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# Practical and Theoretical Considerations for ECMO System Development

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Additional information is available at the end of the chapter

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## Abstract

Extracorporeal membrane oxygenation (ECMO) is a well-established therapy for the temporary substitution for the heart and/or lungs in patients with acute cardiac or pulmonary failure. Recently, the development of portable systems has allowed for implementation of therapy outside of the intensive care units. ECMO can even be initiated in out-of-hospital situations to allow for patient stabilization and subsequent transfer to an appropriate hospital. This chapter will focus on the authors' development of a perfusion system based on a new double chamber pump. This unique design will, in theory, allow for a more complete and effective circulatory support to allow for myocardial and pulmonary recovery. The evolution from bench-top to animal testing will be described. The theoretical issues—including the advantages and disadvantages of roller and centrifugal pump designs—will also be discussed.

**Keywords:** blood pump, pulsatile flow, resuscitation, circulatory support

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## 1. Introduction

The use of extracorporeal membrane oxygenation (ECMO), as a therapy for acute cardiopulmonary failure, as a form of “substitute” for the full circulation has undergone extensive development over the years. ECMO is a method of temporary replacement for cardiac and/or pulmonary function in cases of failure to wean from cardiopulmonary bypass after open-heart surgery, or cardiac arrest, or acute respiratory failure. As a result, ECMO has the ability

to provide a broad spectrum of support options for patients with severe combined heart–lung, or isolated cardiac or pulmonary diseases. The therapy is based on the temporary replacement of native vital organs (heart and lungs) with artificial analogs (blood pumps and oxygenators) in the clinical scenarios of a critical impairment or temporary absence of their functions [1, 2].

Historic milestones of ECMO development track closely the rapid development of other similar medical technologies over the past 50 years—specifically, the development of a number of clinically useful portable extracorporeal biocompatible blood pumps and membrane oxygenators. As with other developing medical technologies, the initial applications clinically tended to be in extremely high-risk or near-futile cases in which the chances of meaningful survival, even with technical success, was rare. Therefore, as with new methods for external blood circulation (extracorporeal support), membrane oxygenation was used in cases of dying patients and the outcomes, predictably, were poor [3]. Consequently, successful cases were uncommon. Hence, prior to the creation of modern membrane oxygenators, ECMO was rarely used. In subsequent years, the indications for the use of oxygenators widened and ECMO used became more common in children after cardiac surgery and in newborns with severe respiratory distress.

Regarding the terminology, according to the nomenclature of Extracorporeal Life Support Organization (ELSO-1989) a modern term—extracorporeal life support (ECLS) is often used instead of the term extracorporeal membrane oxygenation (ECMO). It is believed that ECLS simultaneously involves the use of other methods of circulatory support—ventricular assist device (VAD) as well as extracorporeal circulation (ECC) circuits [4].

In recent years, despite considerable expense, there is a trend toward a significant increased use of ECLS clinically. Annually published ELSO registry data from the 36,000 patients worldwide treated with ECLS as of 2008, more than 26,000 (72%) survived. Among the patients requiring extracorporeal cardio-pulmonary resuscitation (ECPR) 26% survived.

By 2012, nearly 51,000 patients had been treated with ECLS. Thirteen thousand patients were treated with ECLS for the purpose of circulatory support during the cardiac arrest or cardiogenic shock. Accordingly, in cases of ECPR, a 40% survival rate was observed in newborns, 49% in children, and 39% in adult patients [5, 6].

## 2. Types of pumps for extracorporeal perfusion

Depending on the clinical application, ECLS support differs in the manner in which the patient is connected to the artificial system, the configuration of bypass circuit, the character of pulse wave, and whether “arterial” or “venous” blood enters into the machine. The components of technical devices themselves also vary considerably as well. In order to understand the essence of the ECLS therapy, it is necessary to consider the configuration of partial (or in some cases full) blood bypass using an artificial pump and the integrated blood oxygenator [7, 8].

Thus, for the treatment of acutely and potentially reversible respiratory, cardiac, or combined failure, refractory to standard therapy, the usage of veno-venous (VV) or veno-arterial (VA),

ECMO is indicated. While VV ECMO is used in cases of severe respiratory failure, VA ECMO is mainly used with severe heart failure. The differences between them lie in the blood bypass configuration and how the system is “connected” to the patient.

In cases of veno-venous support:

- The blood intake is drained out from the inferior vena cava through a cannula, typically, inserted into the femoral vein. As for the pumping, it is returned into the right atrium by a separate cannula, inserted through the right internal jugular vein or the contralateral femoral vein;
- With a dual-lumen cannula, inserted through the right internal jugular vein (often requiring ultrasound or fluoroscopic guidance), intake of the blood may be performed from the right atrium, pumped it through the second inflow of the catheter with flow directed across the tricuspid valve into the right ventricle.

In cases of veno-arterial support:

- The blood intake is carried out from the right atrium by means of cannula inserted through the right internal jugular vein or either femoral vein, and actively pumping into the arterial system via either the right common carotid artery (in neonates), the axillary artery, or by direct cannulation of the ascending aorta;
- Alternatively, peripheral arterial return can be provided via the femoral artery.

Each of the described methods has its own indications, advantages, and disadvantages. But, in general, veno-venous bypass is used in case of respiratory insufficiency while veno-arterial can be used for either respiratory or cardiac insufficiency [9, 10].

For cardiac arrest and cardiogenic shock developing in the hospital or in an out-of-hospital situation, the complete setup of machine is similar. The system can be assembled as a mobile, portable ECLS system is used for the ECPR [11]. Teams experienced with emergency cardiopulmonary resuscitation are required to successfully use these devices. The purpose of using ECLS during cardiac arrest (ECPR), first of all, is the restoration of blood circulation in the patient. In these instances, artificial pump replace the ejecting function of the heart. In extreme conditions, when surgical venous and arterial cut-downs cannot be performed, percutaneous cannulation of large peripheral vessels (in most cases cannulation of the femoral artery and vein) can be performed. Such configurations of ECLS implementation (veno-arterial), require, by definition, a membrane oxygenator with heat exchanger, in addition to the main blood pumping components [12–15].

