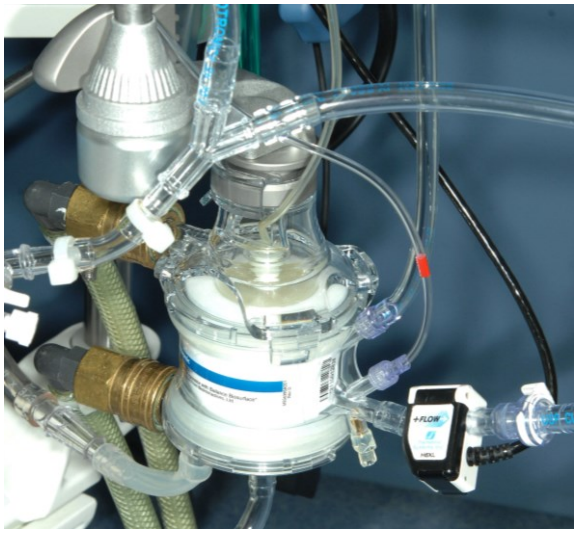

Figure 7: Affinity® Pixie oxygenator

In the tubing line before and after the oxygenator two flow meters are installed for measuring the blood flow and the gradient in between. The first flow meter measures the

suction, which depends on the centrifugal pumps power. If the suction increases the blood flow drops. This is the case when the venous cannula sucks itself because the patient is hypovolemic or the blood volume in the HLM declines. The second flow meter measures the oxygenators outflow. The degree of the gradient between the two measuring points shows the quality of the oxygenator. When the difference is low, the oxygenator has an appropriate flow rate. If a problem occurs in the arterial line, the resistance behind the oxygenator increases which leads to a decline of the gradient. Adhesion of the arterial cannula to the aortic wall may be a reason for that. The gradient rises when the blood viscosity or the hematocrit increases, when blood temperature falls or if the blood forms thromboses inside the oxygenator. All of these events endanger the correct operation of the heart-lung machine. Therefore, to ensure the safety of the P-MEC, those two flow meters as well as the air traps have been installed.

Another ultrasonic fluid sensor is placed behind the oxygenator to detect air and microbubbles, which may emerge from the membrane oxygenation. Additionally, the Affinity® Pixie™ Arterial Filter system is integrated into the arterial line to avoid submerging of foreign particles or bubbles into the arterial vascular system of the patient. To create a closed circuitry, the venous plus the conventional cardiotomy reservoir have been disposed. For safety reasons a modified cardiotomy reservoir is installed in the P-MEC as emergency backup. This cardiotomy reservoir collects the blood from the surgical field, that gets aspirated by an additional pericardial suction drain plus a vent cannula placed in the left atrium via the right superior pulmonary vein. To guarantee the avoidance of blood-air interaction, this modified reservoir is totally separated from the closed circuitry. Just in case that the patient´s blood volume declines or an emergency conversion to open bypass due to excessive bleeding gets necessary, the perfusionist is able to add the suctioned blood to the venous line by opening a connecting tube. With the conversion to an open bypass circuitry, the cardiotomy reservoir turns into the venous reservoir. The application of this separated cardiotomy reservoir as backup is another way to reduce transfusion requirements without abdication of security standards.

Before and after extracorporeal circulation, the Medtronic Cell Saver® device is used to collect the blood from the surgical field. This autoLog® Autotransfusion system allows recycling of erythrocytes. The vacuum-controlled aspiration goes on while heparinized saline or citrate is added simultaneously. Afterwards the blood is washed with saline and the red blood cells are separated from the fluid by centrifugation. The washed erythrocytes are returned to the patient by the anesthesiologist.

For monitoring the patient´s vital signs and blood parameters, it is possible to perform inline-measuring directly on the HLM with noninvasive flow-through spectrometric devices in the arterial and venous lines. It provides measurements of pH, pO_2, pCO_2, BE, HCO_3^- and S_aO_2 in the arterial blood. In the venous line the hematocrit and hemoglobin values plus the mixed venous oxygen saturation S_vO_2 get detected. Supplementary the perfusionist collects arterial blood samples every thirty minutes.

With its numerous ports, the P-MEC system also offers the feasibility of connecting an ultrafiltration device for removing plasma water and excess fluid. Because of its reduced priming volume and the moderate hemodilution degree, the ultrafiltration to raise the hematocrit level becomes redundant in the P-MEC system.

The complete clinical process, including diagnosis, surgery indication, preoperative management, operation method and the postoperative treatment, has been the same as it is performed in surgical treatments with the conventional heart-lung machine.

2.6. Monitoring

Perioperative monitoring was performed routinely, including measuring of the heart rate, arterial and venous blood pressure, oxygen saturation via pulse oximeter, partial pressure of carbon dioxide and temperature, with use of radial artery catheterization, electrocardiography, capnography, pulse oximetry, central venous pressure, trans-esophageal echocardiography and double temperature measuring. Arterial blood gases were collected by both the anesthesiologist and the perfusionist at 6 approximate points of time, including preoperatively, before CPB, immediately after onset of CPB, during CPB, after bypass ending and postoperatively. These blood samples were analyzed with a point-of-care testing (POCT) device, regarding blood parameters as pH, p_aO_2, p_aCO_2, S_aO_2, S_vO_2, hematocrit, base excess, lactate and potassium levels.

A near-infrared spectroscopy (NIRS) was used to measure the regional oxygen saturation in the brain. The NIRS was attached to the patient´s forehead to monitor the oxygenation of cerebral tissue noninvasively.

2.7. Postoperative monitoring and follow-up

During the stay on the intensive care unit, the same parameters and measurements as in patients with conventional cardiopulmonary bypass were collected. These include the

complete blood count with blood parameters such as p_aO_2, p_aCO_2, S_aO_2, S_vO_2, red and white blood cell count, hemoglobin and hematocrit, pH and base excess, calcium, natrium and bicarbonate, blood glucose, lactate and potassium levels, renal and liver parameters plus cardiac biomarkers. All vital parameters were monitored routinely. Several transthoracal echocardiograms and chest radiographs were performed postoperatively to control the size and shape of the heart, heart function and ejection fraction and to evaluate possible pleural or pericardial effusions.

Adverse postoperative events included in the analysis were death, sepsis, reoperation due to postoperative bleeding and embolic events. Follow-up lasted 6 months after discharge of hospital and included clinical examination, surface electrocardiogram, chest radiographs and transthoracic echocardiography.

2.8. Statistical analysis

The clinical trial was constructed as an open, prospective, single center study to evaluate the clinical implementation of the P-MEC® system as a new perfusion tool for pediatric cardiac surgery. All surgeries were performed by Prof. Dr. Igor Knez and his team at the Division for Cardiac Surgery, Department of Surgery, Medical University of Graz, Austria. We performed a retrospective data analysis of the clinical results and routinely measured parameters in the patient´s blood with special regard to hematocrit and lactate values plus transfusion requirements. The retrospective statistical analysis of the clinical data was done using the electronic health records and operation reports. The summarized results are clearly presented in charts and diagrams.

3. Results

3.1. In-hospital results

Between August 2011 and September 2013, fourteen pediatric patients underwent cardiac surgery with the new pediatric-miniaturized extracorporeal circulation system (P-MEC®) at the Clinical Department for Cardiac Surgery, Department of Surgery at the University Hospital of the Medical University of Graz, Austria.

The patients´ demographic data is listed in Table 2.

Pat.	Diagnosis	Procedure	Sex	Age (months)	Weight (kg)	BSA (m^2)
1	ASD II	ASD II closure, ds	m	17	8.1	0.42
2	ASD II	ASD II closure, ds	f	82	18.7	0.76
3	ASD II	ASD II closure, patch	m	44	14.5	0.64
4	UVH	TCPC	m	39	15.7	0.65
5	TGA, VSD	SeptEctShunt	f	30	10.2	0.49
6	ASD II	ASD II closure, ds	f	42	15.0	0.64
7	HRH	TCPC	f	49	12.5	0.61
8	ASD II, PS	ASD II closure, ds +RVOT-Rec.	m	34	12.0	0.52
9	SVASD	mod. Warden	m	9	6.3	0.34
10	SVASD	SVASD closure, patch	f	20	9.5	0.46
11	UVH	PCPC	f	7	7.6	0.36
12	ASD II	ASD II closure, ds	f	30	13.0	0.57
13	ASD II	ASD II closure, perforated patch	f	39	12.1	0.55
14	ASD II	ASD II closure, ds	f	49	15.6	0.67
			Average	35.1	12.2	0.55
			+/-	19.3	3.6	0.12

Table 2: Patients´ demographics

The 5 male and 9 female children had a mean age of 35.1 months ± 19.3 (range from 7 months to 6.8 years). 8 patients (57%) had an ostium secundum atrial septal defect (ASD II), which was closed by direct sutures or an artificial patch. One of the ASD II patients also suffered from a stenosis of the pulmonary valve. This congenital defect was corrected by an ASD closure with direct sutures plus a commissurotomy, valvuloplasty and RVOT-Reconstruction. 3 patients (21%) were born with a functional univentricular heart (UVH), respectively a hypoplastic right heart syndrome (HRH). Two of them underwent a Fontan procedure with an extracardiac total cavopulmonary connection (TCPC), the other one received a Glenn procedure, also called partial cavopulmonary connection (PCPC). Another 2 patients (14%) had a sinus venosus atrial septal defect (SVASD). The one with the supracardiac total anomalous pulmonary venous return (TAPVR) was corrected with a

modified Warden-Repair. The other case of sinus venosus ASD had a partial anomalous pulmonary venous connection to the right atrium, which was corrected with a single patch. Another child was born with a transposition of the great arteries (TGA) and a ventricular septal defect (VSD). These were treated palliatively with an excision of the atrial septum and aortopulmonary shunt ligation (SeptEctShunt).

With an average weight of 12.2 kg ± 3.6 kg (range from 6.3 kg to 18.7 kg) and a mean body surface area (BSA) of 0.55 m^2 ± 0.12 m^2, the P-MEC system was filled with a priming volume ranging from 189 ml to 350 ml, depending on the patients´ BSA and the predefined priming of the circuit components. The body surface area was calculated with the Mosteller formula:

$$BSA\ [m^2] = (height\ [cm] \times weight\ [kg]/3600)^{1/2}$$

The averaged target flow rate was at 1540 ml/min ± 342 ml/min. The target flow rate results from BSA [m^2] multiplied by the Cardiac Index [L/min/m^2]. The Cardiac Index (CI) relates the cardiac output, calculated with stroke volume (SV) multiplied by heart rate (HR), to body surface area with the formula: CI = SV x HR / BSA. For use in pediatric CPB, a Cardiac Index of 2.8 to 3.0 is assumed, depending on the BSA. The smaller the patient, the higher the Cardiac Index.

