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A WEARABLE MECHATRONIC DEVICE FOR EXTRACORPOREAL BLOOD ULTRAFILTRATION

Ph.D. scholarship with the financial contribution of Fondazione Cariverona

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DISPOSITIVO MECCATRONICO PER L'ULTRAFILTRAZIONE EXTRACORPOREA DEL SANGUE

Tesi redatta con il contributo finanziario di Fondazione Cariverona

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Summary

Abstract

The interest in the design of portable and wearable medical devices is related to both the relevant clinical and social benefits for patients and the potential economic savings for national health services. Biomedical technologies are improving at a very fast rate and represent an extraordinary means to develop innovative portable and wearable devices which can help people live in a prosperous way, in particular reducing sorrow in case of disease. This leads to a widespread effort to develop devices which can execute at home therapies that are usually performed in hospitals.

This thesis presents a new wearable and portable device for extracorporeal blood ultrafiltration, named WUF (Wearable UltraFiltration device), able to remove excess fluids from fluid overload patients with chronic kidney disease and/or congestive heart failure.

The design requirements that a modern wearable device for extracorporeal ultrafiltration must meet have been identified thanks to a thorough literature review on previous similar proposals followed by an extensive risk analysis.

The design of the WUF prototype has faced several difficulties, ranging from the identification or conceivement of safe and reliable components to the design of a compact and neat layout. For most components it was possible to identify commercial (off-the-shelf) products meeting the requirements, nonetheless for some others, specific investigations, studies and developments were needed and led to the design of customized solutions or the formulation of original approaches.

The design of an effective, efficient, safe and reliable control architecture, based on two microcontrollers and one microcomputer, the implementation of the control logic and of a graphical user interface have been carried out too being essential features of such a mechatronic device.

A backpack/trolley design has been chosen as the layout for the device, since such a solution guarantees the best tradeoff between miniaturization and ergonomics. The design introduces an original positioning of the vast majority of components in three independent planar panels: one for disposable components, one for non-disposable devices and one for electronic boards and controllers. This arrangement of components can drastically simplify and speed up the in-hospital operations needed before and after a therapy with the WUF

1. Introduction

Fluid overload is a clinical condition in which the accumulation of water in the body cannot be excreted. One of the main consequences of fluid overload is electrolytes imbalance, in particular of sodium (whose normal level is diluted), which possibly determines digestive problems, behavioral changes, brain damage, seizures and sometimes even coma. Since the brain is the most susceptible organ to fluid overload, one of the first symptoms coming from an excess of water is a change in behavior: patients may become confused or inattentive, shouting and even being delirious. Other symptoms may be muscle cramps and twitching, paralysis of part of the body, rapid breathing, sudden weight gain, nausea and vomiting. Blood pressure may be higher than normal, but sometimes it can be a hidden consequence, although the degree of water intoxication is serious. In the worst case, fluid overload condition can cause acidosis (abnormal high acid content in blood and body tissues), anemia, cyanosis (sharp drop of blood oxygen levels), hemorrhage, and shock [1].

When the clinical condition of accumulation of water in the body is chronic, the causes are related to organ diseases. In particular, the organs that lead to fluid overload are kidneys and heart.

1.1 The kidneys and kidney diseases

The kidneys are a fundamental part of the urinary tract and perform crucial functions for the entire body. In particular, their functions can be summarized as:

- regulating the water fluid levels;
- regulating the electrolytes balance;
- blood filtering and extraction of waste solutes and other substances (e.g. drugs);
- maintenance of an important sector of the regulation of acid-base balance;
- release of systemic hormones for regulating blood PH and blood pressure;
- secretion of hormones such erythropoietin (fundamental for the production and maturation of red blood cells), renin and prostaglandin (for the regulation of arterial pressure)
- production of an active form of vitamin D that promotes strong, healthy bones;
- metabolism of carbohydrates.

In case of damage, the different tasks and functions of the kidney involve also the functionality of all the other organs of the patient.

The two symmetrical kidneys are in a retroperitoneal position, between the eleventh chest vertebrae and the third lumbar vertebrae. In an adult person, their average weight is 150 g, with dimensions of 12 cm × 6.5 cm × 3 cm. Each kidney is irrorated by the renal artery, that is a side branch of the abdominal aorta. It is divided into smaller branches that, becoming smaller and smaller, reach the capillarization and form a vascular cluster, the so-called renal glomeruli, constituting the kidney filtration system (Figure 1).

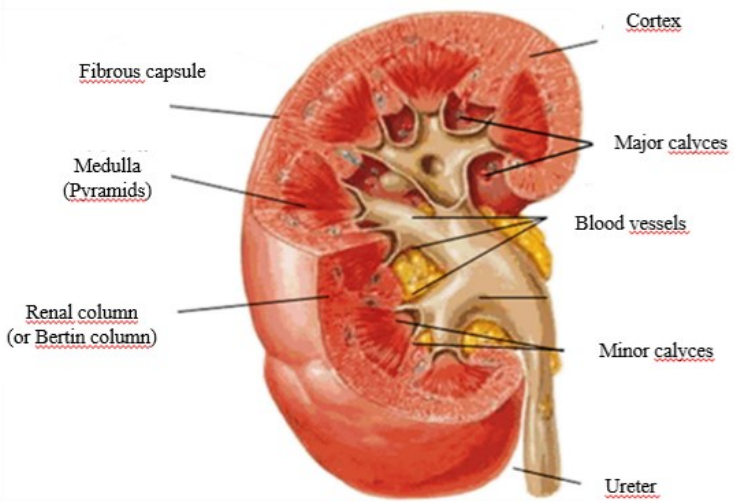


Figure 1. *Macroscopic structure of the kidney*

The nephron is the renal functional unit. For each kidney, there are one million nephrons and their main function is the urine production. Each nephron is basically constituted of two main components: the renal corpuscle and the renal tubule (Figure 2).