When connecting an artificial perfusion system to a living body, an interdependent biotechnical system is created. In other words, complex of biological to mechanical (bio-object) system is created for the purpose of the functional support (temporary or permanent replacement of the function) of vital organs. To understand the processes taking place within this complex system, it is necessary to consider all the parameters of the operation of the artificial components of the system, their technical characteristics affecting the bio-object and disad-

vantages, causing certain morphological and functional changes within the extra and intra-corporeal system [10, 11].

Advanced extracorporeal life support (ECLS) systems consist of three main components: the pumping unit, the unit for gas exchange and blood flow temperature support, and the monitoring unit. Each of them, individually, has evolved through a long path of development and formation, with each becoming specific components of the perfusion system. This applies to blood pumps as well, which are key parts of the perfusion system.

From a technical point of view, all the pumping equipment designed for pumping liquids are divided into two main classes: dynamic (so-called continuous current) and volumetric (so-called shifting volume). In dynamic pumps, liquid entered into them and then get ejected in a continuous fashion. The driving force in them becomes inertia. For volumetric pumps—pumping process is based on the alternate filling in with liquid of the operating chamber and ejecting the liquid. For dynamic pumps, there is a characteristics double conversion of energy. On the first stage, mechanical energy is converted into kinetic energy, and on the second stage, the kinetic energy is converted then into potential energy. As for volumetric pumps—liquid is transferred, under pressure at its surface, with periodic changes in the pump chamber volume, which is alternately intercommunicating with the inlet and outlet of the pump. There is only a single energy conversion. It means that mechanical energy is directly converted into potential energy. Both classes of pumps are divided into main sub-groups (Tables 1 and 2).

	VV ECMO	VA ECMO
Advantages	<ul style="list-style-type: none"><li>• The ability to avoid arterial cannulation</li><li>• The ability to use a single cannula</li><li>• Provides direct pulmonary oxygenation</li><li>• Improves coronary oxygenation</li><li>• Reduces the risk of neurological disorders</li><li>• May improve cardiac output</li></ul>	<ul style="list-style-type: none"><li>• Provides cardiopulmonary support</li><li>• Reduces preload right ventricle (RV) and left ventricle (LV)</li><li>• No risk of blood recirculation</li><li>• Better oxygen delivery</li></ul>
Disadvantages	<ul style="list-style-type: none"><li>• Adequate oxygenation may be not achieved</li><li>• There is no direct support for the heart</li><li>• High risk of recirculation</li></ul>	<ul style="list-style-type: none"><li>• Increases LV post-load</li><li>• Reduces pulse pressure</li><li>• Coronary perfusion from the left ventricle</li><li>• Stunning</li><li>• Certain artery cannulation</li><li>• Ischemia during peripheral arterial cannulation</li></ul>

Table 1. Comparison of the advantages and disadvantages according to the configuration.

The basic requirements for blood pumps were generally formulated at the beginning of the second half of the twentieth century. Therefore, at various stages of development of the extracorporeal circulation systems industry, pumps were developed and used.

Dynamic	Volumetric
• Centrifugal	• Piston drive
• Axial	• Membrane
• Vortex	• Screw
• Auger	• Peristaltic
• Jet	• Air driven (pneumatic)

**Table 2.** Classification of pumping equipment for pumping over fluids.

These pumps belonged to most of the above-mentioned sub-groups with various names assigned to each design (roller, finger, rotor, rotating in a liquid, centrifugal, axial, etc.). Over time, the requirements and details were continually refined and depended on the type of perfusion system as well as their particular purpose.

Hence, we believe that a modern extracorporeal blood pump should have:

- Maximum biocompatibility (biochemical and hemocompatibility);
- Maximum atraumaticity (not to injure the plasma and formed elements—that is, blood cells);
- The ability to pump up to 10 l/min of blood;
- Minimum of dilution (to have a minimum amount of filling blood chambers);
- Discharging (outlet) mode, continuous, as well as pulse (controlled pulse flow, from the predetermined, an internal asynchronous rhythm as well as from ECG or pressure curve—cardio-synchronized counter pulsation);
- Compact and transportable (with minimum size and weight) control system and power supply (battery powered for several hours of continuous use).

Based on these requirements, today, the most commonly used ECLS systems are equipped with either a volumetric peristaltic (shifting volume, for convenience are referred to as roller) pumps, or with dynamic centrifugal pumps [16–18].

## 2.1. The peristaltic (roller) pumps

According to the latest classification of blood pumps, proposed at the 94th Annual Congress of the American Association of Thoracic Surgery (Toronto 2014), peristaltic (roller) pumps should be attributed functionally to extracorporeal blood pumps as for mono- or biventricular support; for mechanical short-term circulatory support [up to 4 h on the recommendations of US Food and Drug Authority (U.S. FDA)], as a bridge for the heart recovery.



The operating principle of such a pump is based on the fact that the rollers pinch the tube with a fluid and push the liquid forward while moving along the tube. Usually, it consists of a flexible tube, several (usually two or three) rollers, and the surface (track) against which the rollers compress the tube. There are some designs without a bearing surface as the tube is clamped down on the roller due to the tension applied to the roller.

According to the implementation of the housing roller, pumps can be monobloc (Cased pump) and modular (Close-coupled pump). For the monobloc pumps, the drive, the reducer (gear), and control elements are all within a single unitary case housing. In a modular pump, the modules are also connected to each other, but there is no housing. Capacity of the roller pump depends on the rotational speed of the shaft and the number of rollers. The number of rollers also determines evenness of the fluid flow.

The peristaltic pumps, in contrast to other types of pumps, are not equipped with valves or seals. When in use, the pumped blood is in contact only with the inner surface of the tube. Tubes for roller pump, the most important element of the entire pump, determine: system pressure, volume of inflow, capacity, and durability of the pump. The process of the pump service is minimal, as far as only tubes are changed. Its main hydrodynamic characteristics are as follows:

- Ability to set totally or partially occlusive;
- Positive displacement—pushes blood by “squeezing” raceway;
- Automatically calculated blood flow (stroke volume  $\times$  revolutions per minute);
- Blood flow is not dependent on resistance.