The duration of cardiopulmonary bypass averaged 72 minutes, with a mean aortic cross clamp time of 13 minutes. On average 127 milliliters cardioplegic solution was used to set the heart in diastolic arrest.

Only in one case, an homologous transfusion of packed red blood cells (pRBC) was needed after termination of cardiopulmonary bypass to keep the patient hemodynamic stable. Although the hemoglobin value was not too low with 9.2 g/dl, 120 milliliters of pRBC were administered to the patient to increase the hematocrit oxygen carrying capacity and to ensure sufficient oxygen delivery. All the other surgical interventions were performed without a foreign blood transfusion. During their stay on ICU, three patients suffered from postoperative anemia, which was treated with oral or parenteral iron supplement. Another three infants required an intravenous infusion of packed red blood cells on their first postoperative day, because of a decrease of their hemoglobin levels (shown in Table 5).

Pat.	Procedure	BSA (m^2)	Priming volume P-MEC	Target flow (ml/min)	Duration of CPB (min)	Aortic Clamp (min)	Lowest Temp. (°C)	Cardio-plegia (ml)	Intraop. transfusion
1	ASD II closure, ds	0.42	189	1211	30	9	34.6	50	no
2	ASD II closure, ds	0.76	189	2116	46	15	35.2	200	no
3	ASD II closure, patch	0.64	189	1779	39	16	34.0	200	no
4	TCPC	0.65	250	1848	127	0	34.0	0	no
5	SeptEctShunt	0.49	250	1365	43	7	35.5	150	no
6	ASD II closure, ds	0.64	250	1780	48	19	36.0	100	no
7	TCPC	0.61	250	1736	107	0	35.0	0	no
8	ASD II closure, ds +RVOT-Rec.	0.52	200	1449	70	24	31.0	300	no
9	mod. Warden	0.34	350	952	145	33	32.0	150	no
10	SVASD closure, patch	0.46	280	1278	59	21	32.0	200	no
11	PCPC	0.36	350	1020	143	0	36.0	0	120ml pRBC
12	ASD II closure, ds	0.57	300	1587	64	17	34.6	130	no
13	ASD II closure, perf. patch	0.55	220	1560	53	14	34.0	150	no
14	ASD II closure, ds	0.67	300	1876	36	11	35.0	150	no
	Average	0.55	254.8	1540	72	13	34.2	127	
	Standard deviation	0.12	55.6	342.8	41	9.7			

Table 3: Surigical data

None of the cases required an emergency conversion to an open conventional bypass. Neither death nor any other postoperative complications, including embolism, sepsis or reoperation due to excessive bleeding, occurred in any of the 14 patients. In one case a reoperation was required caused by a newly occurred right-to-left shunt on the third day on ICU. The averaged length of stay on intensive care unit was 6.9 days, whereas the length of stay in hospital amounted to 17.8 days.

3.2. Biochemical results

We used the lactate and hematocrit levels to show the progress of hemodilution with onset of CPB and to evaluate the extent of anaerobic metabolism caused by minder perfusion. The peri- and postoperatively measured lactate and hematocrit values are presented as raw data in Table 4.

Pat	Procedure	BSA (m^2)	Prim-ing (ml)		before CPB	on CPB I	on CPB II	post CPB	after opera-tion	on ICU
1	ASD II closure, ds	0.42	189	Hct (%)	30	22	22	23	26	25
				Lac (mmol/L)	0.8	0.9	0.8	1.0	0.8	0.9
2	ASD II closure, ds	0.76	189	Hct (%)	36	27	28	33	36	36
				Lac (mmol/L)	1.0	0.8	0.8	0.8	0.7	0.7
3	ASD II closure, patch	0.64	189	Hct (%)	32	24	24	25	28	30
				Lac (mmol/L)	1.0	0.8	1.6	1.2	0.8	-
4	TCPC	0.65	250	Hct (%)	46	33	33	33	28	28
				Lac (mmol/L)	0.9	0.8	0.9	0.9	1.3	1.0
5	SeptEctShunt	0.49	250	Hct (%)	56	35	35	42	40	46
				Lac (mmol/L)	1.0	0.8	0.8	0.8	0.9	1.2
6	ASD II closure, ds	0.64	250	Hct (%)	33	28	26	29	30	32
				Lac (mmol/L)	1.2	1.2	1.2	1.2	0.8	0.8
7	TCPC	0.61	250	Hct (%)	45	26	26	25	48	44
				Lac (mmol/L)	1.1	1.0	1.0	1.6	2.4	2.7
8	ASD II closure, ds +RVOT-Rec.	0.52	200	Hct (%)	31	21	23	22	23	19
				Lac (mmol/L)	0.7	0.7	0.9	0.8	0.5	0.7
9	mod. Warden	0.34	350	Hct (%)	29	23	23	26	37	35
				Lac (mmol/L)	0.7	1.3	1.5	1.4	1.5	1.5
10	SVASD closure, patch	0.46	280	Hct (%)	36	25	25	27	27	27
				Lac (mmol/L)	1.1	1.3	1.8	1.4	0.7	0.7
11	PCPC	0.36	350	Hct (%)	45	27	27	28	38	40
				Lac (mmol/L)	0.9	0.8	0.7	1.3	1.1	1.3
12	ASD II closure, ds	0.57	300	Hct (%)	30	23	23	27	29	32
				Lac (mmol/L)	1.3	1.0	1.0	1.2	2.0	2.3
13	ASD II closure, perf. patch	0.55	220	Hct (%)	30	24	23	22	24	29
				Lac (mmol/L)	1.0	1.4	1.2	0.9	0.8	0.8
14	ASD II closure, ds	0.67	300	Hct (%)	29	25	25	24	26	34
				Lac (mmol/L)	1.5	1.5	1.7	1.3	0.8	0.7

Table 4: Course of the hematocrit and lactate values

The course of the hematocrit levels before, at two time points during and after cardiopulmonary bypass, after operation and on ICU is shown in chart 1 (patient 1-7) and chart 2 (patient 8-14).

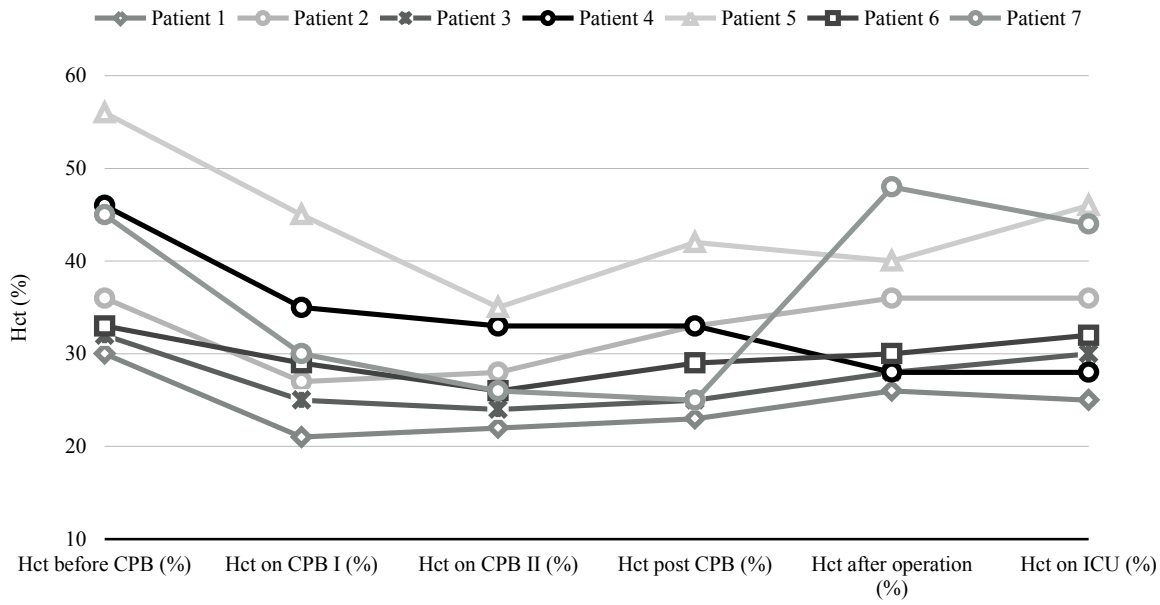

Chart 1: Course of the hematocrit values (patient 1-7)

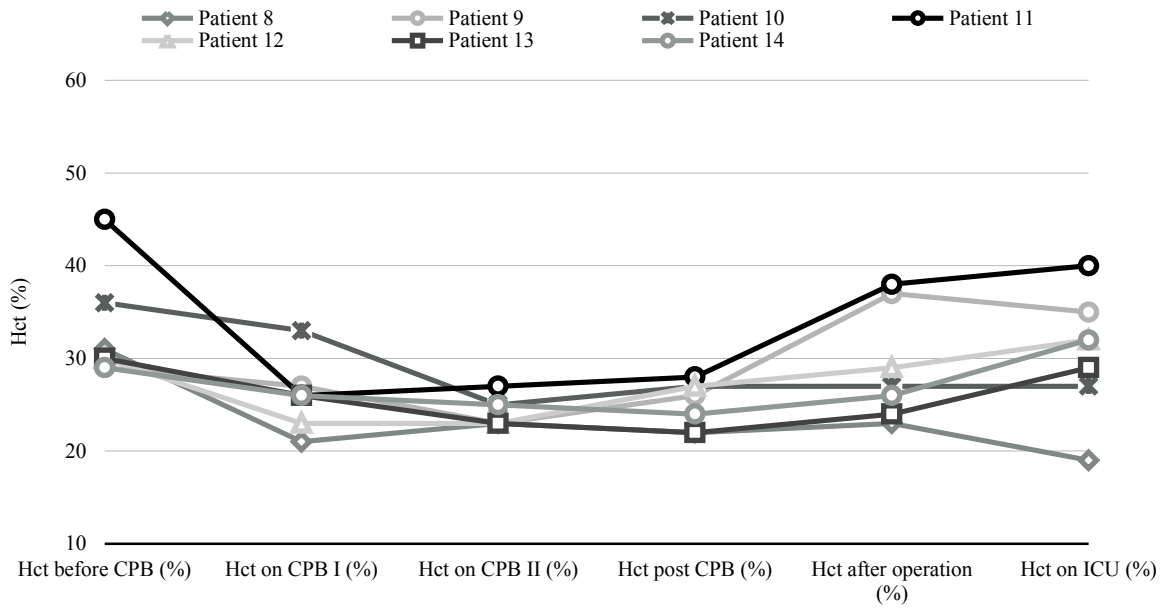

Chart 2: Course of the hematocrit values (patient 8-14)

As presented in the two charts above, the hematocrit level drops with onset of cardiopulmonary bypass, then during bypass a rather stable development and an increase between the termination of bypass and the end of operation. This rise can be explained by reinfusion of the Cell Saver blood. The postoperative course of the hematocrit level depends on the treatment on ICU, with regard to the administered drugs and infusions plus the required volume balancing. The average hematocrit was 36.3 % before bypass, 28 % respectively 25.9 % during bypass (CPB I and II), 27.6 % after cessation of bypass and 31.4 % after end of operation. The hematocrit values on ICU averaged 32.5 %.