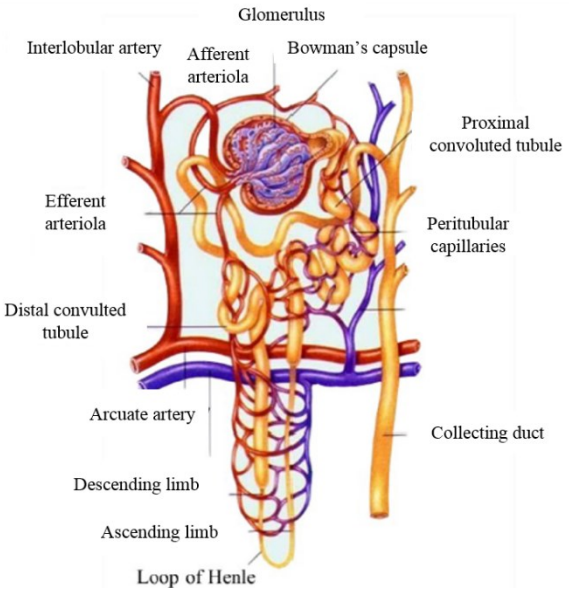


Figure 2. Structure of the nephron

The renal corpuscle, that consists of glomerulus wrapped in a structure named Bowman's capsule, is the main responsible for the so-called ultrafiltration of the plasma: the blood entering into glomeruli

is filtered and the retained one (primary urine or glomerular filtrate) passes through renal tubules, where water and products are secreted or re-adsorbed based on the needs of the organism. At this point the urine is formed and it will be made pass to the bladder through the ureter [2].
Kidneys filter almost 200 l of water every day; of these, only 2 l are excreted as urine, the remaining are re-adsorbed from the organism, recovering all the useful substances that must not be released.

1.1.1 Kidney Function

The main parameter used to measure the kidney function is the glomerular filtration rate (GFR), that defines how much blood passes through the glomeruli per unit of time.
In the clinical practice, the creatinine, a specific metabolism product that is almost completely removed by corporeal fluids through glomerular filtration, is used to estimate the GFR.
As first approximation, the GFR can be calculated as:

$$GFR = \frac{C_{u,Cr} \times V}{C_{p,Cr}}$$

where $C_{u,Cr}$ is the creatine concentration in urine, $C_{p,Cr}$ is the creatinine concentration in plasma and V is the urinary flow.
Other formulas can be used for the estimation of the GFR: CockcroftGault and MDRD (Modification of Diet in Renal Disease) are two examples. These formulas are based on sex, age, race, blood creatinine levels and other biochemical parameters [3, 4].
In a healthy person, a normal GFR value is about 125 ml/min. This parameter is very useful for the detection and classification of any renal dysfunction or disease.

1.1.2 Renal diseases

Depending on the anatomic part of the kidney that is insulted, renal pathologies can be classified in:

- Glomerular
- Tubular
- Interstitial
- Vascular
- mixed

Serious diseases, which can potentially compromise even in an irreversible way the kidney functions, can be basically categorized in:

- Acute kidney injury, where the loss of functionality is sudden, but there are high possibilities of recovery and regression (potential causes may be traumas, accidents or taking toxic drugs);
- Chronic kidney Disease, where the progressive reduction of the functionality of nephrons is irreversible.

The majority of kidney diseases occur when the nephrons are insulted. If the nephrons lose their capacity to filter fluids and solutes, fluid and toxins levels can accumulate in the organism, leading to severe clinical consequences.

The chronic kidney disease derives from the loss of a big number of nephrons. Usually, no serious clinical symptoms appear until the number of working nephrons falls below 70-75%. Indeed, electrolytes plasma concentration can still be maintained in a normal range and the volume of body fluid can remain normal until the number of working nephrons falls below 20-25%. There are different stages to indicate the severity of the disease according to the value of GFR. They are described in the following Table 1, according to the K-DOQI (Kidney Disease Outcome Quality Initiative) guidelines [5]:

Stage	**Description**	**GFR ($ml/(min \cdot 1.73m^2)$)**
1	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease	> 90
2	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease	60-89
3	Moderately reduced kidney function	30-59
4	Severely reduced kidney function	15-29
5	Very severe, or end stage kidney failure	< 15

Table 1. K-DOQI classification for chronic kidney disease (1.73 m^2 refers to the standardized body surface area used to normalize for all variables for an average 70 kg man)

In this case, the renal function slowly decreases over a relatively long period of time, from months to years, and the rate of progression depends on the disease that caused the kidney failure, although a large individual variability is observed.

The major causes of chronic kidney disease are:

- Diabetes and hypertension, responsible for more than two-thirds of the cases;
- Glomerulonephritis, causing inflammation and damage to glomeruli;

- Pyelonephritis and interstitial nephritis, involving the kidneys in their tubular and interstitial components. They can be caused by recurrent infections, drug abuse or chronic illness or obstructive urinary tract pathologies;
- Hereditary diseases (e.g. polycystic kidney disease).

When the kidney failure reaches advanced stages (stage 4 and 5), solutes and fluids accumulate in the organism, and the fluid overload condition is reached. In these cases, the condition of fluid overload becomes important: patients with chronic kidney disease require to consume specific food and must drink small amounts of water and a substitution therapy, represented by dialysis or transplantation, is necessary.

Worldwide, renal dysfunction-related pathologies are one of the most important causes of death and invalidity. In USA, in 2015, it was estimated that more than 660000 people have been treated for kidney failure [6]. In Europe, almost 700000 people [7] have completely or partially lost some of the primary kidney functions (prevalent risk factors were aging, diabetes and obesity), determining a high risks condition and the need for renal replacement therapies (such as extracorporeal hemodialysis, peritoneal dialysis or transplantation). Furthermore, the increasing incidence of chronic kidney diseases all over the world represents an issue in the field of the health economy: hemodialysis treatment costs an average of 89.000 $ per patient annually in the United States [6] and an average of 43.800 € per patient in Italy [8].