These pump properties, as well as high reliability and simplicity of operation, have resulted in widespread adoption clinically. In addition, it has been successfully used in ECMO systems.

## 2.2. The centrifugal pump

The centrifugal pump (rotating in the direction of flow) using the same classification system as roller pumps (Toronto 2014) considers extracorporeal or paracorporeal blood pumps. Centrifugal pumps can be used for uni- or bi-ventricular bypass for mechanical circulatory support for cases that require short-term therapy (up to 9 h according to US Food and Drug Authority—U.S. FDA—recommendations) as a stage for the heart recovery.

A centrifugal pump consists of housing with a tapered shape. Positioned inside is a rigidly fixed wheel consisting of two disks with blades fixed between them. They are bent away from the radial direction in the opposite direction in which the wheel is directed to rotate. Pump connection with inlet and outlet connectors to main lines is used to direct blood flow.

The operating principle of centrifugal pumps is as follows: an impeller rotates in the case filled with fluid (i.e., blood). The result from rotation is a centrifugal force that causes flow of the fluid from the center of the wheel to the peripheral areas. This flow creates a high pressure that begins to displace fluid in the outlet pipe. Lowering the pressure in the center of the

impeller makes fluid to enter the pump through the inlet. Thus, the work for continuous fluid supply is performed [19].

Centrifugal pumps may have a different number of impellers, the shape and number of blades, the slope and volume of the housing cone, the number of rotor rotations per minute (1000–4000 rpm), and so on. But, regardless, the operating principles of centrifugal pumps remain the same—the fluid shifts are performed by the centrifugal force caused by rotating the impeller in the fluid. This last fact is extremely important from the point of view of a blood trauma. However, technological advances and the introduction of new coating materials for the surfaces that are in direct contact with blood, significantly reduced the risk of a blood trauma. The innovation in coating surfaces has resulted in a large number of structurally modified centrifugal pumps (Roto Flow (Jostra); Sorin (Revolution); Delphin (Sarns); Centri-Mag (Levitronix); Capiiox (Terumo); BioMedicus, BP-80 Biopump (Medtronic); Nikkiso (Nikkiso), etc) into clinical practice. In spite of such developments, the hydrodynamic characteristics of these pumps are not significantly different from each other and they generally have the following characteristics:

- Unlike roller pumps, they are totally non-occlusive
- Passive displacement—Cones or impellers create kinetic energy using centrifugal force of fluid constrained vortexing
- Revolutions per minute are proportional to resistance
- Blood flow is inversely proportional to resistance
- Priming volume 30–60 ml
- Blood flow rate 5–10 lpm
- Minimal surface area
- Low blood transit time
- No stagnant areas

Considering the above-mentioned pump characteristics, operation, and management of these pumps require specific conditions, namely

- They are preload and after-load dependent, that is, an increase in downstream resistance decreases forward flow delivered to the patient.
  - This has both favorable and unfavorable consequences.
  - Flow is not determined by rotational rate alone, so a flow meter must be incorporated in the arterial outflow to quantify pump flow.
- When the pump is connected to the patient's arterial system but is not running, blood will flow backward through the pump and out of the patient unless the arterial line is clamped.
  - This can cause reverse flow (left to right shunt), exsanguination of the patient or aspiration of air into the arterial line (e.g. from around the purse string sutures);



- Thus, whenever the centrifugal pump is not running, the arterial line **MUST** be clamped!

➤ Blood flow is dependent on:

- Revolutions per minute's (within limitation as increased rotational rates can result in over pressurization and cavitation);
- After-load;
- Pre-load.

Over the years, there has been a vast accumulated experience in the experimental and clinical use of these pumps in a variety of perfusion systems. Each pump has specific advantages over other types of blood pumps. However, each of them is also characterized by the specific disadvantages that are manifested in the course of their operation—especially during prolonged and long-term applications. Complications, inherent to the specifics of each pump, are associated with the peculiarities of their construction and therefore are hard to overcome.

### 2.3. Disadvantages and complications inherent to used pumps

The literature relating the history of the blood pump development shows a difficult, controversial path, passed by researchers from the second quarter of the last century to the present day. Trying to reproduce the work of the heart by the means of artificial analog has been initially implemented in two directions:

- The maximal work of artificial pump is according to the basic parameters of native heart operation (these systems were known for high complexity, difficult to manage, technological inaccessibility, and high prices)—hence, widespread clinical implementation has not been reached (mainly concerns pumps, shifting volume);
- The complete detachment from the morphological and physiological identity in favor of the simplicity of design, practicality, physiological adequacy, and affordability (such designs had been intensively developed and attained clinical application), while continuing to improve on all of the basic characteristics as described above.

Technical advances along with the introduction of new materials and technologies into clinical practice have led to the rapid development of industries focusing on artificial perfusion. A major area of this focus has been regarding therapies directed to advancing ECMO and ECPR. There are generalized advantages of different pump designs and perfusion benefits achieved as well as the complications and potential disadvantages related to their design. While analyzing the advantages related to the clinical application of roller and centrifugal pumps, we should note the existence of “old” deficiencies and complications, inherent in these pumps. This is interdependence of blood inflow and outflow parameters, lack of counter pulsation, potential for blood trauma, and other problems reflect the inherent limitations of all extracorporeal systems [20].

These theoretical disadvantages limit, to some extent, the effectiveness of such perfusion systems and the clinical applications in which they are being used. In situations, when the perfusion system is used for the treatment of respiratory insufficiency, the main function of

oxygenating blood is performed by a membrane oxygenator. The blood pump then functions in an auxiliary role by serving as a means of transporting blood inside the complex biotechnological system. With veno-veno perfusion, non-pulsatile blood flow, implemented by the pump, is quite acceptable, when the oxygenation (and elimination of carbon dioxide) function of the impaired lung is replaced. A significant disadvantage of such bypass scheme is the risk of blood recirculation, which can partially reduce by modifying bypass circuit. Recirculation is where the inflow and outflow cannulas are physically close to one another and the suction of the outflow cannula actively drains the inflow. An example would be dual-lumen cannula, draining the blood from the right atrium with one lumen and with the other lumen, directed across the tricuspid valve into the right ventricle pumping the blood in which any misdirection of inflow blood is aspirated back into the drainage lumen.