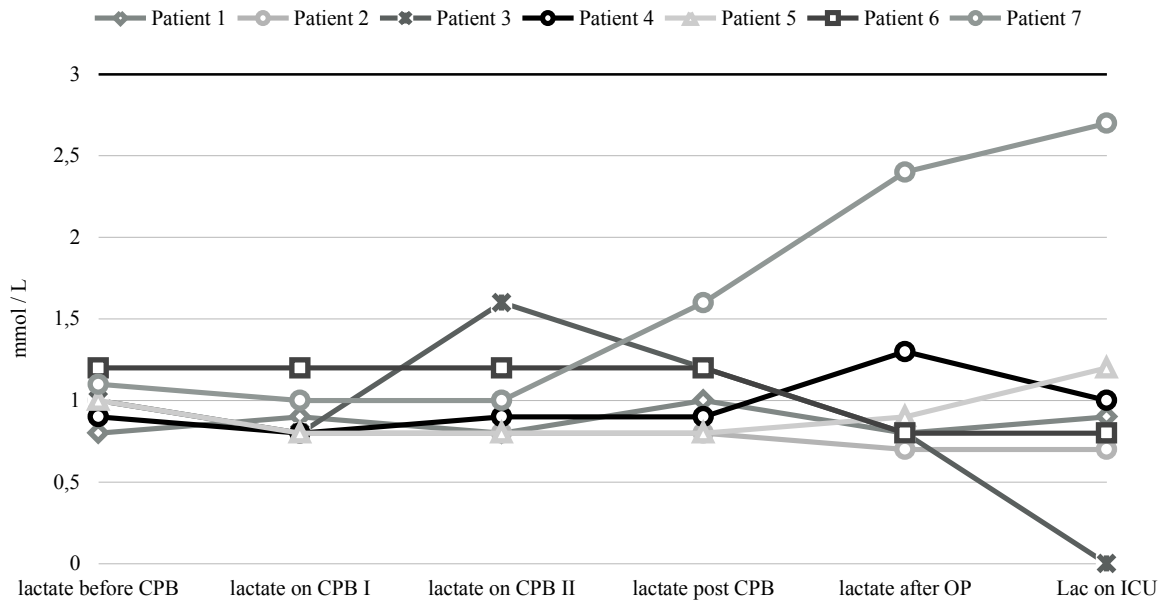

Chart 3: Course of lactate levels (patient 1-7)

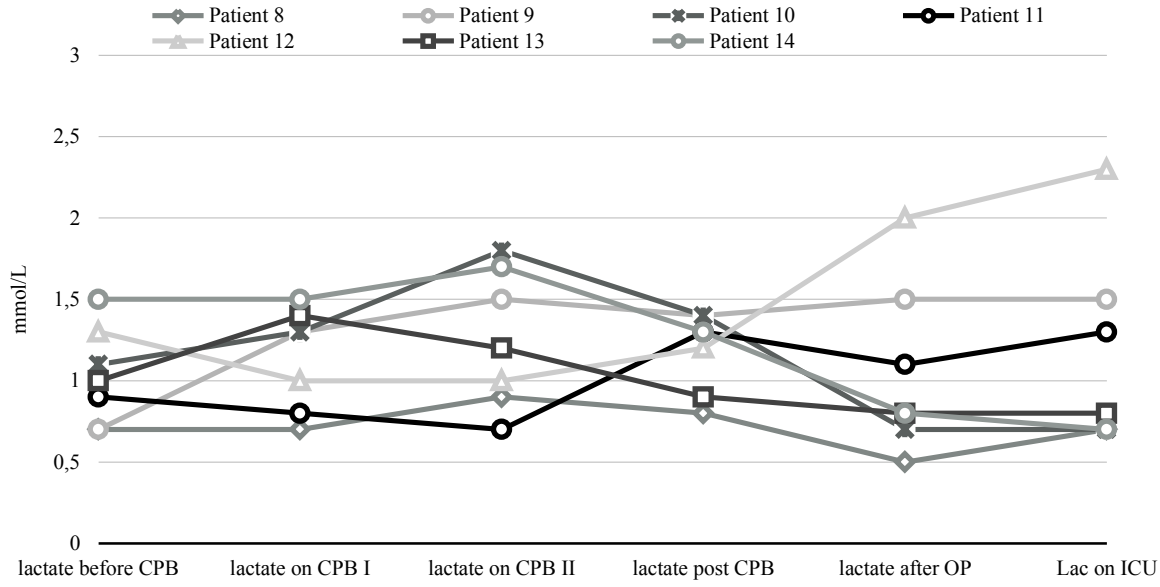

Chart 4: Course of the lactate levels (patient 8-14)

The pre-, intra- and postoperative course of the individual lactate values is presented in the two charts above (chart 3 for patient 1-7 and chart 4 for patient 8-14). There is no significant raise of the lactate level with the onset of extracorporeal circulation or during the CPB. The fact that most of the lactate levels after CPB are not appreciably increased when compared to the preoperative lactate levels is notable. That shows the quality of perfusion flow rate of the P-MEC system.

3.3. Long-time results

Neither death nor any other postoperative complications, including embolism, sepsis or reoperation due to excessive bleeding, emerged in any of the 14 patients. All patients visited the cardiological pediatric clinic after one, three and six months after operation. They underwent clinical examination, surface electrocardiogram, chest radiographs and transthoracic echocardiography to evaluate their recovery. The postoperative course and patients´ follow-up results are presented in Table 5.

Pat	Procedure	Events on ICU	Reoperation	postop. bleeding	Embo-lism	Sepsis	Discharge from hospital	Follow-up
1	ASD II closure, ds	IVC stenosis, right-to-left shunt	ASD closure, patch	postop. anaemia (Hb 7,5 g/dl) → erythropoietin + parenteral iron supplement	no	no	sinus rhythm, EF 75%, hypothyroidism, iron deficiency anemia	no impairments, ASD closed, regr. dilatation RV, sinus rhythm
2	ASD II closure, ds	cardiac support with low-dosed norepinephrine for 2 days, pacemaker dependent, temporary bradycardia and AV block III°, rest ASD (hemodynamic irrelevant)	no	no	no	no	sinus rhythm, EF 80%	no impairments, good biventricular function, AV-node rhythm
3	ASD II closure, patch	cardiac support with norepinephrine for 1 day, then cardiorespiratory stable	no	no	no	no	regressive dilatation of right ventricle	sinus rhythm, no impairments, good biventricular function, EF 70%
4	TCPC	4 days support with cardiac stimulants, then cardio-respiratory stable, SpO_2 92%, nocturnal bradycardia with AV-node rhythm	no	postop. anaemia treated with oral iron supplement	no	no	cardiac symptom-free, sinus rhythm, good univentricular function, SpO_2 94%, start with anticoagulant therapy	no impairments, good univentricular function, EF 65%, SpO_2 93%, cardiac catheterization unremarkable
5	SeptEct-Shunt	cardiac support with catecholamines for 2 days, cardiorespiratory stable	no	no	no	no	SpO_2 78%, good univentricular function,	SpO_2 70% before cardiac catheterization for Blalock-Taussig shuntligation
6	ASD II closure, ds	cardiac support with catecholamines for 2 days, cardiorespiratory stable	no	mild postop. anaemia treated with oral iron supplement	no	no	cardiac symptom-free, sinus rhythm, good biventricular function, RV regressive	no impairments, ASD closed, regular sized ventricles, sinus rhythm