1.2 Heart disease

Although the condition of fluid overload is mainly caused by kidney failures, even heart diseases can determine an accumulation of fluids in the body. Normal pressure within blood vessels is partly maintained by the pumping force of the heart. However, if the heart starts to fail, changes in blood pressure are observed, often resulting in serious water retention. Typically, in such condition, legs, feet, and ankles will swell. Fluid will also build up in the lungs, giving to the patient a long-term cough and/or difficulty breathing and often leading to edemas. Heart failure with this kind of fluid buildup is called congestive heart failure.

Depending on the part of the heart that is affected by the failure, the position of the edema occurs in the body. If the abnormality is in the left ventricle, it means that it cannot pump blood out to the body as fast as it returns from the lungs. Since blood cannot get back to the heart, it begins to back up in

the blood vessels of the lungs. Consequently, part of the fluid in the blood is forced into the breathing space of the lungs, causing pulmonary edema. Symptoms of pulmonary edema can be shortness of breath and tiredness, since oxygen and nutrients circulating in the blood are not enough to supply body's tissues. Abnormalities of the heart structure and rhythm can also be responsible for left ventricular congestive heart failure.

If the abnormality is in right-sided heart failure, it cannot pump blood to the lungs as fast as it returns from the body through the veins. As a consequence, blood engorges the right side of the heart and the veins. Fluids in the veins are forced out into the tissues, causing swelling. Congestive heart failure of the right ventricle is often caused by abnormalities of the heart valves and lung disorders.

When the heart cannot pump enough blood, it is forced to become larger in order to supply the missing oxygen and fluids. By becoming enlarged (hypertrophic), the ventricles can contract more strongly and pump more blood. In this case, the heart chamber becomes larger and the muscle in the heart wall becomes thicker. The kidneys try to compensate for the failing heart by retaining more salt and water to increase the volume of blood. This extra fluid also can cause edema. Kidneys often become weaker if these circumstances are present, leading to a disease that is called cardio-renal syndrome [9, 10].

According to estimations from the European Heart Failure Association, 26 million people have heart failure worldwide and 3.6 million people are newly diagnosed with heart failure every year in Europe alone [11-13]. Similar data can be seen even in the United States. In accordance to the American Heart Association [14, 15], about 4.9 million Americans suffer from congestive heart failure. Sex is not a discriminating factor (50% are males and 50% are females). 0,1% of people over 65 years suffer from this condition.

1.3 Therapies for fluid overload

When the condition of fluid overload becomes severe, therapies for treating such disease must be applied. The treatment of fluid overload may depend on the clinical status of the patient, acuteness of the condition and underlying causes. Basically, treatment consists of:

- Drugs
    - Diuretics to increase urination
    - Vasopressin receptor antagonists (to treat hyponatremia)
- Extracorporeal therapy

Patients with chronic kidney disease have a renal functionality which is completely lost and, consequently, any diuretic results inefficient. On the contrary, congestive heart failure patients still having renal function can take diuretics.

Renal replacement therapies aim to completely substitute the renal function, and consequently to re-establish the correct fluid volume in the body, in patients affected by chronic kidney disease. Between them, three main treatments can be carried out:

- Renal transplantation
- Peritoneal dialysis therapy
- Extracorporeal hemodialysis therapy

The first option involves the transplantation of the kidney from a donor (even a living one) through a surgical intervention; this solution is considered the preferable option, since it allows to completely solve the insufficiency and potentially allows patients to return to normal everyday life. However, in order to perform a transplantation procedure, in addition to the need of a donor and therefore of the organ, it is also necessary that the donor and the patient are hystocompatible. If this is not verified, the patient's immune system will not recognize the transplanted kidney and will generate a strong response of the immunological barriers, eventually causing organ rejection and transplant failure. In order to avoid it, immunosuppressant drugs need to be administered to the transplanted patient.

Peritoneal dialysis is a therapy that can be prescribed when the GFR is less than 10%. It exploits the peritoneal cavity, which is the membrane surrounding the organs' walls of the abdomen and the abdominal organs, by which blood is internally filtered and purified. Inside this cavity, a specific dialysis solution is drained through a peritoneal catheter implanted with a minor surgical procedure. Consequently, the renal function is replaced by the peritoneum which then acts as a filter for solutes and excess fluid in the blood. The dialysis solution has to be periodically replaced with a virgin solution. Currently, two methods for draining the solution are used: the Continuous Ambulatory Peritoneal Dialysis (CAPD), which consists of exchanging 2-3 liters of dialysis solution for a duration of about 30 minutes, cyclically performed every 6-8 hours during the course of the day, or Automatic Peritoneal Dialysis (APD), which automatically regenerates the dialysis solution in a single operation of 8 to 10 hours overnight. One of the main disadvantages of this therapy is the risk of infection of the peritoneum, often due to the peritoneal catheter.

The last renal replacement therapy is the extracorporeal hemodialysis. Usually, hemodialysis patients are treated in equipped hospitals, three times a week, for a period between 4 and 6 hours per session. The blood is drawn by a specific vascular access, made pass through an extracorporeal circuit, filtered

and purified by a specific medical device called hemodialyzer (or hemofilter), and then re-infused into the patient. The actuation and control of all processes are performed by specific machines. The term hemodialysis refers to different techniques that can be applied depending on the clinical aim to reach. If the clinical aim is to remove excess water from a patient, the specific technique to apply is called ultrafiltration.

Congestive heart failure patients with no kidney disease may be treated with diuretic drugs. In order to reduce the overload volume, fluid overload patients are therapeutically treated with diuretics administered intravenously [16-18]. Although diuretics are mainly used for the treatment of acute decompensated heart failure, the use of extracorporeal ultrafiltration (UF) is becoming an alternative strategy for reducing volume overloads in these patients [18]. The chronic use of diuretics has been associated with negative neuro-hormonal effects [19] and, mostly, it might cause drug resistance [20]. Such diuretic resistance has been estimated to occur in 20% or more of patients with decompensated heart failure [21]. Furthermore, diuretic resistance is associated with poor prognosis and higher incidence of morbidity in fluid overload patients with heart failure [22]. For these reasons, extracorporeal ultrafiltration seems to have potential advantages as therapy for the treatment of fluid overload in congestive heart failure patients, including greater control over the rate and volume of fluid removal, greater net loss of sodium, and less neurohormonal activation [23, 24]. Current treatment guidelines state that ultrafiltration is a reasonable approach in patients with congestion that is not responding to medical therapy (class IIa, level of evidence B) [25].