The needs of the pump are greatly increased during combined cardiopulmonary insufficiency, when in addition to the needs of gas exchange replacement (i.e., lung function), the need for cardiac pumping function is also required. In such patients, the veno-arterial bypass configuration, pumping oxygenated blood directly into the aorta (or a major branch—such as the iliac, axillary, or femoral arteries) is used. This configuration allows for replacing the oxygenation function of the injured lung and simultaneously reducing the pre-load of the right heart. However, at the same time, due to the necessity of continuous shifting of the blood volume into the aorta, the after-load of the left ventricle myocardium is increased. This is an important downside of the VA support, particularly evident in patients with left ventricular myocardial dysfunction. The solution was found while using intra-aortic balloon pump (IABP) using counter pulsation in the thoracic aorta and reducing post-load of the left heart.

#### **2.4. Extracorporeal cardio-pulmonary resuscitation (ECPR)**

Since the beginning of the twentieth century, ECLS has been intensively for circulatory support in the cases of cardiogenic shock or cardiac arrest. ECLS can be applied in a variety of clinical settings—such as in out-of-hospital conditions. In cases within the hospital setting, determination the indications for use, implanting the ECLS system, and managing its operation is provided by qualified hospital staff. In out-of-hospital conditions, these activities are performed by specially trained teams of medical and technical personnel, emergently called to the scene of a witnessed cardiopulmonary arrest [21–23]. In cases where conventional cardiopulmonary resuscitation (CPR) is ineffective, an essential component of success is the speed and quality of the initiation ECLS machine and restoring systemic circulation. This more aggressive approach to extracorporeal cardio-pulmonary resuscitation (ECPR) has no other alternatives. According to recent literature, this approach is considered to be the most effective, as is quite justified from etiological and pathogenic points of view. This is confirmed by encouraging outcome data, accordingly, successful ECPR cases exceeds 60% on average, while same outcomes of the standard CPR varies—often within the range of 15% [6, 24].

The bypass configuration during ECPR is veno-arterial, but there can be used different cannulation sites. In order to connect the perfusion system, options include the femoral vessels (arterial and/or vein), jugular vein and carotid artery (inflow connection) or a combination thereof (mixed connection). Moreover, the careful selection of the cannula to ensure adequate,

smooth, and even flow of blood to the pump from the venous bed and then pumping, according to the predefined hemodynamic requirements to a particular arterial tissue bed is essential. Modern venous cannula and technique of great vessel cannulation allow for delivery of up to 70% of the circulating blood volume (CBV) through the common jugular vein from the right atrium. At the drainage location of the end of venous cannula (when it is located not in the right atrium, but in the lumen of a vein), the prevention of the suction of the venous walls should be considered, which is achieved by controlling the value “pressure gradient,” in addition to using special cannulas to avoid such “suction events.” Depending on specific ECPR method, in most cases for returning blood (particularly in terms of out-of-hospital conditions), the femoral artery is used. In the case of veno-arterial ECMO oxygenated blood is pumped into the aorta in a retrograde manner. Therefore, depending on position of the end of the cannula, oxygenated blood is mainly returned to the distal part of a patient’s body, and the brain and ventricular myocardium are still in more unfavorable perfusion condition. In such cases, we speak of uneven redistribution of oxygenated blood at the level of the aorta and its branches, called the “Harlequin Effect.” Thus, in theory, the optimal location for the location of the end of the cannula should be considered as the ascending aorta or arch.

Depending on the specific ECPR approach, important is the providing the appropriate system for safe, quick, and easy to initiate therapy. Requirements for the system include portability, mobility, flexibility, minimum weight, a complete set components, and ease of management. Obviously, affordability is also important. The basic unit of this system, of course, remains the blood pump. Modern devices in most cases are equipped with centrifugal pumps. The relatively small size, a small amount of filling, reliable control, and monitoring of the entire system all increase the chances of clinical success and a good outcome. However, considering the fact that centrifugal pumps rotate in the flow and belong to a class of dynamic pumps, they are capable of producing only a continuous, steady stream of flow. Therefore, realizing 70% of the blood flow, it can be effective even in cases of asystole. However, in cases of successful ECPR and restoration of cardiac activity, operation of the pump in continuous mode can increase the after-load of left ventricular myocardium hence limiting adequate cardiac recovery, worsening ischemia (or other pressure and/or volume overload variables). It is necessary to take into account the nature and localization of the pathological process (zone of ischemia) caused by the cardiogenic shock, especially if it covers the area of the heart and the left atrial septum. In such cases, the overall outcome of ECPR may be worsened and impact patient outcomes. Regardless, during the period of therapy in the case of ECPR, the phases of therapy can be divided into two periods—each requiring maintenance of different blood inflow and pumping options:

- I—The period before the restoration cardiac activity
- II—The period after the restoration of cardiac activity

In period I of extracorporeal resuscitation, the recovery of hemocirculation using continuous blood flow in the cardiovascular system is far preferable to blood flow, implemented by external heart massage (providing not more than 5% of cerebral blood flow). Artificial perfusion with oxygenated blood, in which the desired temperature mode, the acid-base

balance (ABB) and drug saturation can be easily maintained, is able to provide adequate tissue and organ blood flow. In case of a high-end location of the aortic cannula, the adequate coronary perfusion is also possible. Such perfusion is able to support the required electrical activity of the myocardium and the restoration of sinus rhythm, sometimes even without defibrillation.