Pat	Procedure	Events on ICU	Reoperation	postop. bleeding	Embo-lism	Sepsis	Discharge from hospital	Follow-up
7	TCPC	protracted ventilation due to atelectasis, cardiac support with catecholamines for 2 days, EF 71%, bradycardiac sinus rhythm	stenosis of the extracardiac conduit into the left+right pulmonary artery → condensing of conduit (2 months after TCPC)	no	no	no	SpO_2 90%, EF 65%, hemodynamic irrelevant stenosis of the IVC, also a stenosis in the extracardiac conduit, sinus rhythm	massive pleural effusion, RPA stenosis; after revision of the extracardiac conduit still massive pleural effusion (500ml/d), lymphedema
8	ASD II closure, ds +RVOT-Rec.	cardiorespiratory stable, no catecholamine support needed	no	postop. Hb 6 g/dl → 60ml pRBC,	no	no	good biventricular function, EF 75%, RVOT-Obstruction regressive	chronic obstipation, no cardiac impairments, sinus rhythm, regular sized cardiac chambers
9	mod. Warden	EF 61%, RV dilatation, bradycardia with AV-node rhythm, diaphragmatic paresis left, cardiac support with catecholamines for 2 days	no	no	no	no	SpO_2 98%, EF 70%, RA+RV hypertrophy	no cardiac impairments, SpO_2 96%, sinus rhythm, regressive RA+RV hypertrophy, stenosis of the left pulmonary veins
10	SVASD closure, patch	cardiac support with norepinephrine for 1 day, cardiorespiratory stable, SpO_2 97%	no	no	no	no	SpO_2 94%, LV-EF 68%, RA+RV hypertrophed, all 4 pulmonary veins into left atrium, sinus rhythm	no cardiac impairments, SpO_2 98%, sinus rhythm, regressive RA+RV hypertrophy
11	PCPC	cardiac support with norepinephrine and Ca-Sensitizer for 2 days, cardiorespiratory stable, SpO_2 85%, EF 50%, pericardial effusion after 6 days	no	100 ml pRBC	no	T 38,9°C, 8mm pericardial effusion, either postcardiotomy syndrome or infection	SpO_2 89%, good univentricular function, good response to antibiotics and steroids, small pericardial effusion	no cardiac impairments, SpO_2 84%, sinus rhythm, good univentricular function
12	ASD II closure, ds	cardiac support with milrinone for 1 day, cardiorespiratory stable, pleural effusion	no	120 ml human plasma protein	no	no	SpO_2 100%, good biventricular function	no cardiac impairments, SpO_2 99%, sinus rhythm, good biventricular function
13	ASD II closure, perforated patch	cardiac support with milrinone for 1 day, cardiorespiratory stable	no	Hb 8,1 g/dl → 120 ml pRBC	no	no	SpO_2 93%, good biventricular function, pulmonary hypertension	still pulmonary hypertension with 2/3 systemic pressure in RV/PA and tricuspidal insufficiency I°, EF 65%, SpO_2 99%, sinus rhythm, no cardiac impairments
14	ASD II closure, ds	cardiorespiratory stable, no catecholamine support needed, pleural effusion	no	no	no	no	SpO_2 100%, LV-EF 67%, RA + RV dilated, no pleural effusion	no cardiac impairments, SpO_2 100%, sinus rhythm, good biventricular function

Table 5: Postoperative course on ICU and follow-up

3.4. Perfusionist´s calculations

The aim of our investigation were the advantages of our P-MEC system in terms of the savings of priming volumes and foreign blood transfusions. Therefore we calculated the amount of packed red blood cells to maintain an hematocrit level of 20 % respectively 25 % during performance of conventional cardiopulmonary bypass. These calculations are based on the priming volumes for open bypass circuits, such as the Stöckert console with the Terumo Capiox FX 05 and FX 15 oxygenator, which are used at our department for conventional pediatric CPB.

Pat.	BSA (m^2)	Priming P-MEC (ml)	Priming conv. bypass (ml)	Needed pRBC for Hct 20% (ml)	Needed pRBC for Hct 25% (ml)
1	0.42	189	350	-92	-6
2	0.76	189	750	-161	35
3	0.64	189	750	19	183
4	0.65	250	750	-304	-131
5	0.49	250	350	-147	-46
6	0.64	250	750	10	178
7	0.61	250	750	-69	82
8	0.52	200	750	126	274
9	0.34	350	400	0	0
10	0.46	280	400	-59	41
11	0.36	350	450	^	5
12	0.57	300	700	62	212
13	0.55	220	800	109	261
14	0.67	300	700	43	213

Table 6: Alternative priming volumes for conventional CPB

The perfusionist calculates as follows: the patient´s weight is multiplied by the assumed blood volume of a child with 80 ml/kilogram body weight to receive the total blood volume. For example, a child with 13.0 kg weight has an estimated total blood volume of 1040 ml.

Age	Blood volume
0 - 3 months	90 ml/kg
3 - 6 months	85 ml/kg
1 - 10 years	80 ml/kg
male adult	70 ml/kg
female adult	60 ml/kg

Table 7: Norm values for human blood volumes

An hematocrit of 30 % equates to 312 ml red blood cells (RBC). The 1040 milliliters total blood volume of the patient plus the CPB priming volume, e.g. 700 ml, make 1740 ml of system volume. In those 1740 ml, 312 ml RBC equates to 17 % hematocrit. To achieve an

hematocrit level of 25 % in 1740 ml, we need 123 ml RBC more (25 % = 435 ml in 1740 ml). Since packed red blood cells (pRBC/ erythrocyte concentrate) only have an hematocrit of 58 percent, 212 milliliters are required to gain an hematocrit of 25 % in 1740 ml of the system volume.

Table 6 presents the alternative priming volumes and the required amount of pRBC for the conventional CPB. In some cases, the calculated results for needed pRBC are negative. This shows that no erythrocyte concentrates would have been required to prime the conventional bypass circuit.

In case of using conventional cardiopulmonary bypass, six children would have needed a CPB priming with pRBC to maintain an hematocrit level of 20 %. And for an hematocrit level of 25 % ten children would have received a pRBC transfusion to prime the cCPB circuit.

4. Discussion

Although cardiopulmonary bypass is indispensable to perform open-heart surgeries, the use of extracorporeal circulation entails adverse effects on the patient´s body. Not only an immunologic defense reaction causing a systemic inflammatory response is implemented, but also the activation of the complement system plus the coagulation cascade is started up. Excessive hemodilution due to large priming volumes results in perioperative coagulation disorders, blood loss and thus in increased transfusion requirements. Embolic events, strokes and other neurological impairments are the most dreaded complications among the patients. But also renal or pulmonary dysfunction increases the CPB-related mortality and morbidity risks. Different approaches to attenuate that damaging impact of cardiopulmonary bypass have been developed in the recent years. One of the best evidence-based new bypass technique is the miniaturized extracorporeal circulation (mini-ECC) system. Its setup consists of a closed circuitry with a membrane oxygenator and a centrifugal pump, but without the venous reservoir. This results in a reduced priming volume, decreased surface area and less blood-air interface. Additionally, the biocompatibility is increased as a result of the heparin-coated surface. The beneficial application of mini-ECC circuits has been verified by numerous studies. Vohra et al. performed a large review of literature (Level of evidence A, Class I) in 2009, with regard to a softened inflammatory response and reduced need for blood transfusion when using a mini-ECC system instead of a conventional CPB [110]. The studies of Fromes et al. plus Remadi and associates showed a decrease of inflammatory markers such as CRP, leucocytes and cytokines leading to a lowered systemic inflammatory response [27], [15]. According to the trials of Remadi and Immer, the modified mini-ECC setup saves priming solution, which causes only moderate hemodilution with higher hemoglobin plus hematocrit levels and less need for blood transfusion [15], [31]. Immer et al. also noted an earlier extubation and shorter stay on ICU in their prospective, non-randomized, single center study (Level B, Class IIa) with 1053 patients undergoing cardiovascular surgery with the closed Jostra MECC system (Jostra AG, Hirlingen, Germany) [31]. Wiesenack and associates performed a large retrospective data analysis of 970 CABG patients (Level of evidence C, Class IIa) and reported on their four years experience with the Jostra MECC system. They found higher intraoperative lactate levels and more consumption of blood products in the conventional CPB group. Also an increased incidence of postoperative complications including stroke, myocardial infarction, atrial fibrillation, low cardiac

output, renal failure and rethoractomy [30]. Referring to this, Alevizou and associates reported on the best evidence topic regarding the question if the miniaturized bypass technique can reduce the postoperative complications after cardiac surgery. After performance of a large literature search and evaluation of 144 papers, they included randomized studies with more than 20 patients and non-randomized studies with a sample size > 150 patients. They finally subsumed 14 papers, that gave the best evidence that mini-ECC systems are a new and promising alternative to conventional CPB [111].

Of course, criticism concerning this new perfusion technique also exists. Nollert et al. stopped any further investigations with the miniaturized bypass systems as a result of their bad experiences with 15 CABG patients in 2005. Two cases of dangerous air leaks occurred in their mini-ECC group. Furthermore the operative handling of venting and fluid management proved to be difficult. Therefore, Nollert et al. concluded that the safety lacks of the closed circuitry predominate its advantages [112]. Other authors share these safety concerns. Ranucci and associates also were skeptic about the promised benefits of the mini-ECC, because clinical studies about the effectiveness of improved postoperative outcome with large patient population were missing. So, Ranucci performed a large retrospective data analysis of 1663 patients treated with a minimally invasive CPB (MICPB). Their control group consisted of 2877 CABG patients. They detected shorter stays on the ICU and in hospital, a lighter postoperative increase of serum creatinine and bilirubin concentration, lower incidence of atrial fibrillation and ventricular arrhythmias plus less postoperative blood loss in the MICPB group [113].

Table 8 lists the studies and papers that were used for the discussion and gives a review of its level of evidence pursuant to the current guidelines from the European Society of Cardiology (ESC) [114].

Author	Summary of study content	Study type	Level of evidence	Classes of recommen-dation
Vohra et al., 2009 [110]	review of current literature concerning use of mini-ECC with regard to lowered systemic inflammatory response and reduced postoperative complications plus less transfusion requirements	review of literature	Level A	Class IIa
Immer et al., 2007 [31]	1053 patients undergoing CABG with mini-ECC, reduced inflammatory markers, earlier extubation, shorter stay on ICU, less need for inotropic support and blood transfusion	prospective, non-randomized single-center study	Level B	Class IIa
Wiesenack et al., 2004 [30]	485 CABG patients with mini-ECC perfusion, heparin coated circuit, lower incidence of postoperative complications, reduced perioperative transfusion of pRBC	retrospective data analysis, not randomized	Level C	Class IIa