1.3.1 Ultrafiltration Therapy

Ultrafiltration therapy is an extracorporeal technique which allows a slow but continuous removal of excessive water from the blood in extracorporeal circulation. The patient's clinical tolerance to fluid removal is the key issue to perform a successful extracorporeal ultrafiltration [26]. In order to achieve an adequate fluid removal and to maintain an acceptable hemodynamic stability in a patient, it is fundamental to accurately define the amount of fluid to be removed, to reach an optimization of the rate of fluid removal and to maintain the circulating blood volume [27]. If plasma water removal is too aggressive, blood volume may decrease in consequence of a too slow intravascular refilling, that is the rate of water movement from the interstitial space to the vascular space. If this happens, severe hemodynamic instability may occur. On the other hand, in the presence of a slow continuous ultrafiltration, an effective correction of the extracellular fluid volume takes place due to a progressive intravascular refilling from the interstitial spaces.

The extracorporeal blood ultrafiltration therapy is carried out through specific machines in hospital. In order to take out blood from a patient's vascular circulation, a specific vascular access needs to be implanted. The most used vascular access for this type of therapy is a dual lumen catheter, which allows to take out and re-infuse blood to the patient punching the vessel only once. Typically, the catheter is positioned in the jugular of femoral vein, which is a large-caliber blood vessel, in order to guarantee high blood flows flowing inside the extracorporeal circuit. Another possibility of vascular access is a clinical connection of an arteriovenous shunt, called arteriovenous fistula. In extracorporeal therapies, the blood flow is typically 100-150 ml/min in adults. Blood, from the catheter, circulates into a disposable extracorporeal circuit that shall be adapted with the interface of the so-called "hardware" of the ultrafiltration machine [28, 29].

Since blood exits from a vein and returns to the same vein, an external pump generating a pressure gradient is necessary in order to perform extracorporeal circulation. Modern ultrafiltration machines are equipped with hemo-compatible peristaltic pumps and safety mechanical components that must guarantee safety of patients during the process. The core of the filtering process takes place inside a disposable component called hemodialyzer or hemofilter (Figure 3): it is a device constituted of a semipermeable membrane that allows the filtration of plasma water and suspended particulates (among which electrolytes like sodium and potassium) and the retention of components that do not have to be removed from patients, like many proteins and red blood cells.

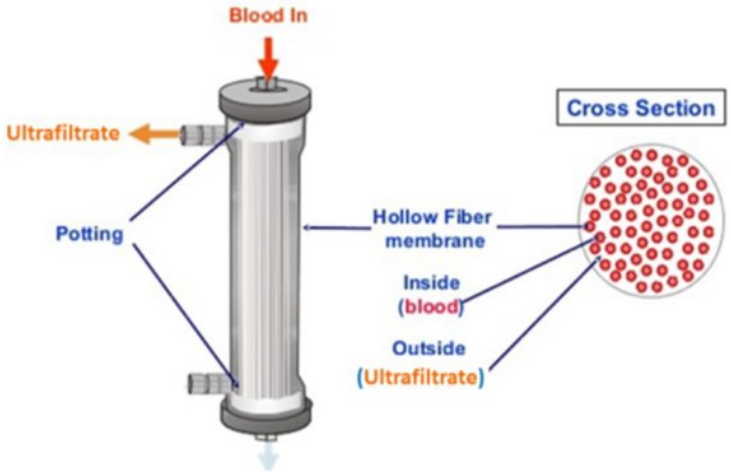


Figure 3. Typical design and components of a hemofilter for blood ultrafiltration

The membrane is made by several (a number between 2500 and 10000) hemo-compatible polymeric hollow fibers, porous on the surface, through which blood flows. In the space between fibers, the removed fluid (ultrafiltrate) is collected (Figure 4) and then removed. The physical phenomenon of

filtration is called ultrafiltration, because pores have an average diameter smaller than 100 nm. Usually, the cut-off value of the membrane is expressed in Daltons (Da), indicating the molecular weight of the smallest solute that statistically can cross the membrane.

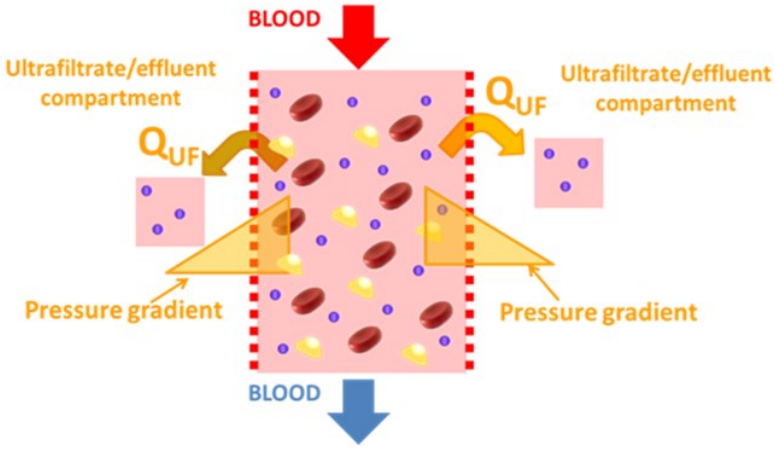


Figure 4. Principle of blood ultrafiltration

The driving force promoting the separation is the hydrostatic pressure gradient across the membrane: a negative pressure is applied in the ultrafiltrate compartment of the filter through a pump (the ultrafiltration pump) in order to generate a positive transmembrane pressure (TMP). In details, the TMP can be expressed by the following formula:

$$TMP\ (x) = P_b(x) - P_{UF}(x) - \Pi(x)$$

where $P_b(x)$ is the pressure in the blood compartment, $P_d(x)$ is the pressure in the ultrafiltrate compartment and $\Pi(x)$ is the oncotic pressure exerted by blood proteins, along the axial coordinate x of the length (L) of the filter. In order to have movement of plasma water from blood compartment to ultrafiltrate compartment, $\left(\int_0^L TMP\ dx\right)$ has to be positive.