In period II of ECPR, after the restoration of cardiac activity, the pump must carry out support for the systemic circulation. The goal should be maximum unloading of the myocardium for the gradual, smooth and simultaneous recovery of the myocardium, weakened by “disaster”. In other words, the perfusion mode should ensure that pumping of a certain volume of blood from the right atrium to the aorta not to impede the emptying of the natural ventricular. Left ventricular ejection must continue—as because stagnation of blood in the cavity can result, even in the setting of adequate anticoagulation, clotting of blood which when ejected can be fatal. Therefore, unloading of the myocardium of both ventricles in terms of volume and pressure must be considered as the best option. Such perfusion therapies, for example, are characteristic for the pulsating types of left ventricular assist devices (LVADs) with the pumps serving to shift the volume. A pump operating in counter pulsation mode, taking up a blood from the right atrium, will unload right heart in terms of volume. By pumping this volume back into the aorta, it also bypasses the left heart, also unloading it in terms of volume, while at the same time contributing to additional after-load reduction of the right heart. Finally, if the volume of blood is pumped into the aorta during diastole (provided the aortic valve is closed), there will be additional after-load reduction of the left ventricle—and much like the function of an IABP, coronary perfusion with oxygenated blood will also increase [25–28].

#### *2.4.1. Pulse wave properties at extracorporeal circulation*

Probably, the largest and longest standing debates between the experts about the advantages and disadvantages of the blood flow are the nature of extra-corporeal blood flow/wave properties. Specifically, it is the comparison of non-pulsatile, continuous flow with a pulsatile flow synchronized with the cardiac cycle of native heart flow. The main argument supporting non-pulsatile flow is the significant decrease of the pulsatile flow from the aorta and its major branches to the thin peripheral arteries—arterioles, and then the eventual elimination, or “smoothing out” of the pulse wave as it reaches the capillaries. According to this logic, if the transcapillary flow in normal physiological conditions has a continuous, non-pulsatile nature, then in case of artificial continuous flow (i.e., ECMO), cell and accordingly tissue blood flow should not be affected. On the other hand, supporters of pulsatile flow, in case of the artificial perfusion, insist on the need of maintaining the pulsatile wave, especially in the central part of the cardiovascular system. Numerous investigations suggest that besides the large arteries, arterioles, particularly those in kidneys, contain baroreceptors. In addition, the baroreceptors of the aortic arch trigger neural and humoral reactions that impact the regulation of circulating blood volume and arterial blood pressure by increasing sympathetic tone and activating the renin–angiotensin system and vasopressin release. The large main arteries provided with baroreceptors instantly and quite sensitively react to the slightest pressure changes within this system and participate in the redistribution of blood volume, depending on the needs of the



body. In the process of blood flow redistribution, little to no function is performed by the arterioles, which are called “taps” of the vascular system or “resistance vessels.” About 50–60% of the total resistance to blood flow is contributed to by these vessels. Arterioles determine the systemic blood flow at the regional and microcirculatory level. Total vascular resistance at different parts of the body contribute to the systemic diastolic blood pressure, changes it a certain level as the result of common neurogenic and humoral changes of the tone of these vessels. Differently directed changes of the tone of different regional arterioles provide volumetric blood flow redistribution between regions—this complex feedback mechanism controls the microcirculation. The cardiovascular system (especially the large, main arterial vessels), which are evolutionary adapted to such neuro-humoral regulation, if not receiving the normal physiologic (or even pathophysiologic) baro-excitation, results in the adverse operating conditions. Thus, in a continuous flow, they react adversely to the non-physiological artificial perfusion. This results in repeatedly described situations of inadequate peripheral circulation, secondary impairment of the microcirculation, impairment of organ blood flow, the accumulation of toxic metabolites, and buffer shifts with homeostasis dysfunction. However, clinicians over the years have learned to correct these shifts timely, both by means of medications and fluid (crystalloid and colloid) as well as the use of technical devices (i.e., dialysis and renal replacement therapies). But, despite all attempts and various degrees at correction of these biochemical abnormalities, the damages continue to exist as they are believed to be related to the non-physiological flow of artificial perfusion [29–31].

In cases of ECLS, carried out during cardiac arrest or cardiogenic shock, there are additional reasons to employ synchronized pulsatile flow. Specifically, the need of reduce both pre- and after-load in the weakened ventricular myocardium. To do this, blood, taken by the pump from the right atrium, should be returned, provided with the required kinetic energy, to the aorta during diastole (after closing aortic valve—critical to preventing LV distention). None of the above-discussed structures of the pumps, which are commonly used clinically are able to carry out such a specific counter pulsation. Therefore, we can conclude that despite certain clinical successes of the different ECLS methods, the technology is far from perfect and there is a critical need for improvement of blood pumps. Given this, the goal of the researchers is the creation of universal extracorporeal pump is understandable. The structure of such pump, regardless of the nature of the blood flow, should allow for the desired pumping of flow both in non-pulsatile mode as well as in a controlled counter pulsatile mode [32].

## **2.5. Description of blood pump with own design**

Since 2000, our team has been developing paracorporeal blood pumps for perfusion in ECLS systems. Currently, many of our pump designs are protected by national patents. These pumps, which are handmade, are tested in systems of cardiopulmonary bypass, ECMO systems, portable systems to be used for ECPR and in retrofit systems for the perfusion of isolated organs and organ systems “in situ.”

After the bench testing, the systems are tested in various experimental models on animals. In addition to blood pumps, the complete circuit of these systems generally includes the parts and accessories for single-use perfusion sets for cardiopulmonary bypass: oxygenator with

heat exchanger, the arterial filter, a set of flexible connecting tubes from PVC or silicone, various fittings, taps, etc. The blood pump itself belongs to the class of volume shifting pumps. With regard to the sub-group, it is a hybrid between membrane and pneumatic pumps. It is equipped with two chambers, connecting tubes (lines) for blood and air, external electronic clamps of the tube-lines, the pulsator, and a control system.

In the design of the pump, in order to separate the functions of filling and ejection, we have chosen a two-chamber circuit in which both chambers perform the opposite function at the same time. At the time, when in one of the chambers experiences blood inflow through the inlet branch conduit and it is filled, the blood from other chamber is ejected through the outlet branch conduit and the chamber is emptied. This allows controlling parameters of inlet and outlet separately. This is in contrast to similar parameters in roller or centrifugal pumps and is a significant distinguishing feature of this pump.