Author	Summary of study content	Study type	Level of evidence	Classes of recommen-dation
Mahmood et al., 2012 [115]	perfusion with heparin-coated bypass systems is preferably to uncoated CPB because of reduced blood loss and transfusion requirements, reoperation rates, LOS on ICU and in hospital; heparin-bonded circuits have improved biocompatibility with less leucocyte and complement activation	best evidence topic with 792 papers reporting on the search, of which 13 papers present best evidence	Level A	Class I
Alevizou et al., 2009 [111]	10 prospective randomized controlled trials (PRCT) reported on benefits such as reduced hemodilution, decrease of bleeding and transfusions, shorter ICU stay and better renal, inflammatory and neurological function with use of mini-bypass circuits	144 papers related to addressed question, 14 papers gave best evidence topic	Level A	Class I
Harvey et al., 2011 [116]	summary of the worldwide extent of new perfusion techniques and devices such as closed venous reservoirs, bubble detectors, oxygen analyzer, surface coatings, VAVD, roller or centrifugal pumps and arterial filters	web-based survey of current perfusion practice in pediatric cardiac surgery	Level A	-
Hirsch et al., 2012 [59]	neuromonitoring and neuroprotecting strategies during infant CPB, avoidance of extreme hemodilution with an hematocrit of 24% was best evidence-based procedure	systematic review of literature, including 162 papers	Level A	Class I
Wypij et al., 2008 [91]	hematocrit level of approximately 24% is associated with higher PDI scores and reduced lactate levels with low-flow CPB	two prospective randomized, single center trials, 271 pediatric patients	Level B	Class II
Richmond et al., 2012 [63]	perioperative need for blood transfusion is related to the CPB prime volume; priming volume is an independent predictor of transfusion; even a decrease of 10-20 ml in priming volume effects the consumption of pRBCs in pediatric cardiac surgery	retrospective review of 2178 pediatric patients, single center, non-randomized trial based on observational data	Level C	Class II
Koster et al., 2009 [23]	13 neonates (< 28 days) underwent cardiac surgery with new miniaturized CPB system; setup contains the Stöckert mast-mounted console with a low-prime oxygenator and arterial filter, 110 ml priming volume, open circuitry; 6 Patients had transfusion-free surgery	retrospective analysis of patient´s data; summary of experiences in a single-center, non-randomized trial	Level C	Class IIa

Table 8: Papers with level of evidence & classes of recommendation according to ESC guidelines [114]

According to Mahmood et al., the use of fully heparin-coated bypass systems is the best evidence-based strategy to improve the biocompatibility of extracorporeal circulation tools. They performed a large literature review concerning the question if a fully heparin-bonded CPB circuit is superior to a standard CPB. 13 papers out of 792 represented the best evidence on the topic. Perfusion with heparin-bonded, respectively the third-generation heparin-polymer-coated circuits produces less proinflammatory cytokine production and complement activation. The increased platelet preservation as a result of the improved biocompatibility is associated with a reduced blood loss plus less transfusion

requirements. This has a positive impact on the reoperation rates, duration of ventilation and on the length of stay on ICU and in hospital [115].

Although numerous studies proved mini-ECC systems to be favorably and superior to conventional CPBs in terms of adverse effects and outcome, the clinical acceptance and application of mini-ECC in adult cardiac surgery is not widely spread. Most heart centers still use conventional CPB, probably because it is hard to change daily routine and to leave the safe pathway. In pediatric cardiac surgery it is even worse. Harvey et al. presented their 2011 survey results about the pediatric perfusion practices at the 50th International Conference of the American Society of Extracorporeal Technology at New Orleans in 2011. They performed a large electronic survey with 107 questions about equipment, techniques and current clinical practices of pediatric perfusion by sending this request to 289 congenital surgery centers all over the world. Only 10 percent of the centers reported to use closed venous reservoir systems [116]. This status is reflected in the current literature. Most clinical trials deal with open miniaturized bypass systems for perfusion of pediatric patients. Those systems are downsized in regard to their priming volume, but still have an open venous reservoir. The miniaturization indeed reduces the mismatch between the patient´s blood volume and CPB priming volume, but does not include the favorable prevention of blood-air contact like a closed mini-ECC system would.

Moderate hemodilution as a result of minimized priming volume is associated with higher hematocrit and hemoglobin levels during and after extracorporeal circulation. Numerous studies proved that higher hematocrit levels offer a sufficient oxygen delivery to all tissues and hence a better postoperative outcome. Wypij et al. performed two randomized trials of hematocrit strategies in 271 pediatric patients. An hematocrit level of 24 % is related with higher Psychomotor Development Index (PDI) scores at age of 1 years and decreased peri- and postoperative lactate concentrations [91]. Hirsch and associates drew the same conclusion in their systematic review of literature concerning protection strategies for the infant brain. 162 papers met inclusion criteria and enabled an evidence-based evaluation of neuromonitoring and neuroprotecting practices. They recommended only one strategy with clear evidence for effectiveness: avoidance of severe hemodilution and maintenance of an hematocrit level of 24 % [59].

A detractor of the P-MEC system could argue that using modified ultrafiltration (MUF) after extracorporeal circulation also reduces the hemodilution and increases the patient´s hematocrit concentration. Here is to say, that MUF really raises the oxygen carrying capacity by removing additional plasma water, but only after the termination of bypass. By

using the miniaturized P-MEC as perfusion tool, an excessive hemodilution is prevented right from the start of bypass. This results in better oxygen delivery and less dilution of coagulation factors already during extracorporeal circulation, which is related to a less perioperative blood loss and reduced consumption of blood products.

Before the invention of miniaturized bypass systems it has been impossible to perform transfusion-free cardiac surgery in children. The large disparity in patient´s total blood volume and conventional CPB priming always necessitated red blood cell-transfusion to maintain secure hemoglobin and hematocrit concentrations during bypass. Richmond et al. identified the CPB prime volume as an independent predictor of perioperative transfusion [63]. In the last ten years, various centers for congenital cardiac surgery explored the implementation of minimized bypass circuits and their effect on allogenic transfusion requirements. Kotani et al. reported on their single-center experiences with a low-volume CPB circuit and transfusion-free open-heart surgery. They retrospectively analyzed 536 infantile patients weighing 5 to 20 kilograms. For a flow rate < 1500 ml/min the circuit was primed with 300 milliliters, whereas a required flow rate of 1500 to 2300 ml/min resulted in an CPB priming of 550 milliliters. The mini-HLM was constructed as an open circuitry with the Terumo baby RX05 oxygenator, respectively the Dideco D902 oxygenator. They achieved transfusion-free surgery in 264 of 536 patients [117]. Miyaji and colleagues performed transfusion-free surgery in 45 children with complex congenital heart defects and a body weight of 4 to 7 kilograms by using an open circuit with 140 ml priming volume [20]. Also the team of the German Heart Institute in Berlin, including A. Koster, M. Hübler and M. Redlin, deals with the clinical application of a miniaturized bypass system. They incorporated the low-prime KIDS D100 oxygenator (Sorin Group) into a Stöckert S3 mast mounted pediatric console, an open neonate CPB system (by Stöckert Instrumente GmbH, Munich, Germany). This system has been downsized by shortening all tubing connections, reducing the tubings´ internal diameter and using the Sorin D130 arterial filter. Despite still having a venous and cardiotomy reservoir, Koster et al. managed to reduce the priming volume down to 110 milliliters. With this low-prime CPB circuit, Koster et al. are able to perform complex cardiac surgeries in neonates with a reduced perioperative need for allogenic blood transfusion [23], [24], [25]. Based on the results from these studies, transfusion-free complex congenital cardiac surgeries are performable by using miniaturized bypass circuits. But most of the pediatric patients need pRBCs after the operation during their first days on ICU. That postoperative need for blood transfusions distinguishes the open bypass systems from our closed P-MEC system.

Using the P-MEC bypass technique enables transfusion-free complex cardiac surgeries and results in a reduction of postoperative consumption of foreign blood. Apart from that case of intraoperative blood transfusion after termination of P-MEC bypass, only three of our patients received pRBC infusion due to low hemoglobin values within their first postoperative day on the ICU. Thus we managed to show that the total amount of pRBC transfusion is decreased by the use of the P-MEC bypass system. The calculations of the transfusion requirements for alternative priming of the conventional CPB clearly demonstrate this reduction.

The miniaturized low-volume bypass systems still have one big drawback: they have an open venous reservoir, which permits blood-air contact. Koster et al. also explored bypass systems with further approaches to circuit closure. In their 2005 published pilot study, they draw the conclusion that an increased attenuation of the hemostatic activation could be achieved by reducing the blood-air interface. Of the three tested closed CPB systems, the one with passive venting of the heart into a collapsible venous reservoir significantly reduced the hemostatic activation [118]. Numerous other studies reported the same findings about the impact of blood-air interface on the activation of the hemostatic system and consequential on the systemic inflammatory response. Schönberger et al. detected an higher increase of complement 3a, neutrophil elastase and coagulation factors such as thromboxane B2 and fibrin degradation products in the patient group with open venous reservoir. The group with the closed reservoir system built up of a collapsible venous reservoir had a reduced count of hemolytic cells as well as a decreased need for pRBCs [119]. These findings suggest that closed bypass circuits with reduced blood-air interface, just like our P-MEC system, are associated with less hemostatic activation and higher platelet counts. This results in an attenuated immune reaction plus less coagulation disorders.

And the systemic blood activation induced by blood-air contact is not the only problem that air poses. Air embolism is the new challenge that closed CPB systems come along with. The difficult air handling characteristics plus potential air suction via the venous or vent cannula and consequential air embolism represent the largest objection in terms of omitted venous reservoirs. In particular, the kinetic-assisted venous drainage (KAVD) is thought to be dangerous for entering air. Because of the eliminated venous reservoir, it is hard to detect air bubbles in the venous line and even more to get rid of them. Owing to that security deficiency, the Affinity® arterial filter is incorporated in our P-MEC circuit and serves as an improvised air trap in venous position. This air trap allows to detect the

air bubbles and to discharge them by opening a valve. Additionally, suture strings and tourniquets are placed around the cannulated veins to fix the bicaval cannulas and to avoid air suctioning during total bypass on the P-MEC. Perthel et al. demonstrated a lower count of microbubbles in the venous line of the miniaturized bypass circuit due to an additional sealing of the venous cannula [120]. Especially in congenital cardiac surgery with opened right heart chambers, the fixation of the venous cannulas with tourniquets is routinely used. So, closed CPB systems would not require a change in venous cannulation practices.

Another argument of the critics is the problem with excessive bleeding and the volume handling. In consequence of the omitted venous reservoir, the patient´s vascular system serves as blood reservoir. In case of a decreased venous return due to excessive blood loss, both the CPB circuit and the patient are endangered to drain off. Here it would take too long to reinfuse the collected blood via the Cell Saver device. Therefore we inserted some preventive measures in the P-MEC system to face the danger of excess bleeding. On the one hand we use a modified cardiotomy reservoir to collect the aspirated blood from the additional pericardial suction drain and the venting cannula. This reservoir is strictly separated from the closed circuitry and is only added to the venous line, if more blood volume is needed. On the other hand, the cardiotomy reservoir can serve as the venous reservoir if an emergency conversion to an open bypass is required. This backup reservoir enables the management of all unpredictabilities.