Together with water, even solutes are removed during the ultrafiltration process. The movement of solute is made possible by physical phenomena of convection and absorption.

Convection is bulk-flow of solute across the semi-permeable membrane together with a solvent in a manner that is dependent on transmembrane pressure and membrane characteristics. The convective flux of a solute depends on the ultrafiltration flow set, total membrane surface area, solute concentration in plasma and solute sieving coefficient, that indicates the statistical probability of that specific solute to cross the membrane.

Adsorption is a process in which molecules dissolved in plasma or blood (in particular peptides and proteins) bind to the membrane structure. The characteristics that influence molecule-membrane interaction are typical for each molecule (i.e., dimension, charge, and structure) and for each

particular membrane (i.e., porosity, composition, hydrophobicity, surface potential). The adsorption, during any extracorporeal treatment, has advantages and disadvantages. Indeed, if on the one hand it allows direct clearance of toxic solutes, giving an important contribution to the total removal of solutes, on the other hand it can be considered even an undesirable phenomenon since big solutes, adhering to the walls of the membrane, may increase the resistance to the passage of other solutes and fluids, reducing the hydraulic permeability of the membrane and reducing the filter efficiency.

1.3.2 Machines for ultrafiltration therapy

Ultrafiltration machine includes the non-disposable and disposable (i.e. single use) components of the circuit through which blood flows. The main non-disposable components of a standard ultrafiltration machine, based on current technology and characteristics [29-31], are depicted in Figure 5 on a schematic sketch of machine.

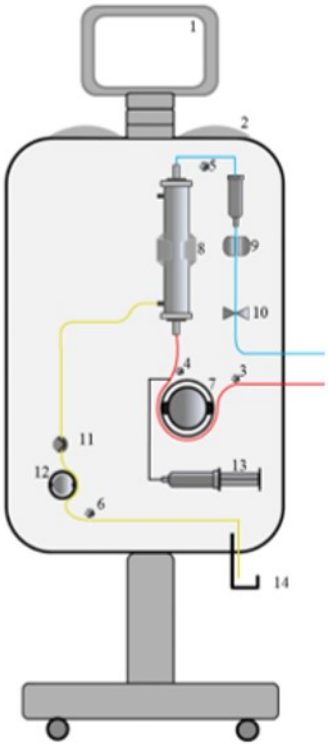


Figure 5. Schematic representation of ultrafiltration machine

The main components are:

1 Screen: the monitor through which the user interacts with the machine.

2 Alarm light and sound indicators: visual and auditory alarms must be clear and comprehensive.

3-4-5-6 Pressure sensors: monitor pressures in the extracorporeal disposable circuit

7 Blood pump: pump that controls the blood flow rate through the extracorporeal circuit.

8 Filter holder: holds the filter or the entire filter-tubing kit on the machine.

9 Bubble detector: transducer that detects the presence of air in the blood out-flow line.

10 Safety out-flow electroclamp: a mechanism that produces occlusion of the blood out-flow line.

11 Blood leak detector (BLD): placed along the effluent line, it identifies unwanted blood leaks from the blood compartment of the filter.

12 Effluent/ultrafiltrate pump: pump that controls the rate of total fluid removal from the filter.

13 Fluid control system: allows direct monitoring of the fluid balance related to fluids exchanged by the ultrafiltration machine during the treatment. It is usually a gravimetric system (using one or more load cells)

Furthermore, it is necessary to include in this category also all the electronic components that implement the machine control logic and functions needed for the correct execution of the therapy in addition to the management of the machine, failures and emergencies. A list of elements that are part of the control system includes:

- Microprocessors
- ADC and DAC converters
- Electric motors and related transducers
- Visual and light indicators (including those in the above point 2)
- Power supply systems and voltage transformers
- Ports for I/O interfaces and data exchange, data bus
- Batteries (if needed)

Disposables (i.e. the single-use components of the extracorporeal circuit) are specific for every machine and are usually designed for specific therapies, such us ultrafiltration. Following the scheme of Figure 5, the main disposables, components and color codes that should mark each tubing line in ultrafiltration modality [29] are:

- Blood access or in-flow line (red), which contains:
    - Segment connecting the patient's vascular access to the filter
    - Segment for pressure measurement upstream blood pump
    - Pump segment line
    - Segment for pressure measurement downstream blood pump
- Blood out-flow line (dark blue), which contains
    - Segment connecting the filter to the patient's vascular access

- Segment for pressure measurement after the filter
- Blood out-flow air removal chamber: allows removal of light air bubbles before blood returns to the patient

- Ultrafiltrate line (yellow)
  - Segment that allows the flow of waste fluids from the filter
  - Pump segment line
  - Segment for pressure measurement in the ultrafiltrate line.

Some of the most recent and representative hardware machines available in the market are shown in Figure 6, and are manufactured by Fresenius Medical Care (1), Baxter (2), Bellco (3), BBraun (4), Asahi Kasey Medical (5).

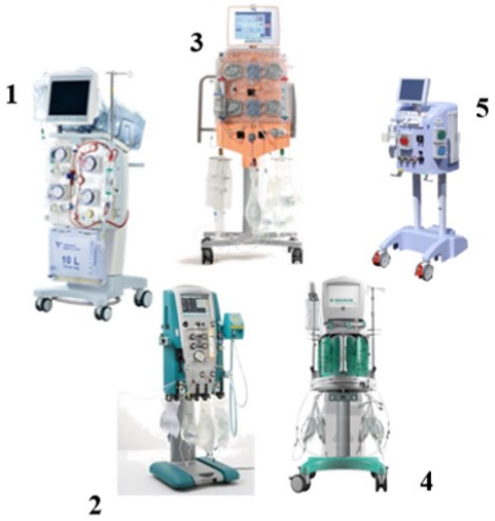


Figure 6. Examples of ultrafiltration machines worldwide used (1 Multifltrate Pro (Fresenius Medical Care), 2 Prismaflex (Baxter), 3 Amplya (Bellco), 4 Omni (BBraun), 5 (Kibou (Asahi Kasey Medical))

The management and set-up of these machines are not easy: consequently, a specialized and trained nursing and technical staff has to be present in all medical facilities that perform this kind of treatments.