The second distinctive feature is the absence of any parts, moving in the flow, hence minimizing affecting blood cells and traumatizing them. So, compressed air (pressure) was chosen for pumping in the capacity of the substance imparting kinetic energy to the blood.

In the pump, running on a pneumodrive (actuator), compressed air, or a vacuum is applied to the rigid chamber from the branch pipes of the compressor with the receivers of positive and negative pressure (**Figures 1–3**). Each of the branch pipes is provided with an electrically operated stop-cock, consisting of external electronic clamps (EEC) on the tubing lines. Thus, each rigid clamp has four holes with branch pipes provided with the EEC. Accordingly, both chambers together have eight such branch pipes. In the filling cycle (diastole) of one of the chambers, two of them are open and two are closed. At this time, in the other chamber, there is a pump cycle, and again, two EEC are open and two are closed. Consequently, in each phase of the pump operation, four of the eight EECs are open, and four are closed.

1 Casing of the first chamber.

1a Bag of the first chamber.

2 Casing of the second chamber.

2a Bag of the second chamber.

3 The blood inlet branch-pipe of the first chamber.

4 The blood inlet branch-pipe of the second chamber.

5 The blood outlet branch-pipe of the first chamber.

6 The blood outlet branch-pipe for second chamber.

7 The common outlet tubing-line of the pump.

8 The common inlet tubing-line of the pump.

9 Sensors of filling and emptying the bags.

10 EEC of the blood inlet branch-pipe of the first chamber.



11 EEC of the blood inlet branch-pipe of the second chamber.

12 EEC of the blood outlet branch-pipe of the first chamber.

13 EEC of the blood outlet branch-pipe of the second chamber.

14, 15 Vacuum line EECs of the chambers.

16, 17 Pneumatic pressure line EECs.

18 Compressor of the positive and negative pressure.

19 Pressure receiver.

20 Vacuum receiver.

21, 22 Pneumatic pressure lines.

23, 24 Vacuum lines.

25 Pulsator.

26 Control system.



**Figure 1.** Variety of pumps developed with our design.



Figure 2. The external view of the pump.

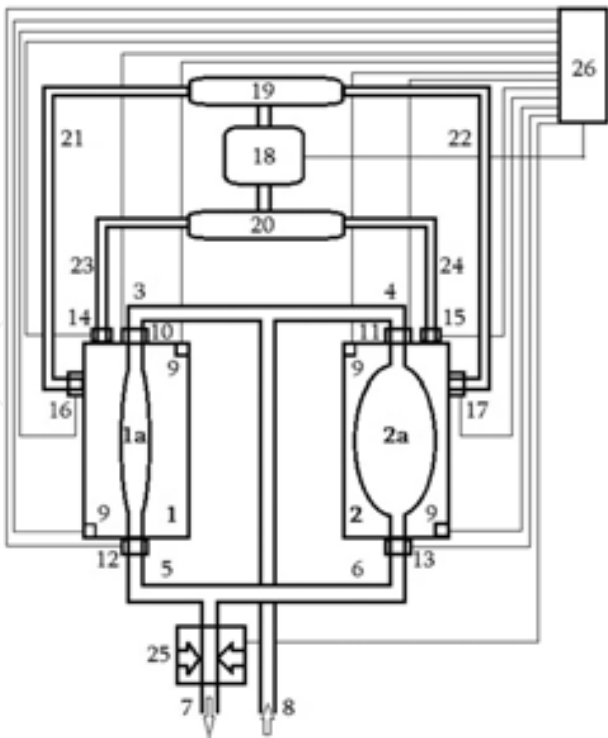


Figure 3. Scheme of the two-chamber pump.

In order to keep the components separate (i.e., blood from the air), the principle of a saccular chamber “Bag in Can” was chosen. This consists of an outer housing—“Can”, which is a cylindrically shaped casing and is made of a transparent rigid material that can withstand pressures up to 3 atm (303.9 kPa). The inner, elliptically shaped, chamber—“bag”, it is a thin-walled, elastic, biologically compatible (polyurethane) blood bag. Inlet and outlet conduits of the blood chamber are located at the poles of ellipsoidal bag and are mounted in the branch pipes of the rigid housing. Blood enters directly, via the inlet branch-pipe, directly into the blood chamber from the one end. After passing through the bag, it is pumped out through the outlet-branch pipe of the rigid housing, located at its opposite end.

Another feature of the pump is that each of the blood chambers filling (storage) and emptying (systole—pumping) functions is integrated. Thus, the filling (diastole) process, as well as emptying, is multi-cyclic. This means that filling (or discharging) chamber can store blood volume, equal to a few cardiac outputs. Accordingly, this increases the amount pump can store as a whole. This feature becomes evident when the pump is in a pulsatile mode. This mode of operation allows, depending on the specific requirements of the clinical situation, the blood to be stored in the blood pump for a certain number of native heart cycles with an arbitrary frequency of pulse cycles of the pump. In addition, it is possible to change the volume and pressure of each pump ejection and arbitrarily. In other words, the pump construction maintains one of the most important characteristics of myocardium—the ability to adapt to the amount of blood inflowing in accordance with the Starling law (in terms of volume and pressure changes).

Each chamber is equipped with electronic sensors for filling and emptying the blood storage “bags” (i.e., bladders). With these sensors, it is possible to set the desired maximum and minimum blood bag filling volume in each chamber. When blood volume exceeds the set value, the sensors are instantly activated and they give impulse to the control system that switches the chambers and changes their function—from filling to ejection.

Both chambers are functionally integrated into a single pump and reservoir unit, acting both—as a blood accumulator (reservoir) and a hydraulic pump. Thus, only changing the chambers of a certain size to the chambers of another leads to creation of the pump with different capacity and identical hydrodynamic characteristics to those, described above. Inlet branching conduits of both chambers are interconnected with a free end connected to the inflow (venous) bloodline of the patient. The outlet branch conduit of the chambers is also interconnected—with a free end serving as the outflow back to the patient.