Of course, this modified P-MEC setup and all the safety devices are associated with higher costs than a conventional cardiopulmonary bypass. But the reduced incidence of postoperative complications and improved outcome with consequential less treatment expenses compensate the higher costs for the surgical intervention. Mozol et al. performed a prospective randomized study about the cost-effectiveness of miniaturized bypass circuits. Although his assessment was based on a small patient population of only 30 infants, Mozol was able to show an improved postoperative outcome and a significant reduce of treatment costs [121]. This reduction of costs is achieved by shorter duration of mechanical ventilation, less consumption of blood products, decreased complication rates and reduced length of stay on ICU and in hospital postoperatively.

4.1. Limitation of the study

One major limitation of this clinical trial is the small patient cohort, that was used for the evaluation of the new P-MEC system. Although the period of time lasted from August

2011 to September 2013, only fourteen children met the inclusion criteria. The feasibility of the P-MEC bypass was determined by the maximum flow rate of the Affinity Pixie® Oxygenator with 2.0 Liters per minute. So, only children with an adequate target flow rate below 2.0 L/min were suitable for P-MEC perfusion with the Pixie oxygenator. This target flow rate presupposed a body weight below 20 kilograms or a BSA smaller than 0.70 m^2.

Because of the small number of adequate patients, no control group for comparison with conventional CPB could be established. The statistical assessment is thereby limited. A descriptive statistic was performed by using the retrospective analysis of the patient´s data and presenting the raw data in tables and charts. Univariate analysis involved description of individual variables (weight, BSA, flow rates, hematocrit and lactate values) including the mean average, the range plus the standard deviation.

The routinely collected blood parameters such as lactate and hematocrit provide a partial assessment of the beneficial low-prime P-MEC system for pediatric cardiac surgery. The hematocrit concentration shows the degree of hemodilution and oxygen carrying capacity, whereas the lactate level reflects the extent of anaerobic metabolism caused by insufficient blood supply. An evaluation of the perfusion quality is enabled by these blood parameters. But these values do not demonstrate the assumed benefits of the avoided blood-air interface. Based on the results from numerous studies and clinical trials that were performed with the closed mini-ECC systems in adult cardiac surgery the closed P-MEC circuit is supposed to be beneficial in terms of the systemic inflammatory response after bypass (SIRAB). To explore the impact of the closed circuitry on the pediatric patient, further collecting of other parameters such as inflammatory biomarkers, neutrophil elastase and factors of the coagulation plus the complement cascade is needed. In the first animal experiment with the P-MEC, arterial blood samples were collected and analyzed with regard to the amount of TNF-α, IL-1β, IL-6 and IL-10 after onset and ending of CPB. But an assessment of these inflammatory markers was not possible as a result of the technical handling in the laboratory, where the test series need to be diluted for the analysis. We relinquished the measuring of the inflammatory parameters within this P-MEC study because the main focus is on the clinical application and the secure feasibility of this new perfusion technique. The impact of the closed P-MEC setup on the infantine immune system should be part of further clinical studies.

The insertion of a study control group would allow comparative statistics of the two groups and provide an explorative assessment of patient´s clinical outcome. This would enable a statistical evaluation of postoperative complication rates, comparison of length of stay on

ICU and in hospital, plus a rating on cost-effectiveness of the P-MEC system compared to conventional CPB.

4.2. Conclusion

The prospective study and the retrospective analysis were performed to examine the clinical application of the P-MEC circuit and its secure feasibility as a new perfusion technique for cardiac surgeries in infants. In collaboration with Medtronic we established a totally closed, miniaturized bypass system containing a low-prime membrane oxygenator, a kinetic-assisted venous drainage by a centrifugal pump, an arterial filter as air trap plus a separated cardiotomy reservoir as security backup. Based on the patients´ data and postoperative outcome, we demonstrated that the modified P-MEC setup is associated with less hemodilution due to reduced priming volume and a beneficial avoidance of blood-air contact by omitting the venous reservoir. These savings in priming volume and blood-air interface enable transfusion-free complex congenital cardiac surgery without the loss of safety margins. More clinical trials with a multi-center, randomized study setting as well as measurements of inflammatory markers pursuant to a predefined study protocol for standardized data acquisition are needed to prove the assumed positive impact of the closed P-MEC circuit on the systemic inflammatory response scientifically.

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6. Appendix

6.1. Timeline

10. Aug. 2012	1. Treffen mit Prof. Knez, Themenbesprechung und Zusage zur Bearbeitung
14. Aug. 2012	Erstellung des Konzeptformulars (Version 1)
22. Aug. 2012	Thema der Diplomarbeit in Mugthesis eingestellt
29. Aug. 2012	Freigabe durch Studienrektor zur Bearbeitung des Themas
03. Sept. 2012	Antrag auf Zugang für das openMedocs-System per Mail
	Sept.-Okt. 2012
	Einlesen ins Thema mittels Studien und Papers aus Pubmed und Buch „Cardiopulmonary bypass-principles and practice“ von G.P.Gravlee
	Kontakt mit Zweitbetreuer Dr. Curcic per Mail
17. Okt. 2012	Assistenz bei OP mit Einsatz des P-MEC Systems
24. Okt. 2012	Assistenz bei OP mit Einsatz des P-MEC Systems, Einweisung in P-MEC
22.-24.Okt. 2012	Literaturrecherche aktueller Studien für die Präsentation bei EACTS-Kongress in Barcelona
08. Nov. 2012	laut KAGes unvollständiger Antrag für openMedocs-Einstieg; Konzeptformular wird nachgereicht
13. Nov. 2012	Besprechung mit Dr. Curcic wegen Konzepterstellung und Inhaltsverzeichnis, Einweisung in Refworks (Programm für Literaturverzeichnis)
14.-19.Nov. 2012	Literatursuche mit Refworks, Erstellen einer Bibliothek in Refworks
19. Nov. 2012	Besprechung des Inhalts der Diplomarbeit mit Dr. Curcic
20. Nov. 2012	Assistenz bei OP mit Einsatz des P-MEC Systems
22. Nov. 2012	Treffen mit Prof. Knez zur Besprechung des weiteren Vorgehens, des Inhaltes der Diplomarbeit Änderung der Sprache auf Englisch
05. Dez. 2012	Einstieg in openMedocs-System erhalten
10. Dez. 2012	Treffen mit Dr. Curcic, Erklärung von openMedocs
19. Dez. 2012	Erstellung des Studienprotokolls für Ethikantrag, geplante Abgabe des Antrages bei Ethikkommission für den 21. Dez. 2012
ab Dez. 2012	Schreiben der Diplomarbeit (Einleitung)
15. Jan. 2013	OP mit P-MEC, Gespräch mit Kardiotechniker
05. Feb. 2013	Gespräch mit Dr. Curcic
22. Feb. 2013	aktuelle Literaturliste in Refworks für Dr. Curcic erstellt
20. März 2013	Studien ausgedruckt
25. März 2013	neue Liste mit Patientendaten für Dr. Curcic erstellt
27. April 2013	Treffen mit Prof. Knez und Dr. Curcic, weitere Planung besprochen, noch kein Ethikantrag bei Ethikkommission gestellt
Mai-Sept. 2013	Auslandsaufenthalt im Rahmen des Praktischen Jahrs, Schreiben der Diplomarbeit (Methoden)
04. Nov. 2013	erneute Freischaltung des Einstiegs ins openMedocs
20. Nov. 2013	Erstellen von Tabellen und Diagrammen für Diplomarbeit
10. Jan. 2014	Treffen mit Dr. Curcic
13. Jan. 2014	Abstract für Präsentation der Diplomarbeit am österreichischen

	Chirurgenkongress 2014 erstellt und eingereicht
14. Jan. 2014	Patientendaten und Messwerte mittels Timelines geordnet
22. Jan. 2014	Bearbeitung des Ethikantrages
30. Jan. 2014	Einreichung des fertigen Ethikantrages
07. Feb. 2014	positives Votum des Ethikkommission, EK-Nummer: 26-206 ex 13/14
18. Feb. 2014	genaue Beschreibung der Tierversuche mithilfe von Dr. Curcic
04. März 2014	Treffen mit Prof. Knez, Besprechung der Einleitung der Diplomarbeit
14. März 2014	Treffen mit Prof. Knez, Besprechung der Diskussion Treffen mit Herrn Suppen, Leiter der Kardiotechnik
26. März 2014	Treffen mit Dr. Curcic, Gespräch mit Herrn Muckender (Kardiotechnik) zwecks detailliertem technischem Aufbau der P-MEC
10. Apr. 2014	Fertigstellung meiner Diplomarbeit
16. Apr. 2014	Diplomarbeit zur Verbesserung an Prof. Knez per Mail geschickt
30. Apr. 2014	Änderung des Themas in Mugthesis
01. Mai 2014	Freigabe zur Bearbeitung des geänderten Diplomarbeitthemas durch den Studienrektor
06. Mai 2014	Treffen mit Prof. Knez, Besprechung der Änderungen und Ergänzungen der Diplomarbeit, geplante Abgabe 09. Mai 2014

6.2. Technical specifications of P-MEC

Custompack Specifications

Hospital Universitätsklinik Graz
City Graz
Country Österreich

Chief Perfusionist Mr. Suppan
Sales–Representative Jürgen Danek

Rev	Date	Draftsman Init	Draftsman Signed	Remarks
A	14.07.2011	J.U.		New drawing
B	13.09.2011	J.U.		Changes in entire drawing
C	30.01.2012	J.U.		Chg. 1–14–18–20–9, add line
D	21.02.2012	J.U.		Chg. 7–5–8–14–18–20

PACKAGING INFORMATION CLEANROOM			NR
Tray	:	Midi Tray Low	1.00
Lid	:	Tyvek Cover	1.00
Bag	:		
Label	:	End–label	1.00

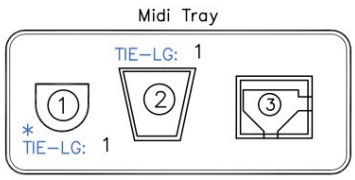
PACKAGING INFO PACKAGING DEPARTMENT			NR
U–Box	:	76x16x41 cm	1.00
M–Box	:	1 SETS IN 1 BOX	
Inserts	:	Midibox insert	1.00
Label	:	End–label	1.00
		IFU Custompack	1.00