Although ultrafiltration machines are efficient for treatments applied in hospitals, they suffer from several drawbacks. Usually, these devices are cumbersome, heavy and must be hooked to electrical outlets. Since fluid overload patients undergoing ultrafiltration therapy must remain connected to these devices for several hours, their ability to perform normal everyday activities is severely limited. In addition, typical ultrafiltration treatments are geared for fast removal of excess fluid. However, the removal of water is only temporary and the excess fluid usually reaccumulates in the patient's body

quickly. The re-accumulation of fluid is harmful to the patients, as the kidneys are further injured by the progress of congestive heart failure and the side effects of the diuretic drugs used to treat the heart. For hemodialysis patients, a further problem with ultrafiltration machines is that repeated reconnection to these devices requires accessing blood flow by puncturing fistula (if the arteriovenous fistula is used). These shunts only last for limited periods of time and are subject to infection, clotting and other complications that result in numerous hospitalizations and repeated surgical interventions. If the used vascular access is a catheter, similar problems also exist.

In view of the above disadvantages and in such a context, there is a substantial need for a wearable ultrafiltration device (WUF) that provides continual, steady and smooth removal of excess fluid from the body.

2. Rationale and aim of the project

Biomedical technologies are improving at a very fast rate and represent an extraordinary means to help people to live in a prosperous way, reducing sorrow even in case of a disease. Additionally, in a society where everything is becoming increasingly mobile, it is not surprising that medical devices traditionally used in hospitals are evolving to become more portable and even wearable, giving the possibility to use them in the home healthcare market so as to reduce patients' hospitalization. Estimations say that the homecare medical equipment market could be worth billions of dollars by 2022 [32]. In response, medical device manufacturers are designing smaller practical solutions. By the same token, smaller components such as sensors, are growing in demand for applications in portable and wearable devices. However, functionality, reliability and mostly safety cannot be sacrificed for smaller form factors. For most manufacturers, budgets are not unlimited, and additionally, national healthcare systems are always seeking for cost savings. This means that low-cost components are the ideal solution when they are proved to be reliable. The advantage to portable medical devices is that they extend care from the doctor's office into patients' home so diseases that are caught earlier are more easily treated. Finally, wearable systems can be broadly defined as mobile devices that can be unobtrusively embedded in the user's outfit as part of the clothing or an accessory.

Based on these considerations, the aim of this PhD project is to develop a mechatronic, miniaturized, portable and wearable device for delivering a complete blood ultrafiltration therapy. Such a treatment is indicated for the slow and continuous (24 hours a day) removal of fluids from blood in patients suffering from a condition of fluid overload.

Generally, as previously mentioned, ultrafiltration machines used for treating fluid overload in patients with chronic kidney disease or congestive heart failure are very bulky and difficult to move, forcing patients to be hospitalized and requiring continuous monitoring by hospital personnel. Several and long hospitalizations in departments such as nephrology or cardiology may possibly lead to an inadequate care of the numerous pathological events that may occur in the hospital, and obviously, force patients not to enjoy a normal life style together with the chronic pathology.

Worldwide, the scientific community is trying to overcome these issues by providing innovative technological solutions for the extracorporeal ultrafiltration therapy. One of the most exciting is the design of portable and wearable devices for continuous ultrafiltration, possibly monitored remotely and autonomously. Such a solution may lead to several benefits depending on the target class of patients which is considered:

- Patients with chronic kidney disease in extracorporeal renal replacement therapy;

- Patients with congestive heart failure.

In the present project, the use and the application of a WUF for patients with chronic kidney disease in extracorporeal renal replacement therapy needs to be intended as an inter-dialysis sessions therapy, meaning that it is performed in days between two hospitalized dialysis sessions. Consequently, ultrafiltration therapy with a wearable and portable device will be supplementary to the standard dialysis. For these patients, the benefits can be defined as:

- Clinical-therapeutic advantages and aspects
    - Inter-dialytic removal of water (although partial) may lead to a reduction of the incidence of cardiovascular complications (decrease of cardiac workload);
    - Reduction of the number of episodes of acute pulmonary edema;
    - Reduction of blood pressure levels, between two dialysis sessions, in hypertensive patients, caused by fluid overload;
    - Reduction in use of diuretics drugs for patients with residual renal function;
    - Reduction of hypotensive episodes during the dialysis session;
    - Reduction of the frequency of dialysis sessions;
    - Time reduction of a single dialysis session;
    - Therapy and device personalization;
    - Improvement of the clinical condition of fluid overload with direct impact on other systems like cardiovascular and gastrointestinal ones;
    - An extra-dialysis fluid removal lead to a solutes blood purification (even if small), as a consequence of a higher fluid assumption (i.e. drinking) by patients.

- Social advantages and aspects
    - Opportunity to have more freedom for patients in food and drink intake;
    - Improvement of the quality of life at the expanse of an additional therapy for patients;
    - Possibility to perform daily activities during therapy by patients.

- Economic advantages and aspects
    - Cost reduction as a consequence of shorter dialysis sessions;
    - Cost reduction as a consequence of a reduced assumption of drugs (diuretics, EPO, beta blockers);
    - Cost reduction as a consequence of a reduced hospitalization in Outpatient Nephrology Units, Inpatient Nephrology Units, Intensive Care Units

Furthermore, the development of such a prototype for chronic kidney disease patients can be a useful exercise towards a future dialysis portable device.