Finally, one of the most important parts of the pump is pulsator. It is located at the connection between outlet tubing of the pump and the oxygenator. The principle of pulsator function is very simple—external clamping of the silicone tubing-line. However, management of this pulsator allows achieving the desired effects of adequate circulatory support, namely

- Carry out pulsation mode in cases of native heart asystole;
- Change the clamping frequency—pump pulsation frequency;
- Change the duration of clamping—the time of “diastole” of the pump;

- Change the duration of time between clamping—the time of “systole”;
- Synchronize pulsation of the pump in accordance with an electrocardiogram or pulse wave in cases even minimal cardiac activity;
- Change the timing ratio of “systole” and “diastole” of the pump in the counter pulsation mode to match the native cardiac cycle.

Although, in terms of universality of the pump, it should be noted that it has the ability to perform not only the pulsatile flow, which attempts to match physiologically arterial flow, but also non-pulsatile flow—a characteristic of the venous bed. It is this feature, which we realized in a number of experiments in the settle of liver transplantation that demonstrated adequate protection of the recipient patient in the anhepatic phase.

By choosing appropriate pump chamber sizes (i.e., volume), it can be adapted to both—perfusion applications (chamber volume up to 1000 ml) for large experimental animals (calves, donkeys—some weighing up to 100 kg), as well as medium-sized experimental animals (dogs, sheep, pigs—weighing 45 kg). We have successfully tested circuits for small experimental animals (rabbit, rat—weighing less than 3 kg) with the chamber volume up to 50 and 20 ml.

#### *2.5.1. Description of the pump operation*

The priming volume of the pump chambers may vary depending on the type and size of the experimental animal and the planned experimental model. For example, in the model ECPR on the sheep (up to 40 kg), we used blood pump with the chamber volume up to 200 ml. The total volume of priming of the entire system with the oxygenator and arterial filter was 750 ml.

##### *I phase*

In the first chamber, after the activation of the blood level sensor, the EEC closes the inlet branch-pipe for blood—a vacuum line then opens the tubing conduit for pressure and blood release. The pumping begins. Simultaneously, by a signal from the level sensor in the second chamber, the EEC closes the outlet branch-pipe for blood—the pneumatic pressure tubing conduit then opens the inlet branch-pipe for the blood and the vacuum line. Thus, the second chamber begins filling.

##### *II phase*

When blood reaches a certain volume level, the sensor switches the position of tubing conduit of the EECs. Thus, the chambers change their functions instantly: Empty changes to filling, and filling starts pumping. By changing the position of the volume level sensor in the circuit, filling level of blood chambers and therefore, the filling level of the pump system may be changed.

Since the chambers function cyclically, all their work can be divided into two opposite phases: the filling phase and the emptying phase (**Figures 4 and 5**). The compressor (#18) is switched

on after priming the blood circuit pump. The receivers (#19, #20) provide excess pressure and vacuum relief valves. Thus, in phase I in the casing of the chamber (#1), the air is supplied from the control system by the EEC (through line #21), under pressure from the receiver (#19). In this chamber under the action of an impulse from the control system, the branch conduits (#10 and #14) are closed and branch conduits (#12 and #16) are opened. Thus, the chamber (#1a) begins to pump blood through the outlet branch conduit (#12) and the outlet tubing-line (#5) to the common output line (#7). The pulsator (#25) is located on this tubing line, and it is also controlled from the general control panel. At the same time, automatically, by remote control impulses in the chamber (#2), the branch conduits (#13 and #17) are closed and the other branch pipes (#11 and #15) are opened. In the chamber casing, the vacuum is supplied through the line (#24) from the receiver (#20). The blood chamber (#2a) begins to fill with blood from the common inflow tubing-line (#8). After reaching a certain filling or emptying blood level, level sensors (#9) are switching over all and EECs of the branch conduits are changed to the opposite position and the chambers then change (reverse) functions and phase II begins.

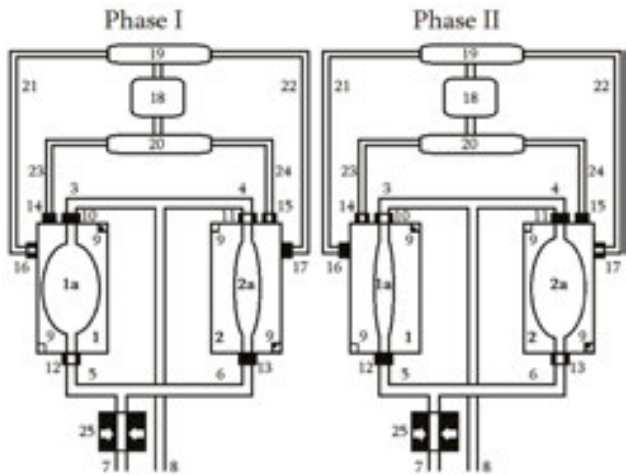


Figure 4. Phases of the pump operation.



Figure 5. Process of the experiment on animal.