DRAWING IS ACCORDING PROC. PE 2004
REF. TO ALL APPLICABLE CLEANROOM PROC.
AND Q.A. REQUIREMENTS
ALL PACKS STERILIZED PER CYCLE 79

Sterilisation load : 0.071 m3

NOTE:*
CUT 20 CM FROM
SPEEDY TIE AT PIXIE

Midi Tray

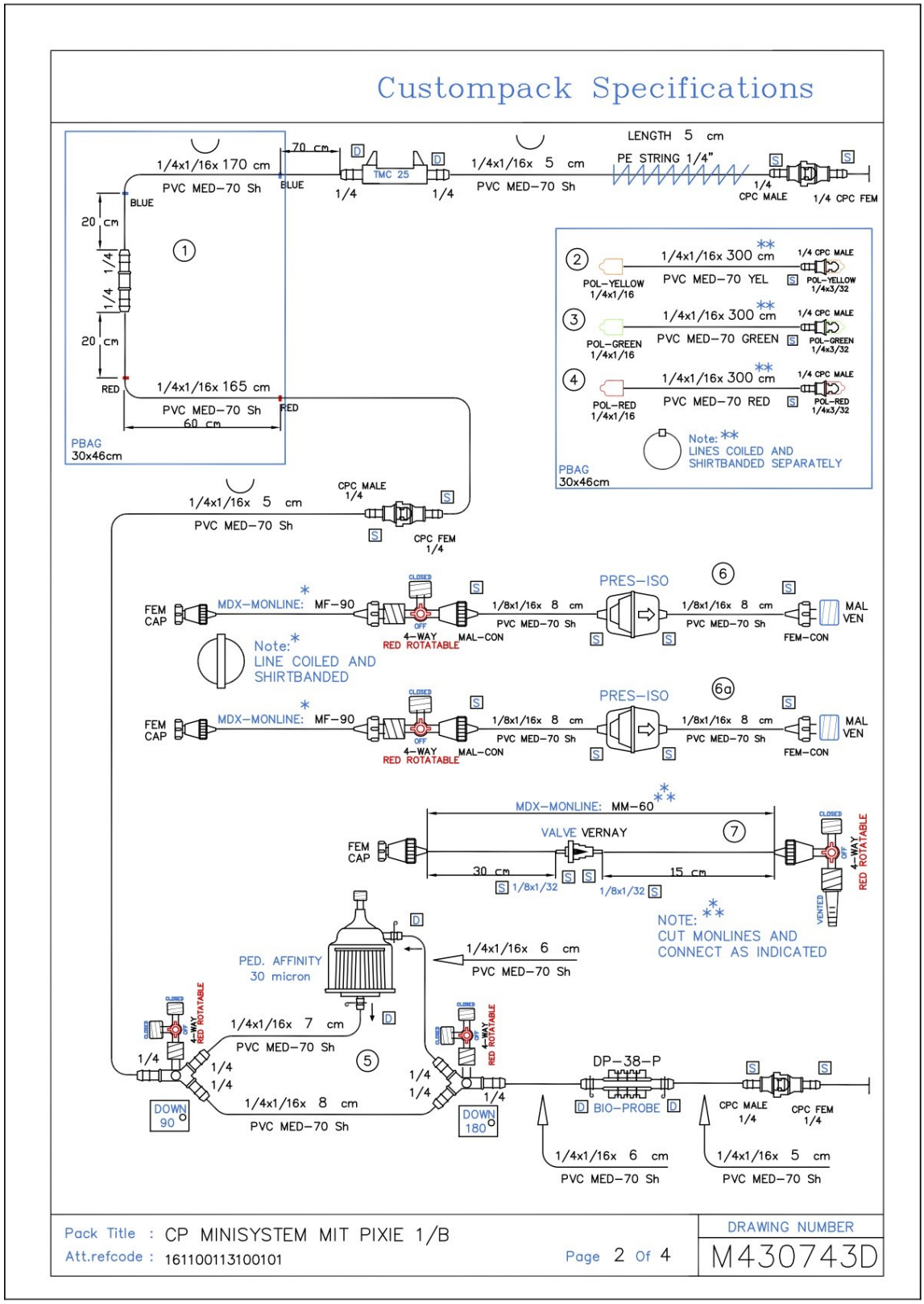


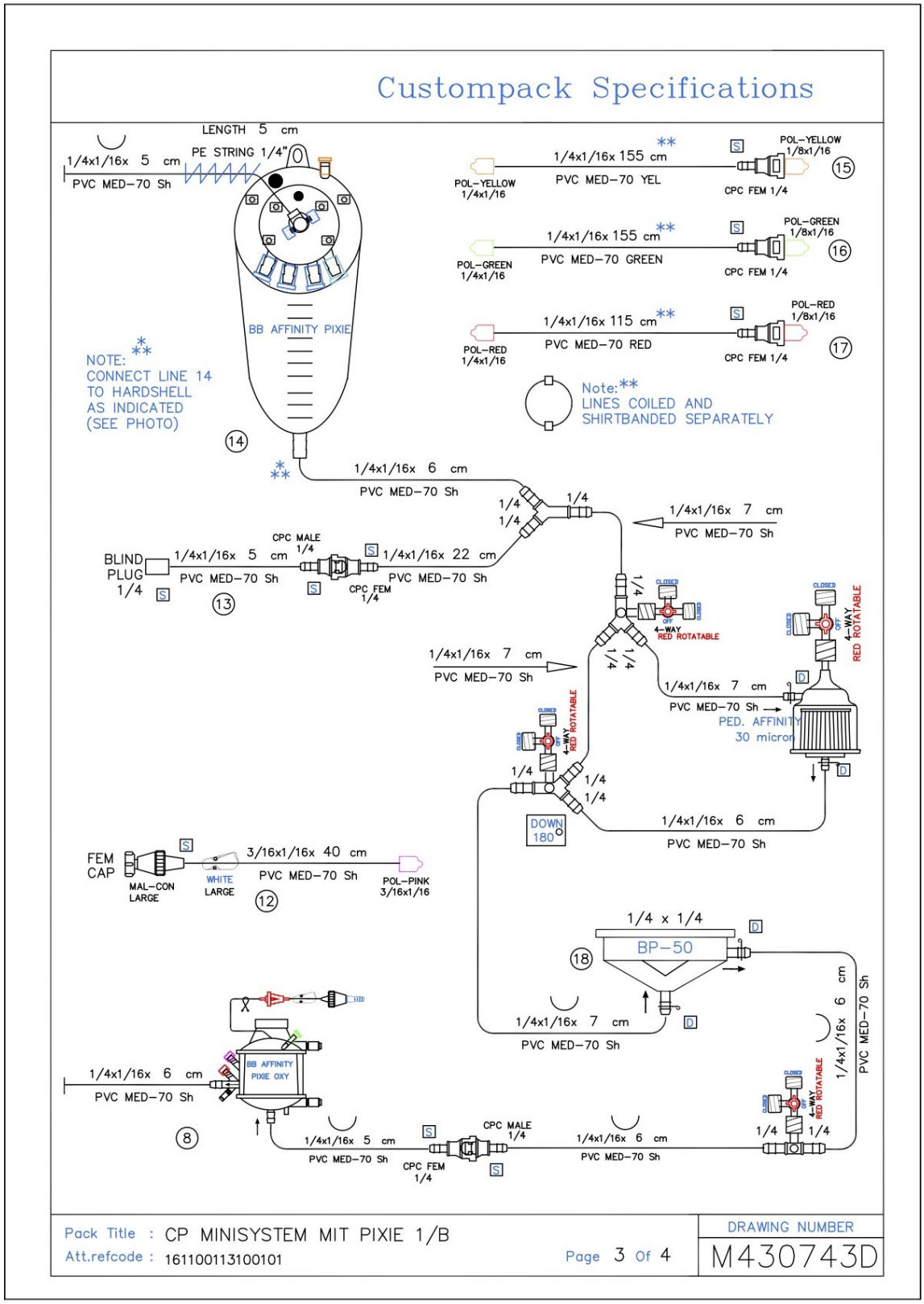
APPROVAL	SIGNED	DATE
ENGINEERING		
MANUFACTURING		
QUALITY ASSURANCE		

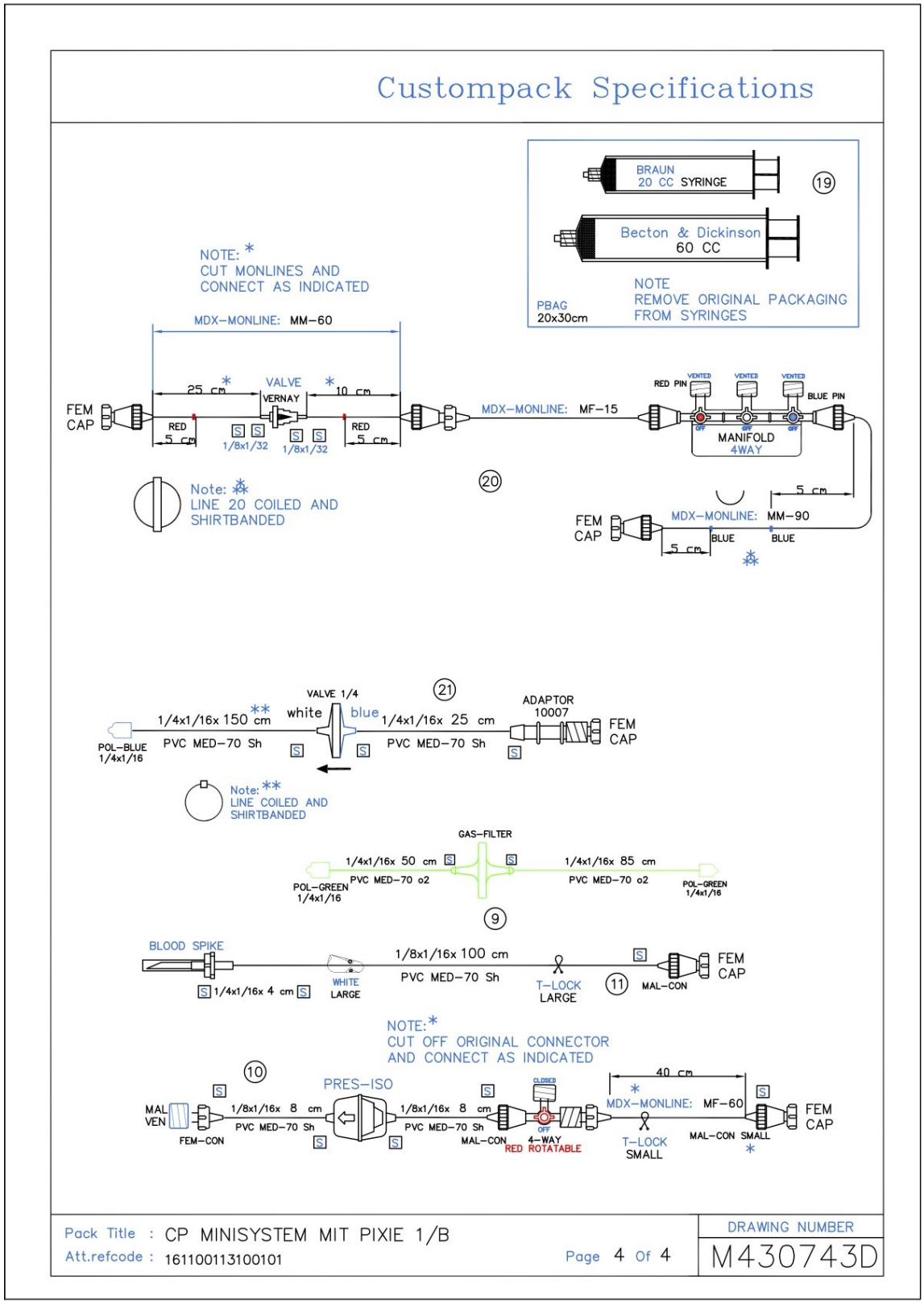
INSERTS:
① PIXIE OXY
② PIXIE HARDSHELL
③ Bio Pump
④ BP Cover