For congestive heart failure patients, the ultrafiltration therapy should be considered as continuous, meaning that it can be applied continuously for 24 hours/day. Consequently, the ultrafiltration therapy with wearable and portable device would be alternative to the one performed with standard machines in hospital or to diuretic therapies. The main benefits for these patients would be:

- Clinical-therapeutic advantages and aspects
    - Reduction of clinical complications related to chronic kidney diseases (cardio-renal syndromes);
    - Reduction and/or removal of assumption of diuretics drugs;
    - Reduction of the risk of worsening of the heart disease;
    - Recovery and/or improvement of cardiac performance;
    - Reduction of the episodes of acute pulmonary edema;
    - Therapy and device personalization.

- Social advantages and aspects
    - Opportunity to have more freedom for the patient in food and drink intake;
    - Possibility to perform daily activities during the therapy;
    - For patients who perform hospitalized therapy, ease of movement between departments for other clinical investigations.

Thus, summarizing, a wearable ultrafiltration device would have the potential to implement a not impetuous blood ultrafiltration therapy out of hospital over an extended period of time, making this process closer to natural body water removing, reducing total therapy costs and improving patients' quality of life.

The PhD activity has been carried out within the framework of a multidisciplinary project "RAP" funded by Fondazione Cariverona and which has involved engineers of the Department of Management and Engineering (DTG - Dipartimento di Tecnica e Gestione dei Sistemi Industriali) of the University of Padova and the medical staff of both the department of Nephrology, Dialysis and Transplantation and the International Renal Research Institute of Vicenza (IRRIV) of the San Bortolo Hospital of Vicenza. The PhD grant has been funded by the project RAP: therefore the PhD and the

project RAP activities have been carried out in a very synergistic way throughout all the 3 years. This thesis only presents the activities the PhD project has been focused on.

The remaining of thesis is organized as follows. After a literature review, specifically focused on wearable devices performing therapies similar to ultrafiltration and on the definition of clinical/technical limitations and potential breakthroughs for each of them (Section 3), an extensive risk analysis has been performed aiming to set the design requirements first in clinical terms and then in technological ones (Section 4). Such an analysis has allowed identifying the essential components of the wearable system, which are discussed in detail in Section 5. For some components commercial (off-the-shelf) products were available, for other ones specific investigations, studies and developments were needed: they are therefore named "critical components". Most of such investigations have been carried out in hospital, using biological fluids (e.g. blood) and simulating a real environment for the application. Then, in Section 6, the design of the control architecture, the implementation of the control logic and of graphical user interface are presented. Finally, in Section 7, after having chosen every single component of the device, the investigation of the most effective device layout is discussed, the objective is finding the best tradeoff between miniaturization and ergonomics. The prototype of the device is finally presented in the Section 8, while concluding remarks are given in Section 9.

3. Literature review

Previous proposals of wearable/portable biomedical devices for ultrafiltration or similar therapies (such hemodialysis, hemoperfusion or peritoneal dialysis) have been analyzed to identify technological breakthroughs and limitations for each of them.

Several prototypes with a similar therapeutic target have been developed to date [33] (Table 2). Although many of them have contributed to a scientific progress in this field, technological limitations still limit the potential clinical application and the industrialization of such devices. In particular, the main technological issues are related to the requirement of combining high levels of safety for patients together with miniaturization of components and low energy consumption.

Name	Year	Therapy	Technological breakthrough	Current status	Chief limitations
The WAK	2007	Hemodialysis (HD)	Pulsatile pump REDY cartridge	Clinical trial	High weight, the bell is bulky
ViWAK	2007	Peritoneal dialysis (PD)	Remote control Double lumen PD catheter	Prototype	PD is a less efficient therapy
AWAK	2008	Peritoneal dialysis (PD)	REDY cartridge Protein regeneration	Before clinical trial	PD is a less efficient therapy
The WHF	2008	Ultrafiltration (HF)	Pulsatile pump	Clinical trial	High weight, the bell is bulky
RAD (IAK)	2009	Hemo-Filtration Reinfusion (HFR)	Nanostructured hemofilter Cell function	Under development	Water cannot be removed
iNephron	2010	Fractionated Plasma Separation Adsorption (FPSA)	Nanostructured sorbents ICT-integration	Prototype	Conceptual prototype
WAKMAN	2011	Hemofiltration (HF)	Pump-hemofilter unit Remote control	Prototype	Only pump-filter unit

Table 2. Previous prototypes and their chief characteristics developed or under development

Apart from two devices (the WAK and WHF, whose components are basically the same), none of the devices listed in Table 2 is under clinical trial. There follows a description of the chief features of each of the devices in Table 2.

WAK

The first and probably the most known wearable and portable device for extracorporeal blood purification therapies developed so far is the Wearable Artificial Kidney (WAK). The device (Figure

7) [34, 35], developed by Professor Gura and his group at the University of California, is a woven belt of a total weight of 2.3 kg, powered by two standard 9V batteries, that can be connected to the patient's vascular access through a fistula or a central venous catheter. The therapy applied with this device is hemodialysis: a counter-current flowing of a specific solution of sterile water and electrolytes (the dialysate) is made pass through the space between fibers, generating a concentration gradient across the membrane and allowing blood toxins to be removed by diffusion. The blood pump is not a traditional roller pump, feature of standard hemodialysis machines, but it is a biventricular pump (so called shuttle-pump) consisting of a double channel pulsatile counter phase flow, one for blood and one for dialysate [36]. The two chambers containing the fluids are disposable. When the blood chamber is full, the dialysate one is empty and vice versa. This implies a pulsatile flow of both fluids and a pressure gradient generated across the membrane of the filter, resulting in a good clearance of solutes to be removed. The dialyzer surface is A= 0.2 m². The dialysate is partially regenerated by a system of REDY [37] absorbing cartridges (three cartridges in series containing urease, active carbon and chloride loaded zirconium oxide together with zirconium phosphate), that consequently reduces the total volume of water necessary to purify the blood to 375 ml. The excess water removed is regulated by a peristaltic ultrafiltration pump and, as in the conventional hemodialysis machines, the device provides for safety systems that stop the bloodstream in case of hazardous situations.