Kind of pump Specifications	Rotary (roller) pump	Centrifugal pump	Our pump on the pneumatic actuator
<b>Design features and capabilities (resources)</b>			
Manufacturer (Brand)	CAPIOX (Terumo)	LIFEBRIDGE (Sorin), CARDIOHELP (Maquet)	Prototype
The volume of the blood chamber (SV—stroke volume)	Variable SV for different-sized patients	Filling volume up to $\approx$ 50 ml	Filling volume up to $\approx$ 150–300 ml
Managing the power component	Electric drive	Electric drive	Pneumatic actuator
Use	As a system of cardiopulmonary bypass during cardiopulmonary resuscitation	As a system of cardiopulmonary bypass during cardiopulmonary resuscitation, preferable for long-term extracorporeal support	As a system of cardiopulmonary bypass during cardiopulmonary resuscitation, as well as in preservation of organs in situ
Maximum capacity	Up to 10 l/min	Up to 8 l/min	Up to 10 l/min
Realizable value of the system pressure	60/40 mm.Hg	60/40 mm.Hg	120/80 mm.Hg
<b>Advantages</b>			
Duration of conducted safe perfusion	Limitation in time several (3–4) hours	Possible long-term perfusion	Possible long-term perfusion
Discharge flow characteristics	Excessive positive or negative pressure	Provides positive and negative pressure (poor)	Provides positive and negative pressure (as close as possible to the created native myocardium)
Specifications filling flow –		–	Adaptation to the venous return
Opportunities	It provides systemic circulation	Higher bypass for right or left ventricles	Maximum bypass the right or left ventricle
The nature of the pulse wave	The possibility of a weak pulsation	The possibility of a weak pulsation	The ability to flow as a non-pulsed and clear counterpulsation
<b>Disadvantages</b>			
Possibility of reverse flow along arterial line	No blood return	Potentially exists	Potentially exists
Embolism	Potentially massive air embolism	Protection against massive air embolism	Protection against massive air embolism
Damage to the blood cells	Hemolysis	Slight hemolysis	No hemolysis



Kind of pump Specifications	Rotary (roller) pump	Centrifugal pump	Our pump on the pneumatic actuator
The possibility of damage to blood contact details	The destruction of tubes	The destruction of rotor blades	–
Additional requirements	Tubing-line occlusion control – is required		An additional compressor with vacuum supply control is required
Additional accessories	The volume of ejected blood is automatically calculated	The flowmeter is required	The flowmeter is required
Possibility of circuit disruption from excessive line pressure buildup	Possible of circuit disruption and termination and termination	No possibility	No possibility
Cost	Low	High	Low

**Table 3.** Comparison of blood pumps used commonly and pump developed by us.

Prototype pumps are made by hand. Bench testing has shown that the main hydrodynamic parameters and efficiency, safety, and reliability are similar to clinically used, commercially available, pumps (**Table 3**).

During bench testing, a dual-chamber pump with a chamber volume of 350 ml was placed at the same level as a volume of liquid, attempting to match clinical flow. Perfusion was carried out in two different modes of blood flow—non-pulsatile and pulsatile. Blood flow was measured in the output tubing-line of pump.

In the non-pulsatile flow mode:

- Pressure in the receiver #20: 1.5 atm;
- Vacuum in the receiver #19:0.7 atm;
- Flow through lines #21, #22: up to 6 l/min;
- Flow through lines #23, #24:1 to 4 l/min;
- Total flow in the line #7: upto 10 l/min.

In the pulsatile flow mode:

- Pressure in the receiver #20: 1.5 atm
- Vacuum in the receiver #19: 0.7 atm
- Flow through lines #21, #22:8 l/min
- Flow through lines #23, #24: upto 2 l/min
- Total flow in the line #7 (after pulsator):10 l/min

### 2.5.2. Experimental studies on animals

The pump was tested in several acute experiments on the animal models in the various perfusion setting:

- Heart–lung bypass (HLB) machine
- ECLS system for ECPR
- Perfusion preservation of isolated donor organs and complexes of organs “in situ”

The dual-chamber pump passed a long-standing test as a heart–lung bypass machine in 68 different experiments on dogs and sheep. In these experiments, the main pump circuit was connected via a standard configuration in cases of an open-chest model, simulating various cardiac surgery scenarios. The pump provided adequate heart–lung bypass for 2–6 h, both with the non-pulsatile and pulsatile flow without difficulty. Hemodynamic parameters were maintained within physiological limits, and therefore, the main parameters of physiology of animals during extra-corporeal perfusion did not require significant correction.

In the ECLS configuration, which was designed for ECPR on sheep, the pump was tested in 14 experimental models of cardiac arrest. A portable, mobile version of the pump and the entire perfusion system complete set with autonomous energy supply was used in these experiments. The effects of extra-corporeal perfusion in a number of experiments on models, within 10 min of cardiac arrest, confirmed the following:

- Successful recovery of the cardiac contraction (in case of non-pulsatile and pulsatile mode);
- Stable rehabilitation of cardiac activity with prolonged perfusion (in a synchronized mode counter pulsation).

In addition, in some experiments on rabbits, the pumps have been tested using a portable system for extra-corporeal isolated preservation of donor organs and organ complexes “in situ.” The standard conserving solutions, as well as whole blood at various temperatures, were used as preservatives.

## 3. Conclusions

In the design of the dual-chamber pump, with saccular chambers modelling the concept of a “Bag in Can,” there are incorporated a full range of opportunities for achieving the desired range of physiologic perfusion parameters similar to that of a healthy native heart. The dual-chamber design, with inter-changing chamber functions, allows for separate control of the different parameters for the filling and emptying functions, thus allowing for optimization of blow independently. In other words, the design allows the pump to be filled with a smooth, non-pulsatile flow, while simultaneously ejecting with physiologic pulsatile flow. The pump design provide minimal trauma of the blood cells due to lack of internal valves and, most importantly, the absence of the rotating parts in the path of flow. Changing only the chamber unit with a different size “bag,” while leaving other components of the unit unchanged allows

for a full range of volumetric hemo-circulatory pump characteristics. In other words, the pump can be easily adapted for extra-corporeal perfusion experimental on animals of different sizes. Consequently, in a clinical setting, it can be used, with only minor changes, for infants, children, and as well as for adults. The pump can perform non-pulsatile blood flow — characteristic for the venous bed while also providing pulsatile flow — characteristic of flow in the aorta and large arteries. Moreover, it can be easily switched from pulsatile flow to non-pulsatile perfusion, depending on the specific necessities, at any time. Finally, counter pulsation during pump operation during ECPR allows continuous unloading of the work of the heart, hence contributing to the actual recovery of the weakened and injured myocardium. Prolonged and stable rehabilitation of cardiac activity in a synchronized counter-pulsation mode can also be accomplished.

In addition, in experiments on rabbits, the pumps have been successfully tested using a portable system for isolated perfusion and preservation of donor organs and organ complexes “in situ.”

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