Pack Title : CP MINISYSTEM MIT PIXIE 1/B
Att.refcode : 161100113100101
Page 1 Of 4

DRAWING NUMBER
M430743D


Custompack Specifications
1/4x1/16x 170 cm
PVC MED-70 Sh
BLUE
70 cm
TMC 25
1/4
1/4x1/16x 5 cm
PVC MED-70 Sh
LENGTH 5 cm
PE STRING 1/4"
1/4 CPC MALE
1/4 CPC FEM
20 cm
1/4
1/4
20 cm
RED
1/4x1/16x 165 cm
PVC MED-70 Sh
60 cm
PBAG
30x46cm
1/4x1/16x 5 cm
PVC MED-70 Sh
CPC MALE 1/4
CPC FEM 1/4
2
1/4x1/16x 300 cm
POL-YELLOW 1/4x1/16
PVC MED-70 YEL
POL-YELLOW 1/4x3/32
3
1/4x1/16x 300 cm
POL-GREEN 1/4x1/16
PVC MED-70 GREEN
POL-GREEN 1/4x3/32
4
1/4x1/16x 300 cm
POL-RED 1/4x1/16
PVC MED-70 RED
POL-RED 1/4x3/32
Note: **
LINES COILED AND SHIRTBANDED SEPARATELY
PBAG
30x46cm
FEM CAP
MDX-MONLINE: MF-90
4-WAY RED ROTATABLE
MAL-CON
1/8x1/16x 8 cm
PVC MED-70 Sh
PRES-ISO
6
FEM-CON
MAL VEN
Note: *
LINE COILED AND SHIRTBANDED
6a
MDX-MONLINE: MM-60
VALVE VERNAY
7
30 cm
15 cm
1/8x1/32
NOTE: **
CUT MONLINES AND CONNECT AS INDICATED
PED. AFFINITY 30 micron
1/4x1/16x 6 cm
PVC MED-70 Sh
1/4x1/16x 7 cm
PVC MED-70 Sh
5
1/4x1/16x 8 cm
PVC MED-70 Sh
DOWN 90
DOWN 180
DP-38-P
BIO-PROBE
CPC MALE 1/4
CPC FEM 1/4
1/4x1/16x 6 cm
PVC MED-70 Sh
1/4x1/16x 5 cm
PVC MED-70 Sh
Pack Title : CP MINISYSTEM MIT PIXIE 1/B
Att.refcode : 161100113100101
Page 2 Of 4
DRAWING NUMBER
M430743D


Custompack Specifications
LENGTH 5 cm
PE STRING 1/4"
1/4x1/16x 5 cm
PVC MED-70 Sh
BB AFFINITY PIXIE
NOTE: ** CONNECT LINE 14 TO HARDSHELL AS INDICATED (SEE PHOTO)
14
1/4x1/16x 6 cm
PVC MED-70 Sh
1/4x1/16x 155 cm **
PVC MED-70 YEL
POL-YELLOW 1/4x1/16
POL-YELLOW 1/8x1/16
CPC FEM 1/4
15
1/4x1/16x 155 cm **
PVC MED-70 GREEN
POL-GREEN 1/4x1/16
POL-GREEN 1/8x1/16
16
1/4x1/16x 115 cm **
PVC MED-70 RED
POL-RED 1/4x1/16
POL-RED 1/8x1/16
17
Note:** LINES COILED AND SHIRTBANDED SEPARATELY
1/4x1/16x 7 cm
PVC MED-70 Sh
BLIND PLUG 1/4
1/4x1/16x 5 cm
PVC MED-70 Sh
CPC MALE 1/4
CPC FEM 1/4
1/4x1/16x 22 cm
PVC MED-70 Sh
13
4-WAY RED ROTATABLE
PED. AFFINITY 30 micron
DOWN 180°
FEM CAP
MAL-CON LARGE
WHITE LARGE
3/16x1/16x 40 cm
PVC MED-70 Sh
POL-PINK 3/16x1/16
12
1/4 x 1/4
BP-50
18
BB AFFINITY PIXIE OXY
8
Pack Title : CP MINISYSTEM MIT PIXIE 1/B
Att.refcode : 161100113100101
Page 3 Of 4
DRAWING NUMBER
M430743D


Custompack Specifications
BRAUN
20 CC SYRINGE
19
Becton & Dickinson
60 CC
NOTE
REMOVE ORIGINAL PACKAGING
FROM SYRINGES
PBAG
20x30cm
NOTE: *
CUT MONLINES AND
CONNECT AS INDICATED
MDX-MONLINE: MM-60
25 cm
VALVE
VERNAY
10 cm
FEM
CAP
RED
5 cm
1/8x1/32
1/8x1/32
RED
5 cm
MDX-MONLINE: MF-15
RED PIN
BLUE PIN
VENTED
MANIFOLD
4WAY
20
Note: ⁂
LINE 20 COILED AND
SHIRTBANDED
5 cm
FEM
CAP
MDX-MONLINE: MM-90
BLUE
BLUE
5 cm
21
VALVE 1/4
ADAPTOR
10007
1/4x1/16x 150 cm **
white
blue
1/4x1/16x 25 cm
FEM
CAP
POL-BLUE
1/4x1/16
PVC MED-70 Sh
PVC MED-70 Sh
Note: **
LINE COILED AND
SHIRTBANDED
GAS-FILTER
1/4x1/16x 50 cm
1/4x1/16x 85 cm
POL-GREEN
1/4x1/16
PVC MED-70 o2
PVC MED-70 o2
POL-GREEN
1/4x1/16
9
BLOOD SPIKE
1/8x1/16x 100 cm
PVC MED-70 Sh
FEM
CAP
1/4x1/16x 4 cm
WHITE
LARGE
T-LOCK
LARGE
11
MAL-CON
NOTE: *
CUT OFF ORIGINAL CONNECTOR
AND CONNECT AS INDICATED
10
PRES-ISO
40 cm
MAL
VEN
1/8x1/16x 8 cm
PVC MED-70 Sh
1/8x1/16x 8 cm
PVC MED-70 Sh
CLOSED
OFF
MDX-MONLINE: MF-60
FEM
CAP
FEM-CON
MAL-CON
4-WAY
RED ROTATABLE
T-LOCK
SMALL
MAL-CON SMALL
Pack Title : CP MINISYSTEM MIT PIXIE 1/B
Att.refcode : 161100113100101
Page 4 Of 4
DRAWING NUMBER
M430743D

6.3. Vote of the ethical review committee

Ethikkommission

Medizinische Universität Graz

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

VOTUM

gültig bis 07.02.2015

EK-Nummer:	26-206 ex 13/14
Studientitel:	P-MEC - Pediatric Minimal Extracorporeal Circulation
Prüfer:	ao.Univ.-Prof. Dr. med. Igor Knez Klinische Abteilung für Herzchirurgie, Universitätsklinik für Chirurgie, MUG
Sponsor:	ao.Univ.-Prof Dr. Igor Knez
Ansprechpartner:	ao.Univ.-Prof. Dr. Igor Knez, 8036 Graz, Klinischen Abteilung für Herzchirurgie
CRO:	-
Antragsteller:	Medizinische Universität Graz
Ansprechpartner:	cand. med. Susanne Samadinger, 8020 Graz, Griesgasse 26a

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 07.02.2014 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 30.01.2014, begutachtet im 'expedited Review' am 07.02.2014	
✓ Cover Letter AnschreibenEthik24.01.14 1.0	24.01.2014
✓ Antragsformular ECS	30.01.2014
✓ Originalprotokoll Final-meinStudienprotkollRetrosp.Studien1.0,22.01.14 1.0	22.01.2014
✓ CV IK 2014_CV 1.0	30.01.2014
✓ Sonstiges: IK 2014_Ethikantrag_P-MEC_1.0_30.01.14 1.0	30.01.2014
Dokumente eingegangen am 30.01.2014, begutachtet im 'expedited Review' am 07.02.2014	
✓ Antragsformular ECS Unterschriftenseiten	30.01.2014

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 07. Februar 2014

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.DDr.Hans-Peter Kapfhammer
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz. www.medunigraz.at
Rechtsform: Juristische Person öffentlichen Rechts gem. Universitätsgesetz 2002. Information: Mitteilungsblatt der Universität und www.medunigraz.at. DVR-Nr. 210 9494.
UID: ATU 575 111 79. Bankverbindung: Bank Austria Creditanstalt BLZ 12000 Konto-Nr. 500 948 400 04, Raiffeisen Landesbank Steiermark BLZ 38000 Konto-Nr. 49510.