The WAK has some limitations, although being the most important wearable prototype developed until now: the belt is rather bulky, heavy and not very ergonomic. Furthermore, although no data are available on overall power consumption of this device, it can most likely be estimated in at least 10 W (the declared power consumption of just the pump unit is 5 W). Furthermore, two 9 V batteries are able to guarantee, in the best case, a power output of 20 Wh, which means a battery life not higher than 2 hours [33, 36].

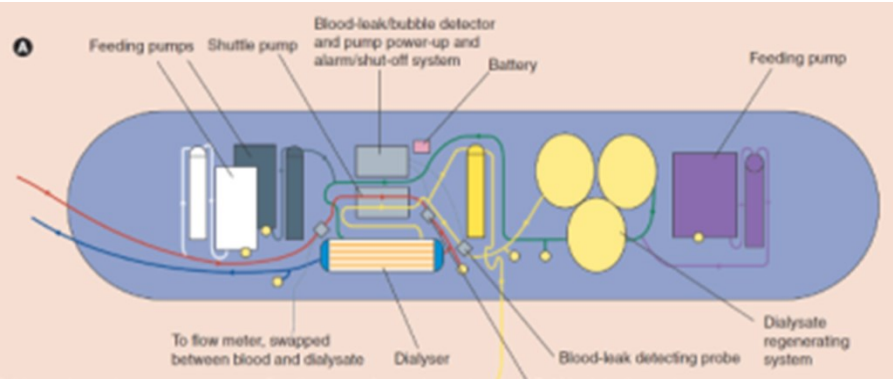


Figure 7. Schematic representation of the WAK

ViWAK

The ViWAK (Vicenza Wearable Artificial Kidney), shown in Figure 8, is a wearable device for continuous flow peritoneal dialysis designed by Prof Ronco and the Italian company Medica Srl (Medolla (MO), Italy) [38].

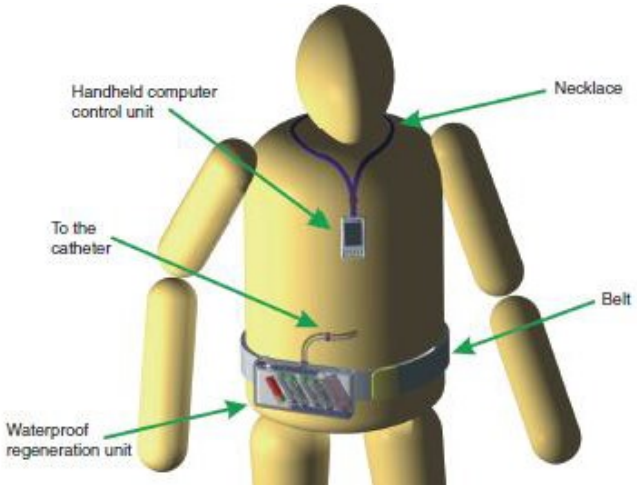


Figure 8. Schematic representation of the ViWAK

The device is only a conceptual prototype. It is connected to the patient by a double lumen peritoneal catheter and includes a miniaturized rotary blood pump and a dialysate inflow/outflow line. A regenerating system of cartridges (active carbons and polystyrene resins) guarantees a small amount of the peritoneal fluid necessary for blood purification. There is also a filter for removing air bubbles and a palmtop as remote-control unit. The therapy involves the infusion of two liters of dialytic solution into the peritoneal cavity and, after about 2 h, the removal of the same solution which is regenerated by the perfusion through the four cartridges. The removal of excess water is performed by simply removing more peritoneal solution than the infused one. The palmtop allows the clinician to prescribe and monitor the therapy by providing real time information on cartridge status, flow conditions, pressures, and possibility of intervention on the treatment. The disadvantages are related to the fact that peritoneal dialysis is a less efficient therapy with respect to the extracorporeal blood purification. Furthermore, the fact that the required injection of bicarbonate and glucose has to be done manually is a limitation, together with the risk of pH instability of peritoneal solution are both limitations.

AWAK

Professor Lee and Roberts' research led to the development of the WAK automated (AWAK) prototype [39] (Figure 9), based on continuous peritoneal dialysis therapy with regeneration of the

peritoneal solution by a modified SORB cartridge (SORB™, SORB™ Technology, Inc., OK, USA). The peritoneal dialysis regeneration is performed at a rate of 4 l/h by the cartridge. Through a single-lumen catheter, the peritoneal fluid flows in two phases, inside and outside the patient, using an external containment chamber. The device includes two modules, one for disposable components of the system (absorbing cartridges), and the other one for reusable components (part of power supply and pump for fluid infusion), that need to be changed monthly. The device weighs 250 g and, depending on the prototype, can be equipped with 750 g absorbing cartridges, used for a duration of 7 h and a flow rate of 2 l/h, or with a cartridge by 1.7 kg, used for 12 h of treatment with a flow of 4 l/h. As previously said for ViWAK, the main limitations regard the peritoneal dialysis, which is a less efficient therapy than the extracorporeal blood circulation one, and makes it necessary to use bicarbonate and glucose injection systems for electrolytic and acid-base equilibrium.

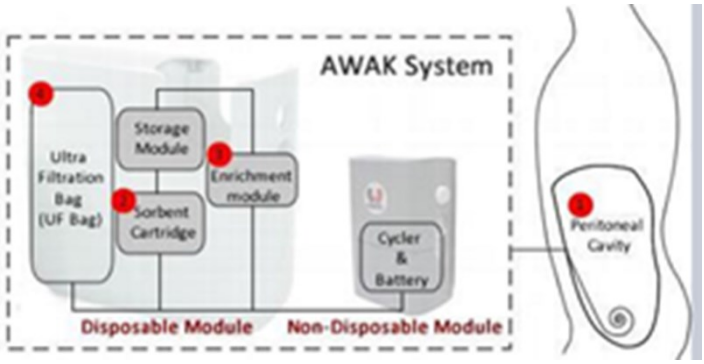


Figure 9. Schematic representation of the AWAK

WHF

The Wearable Hemofiltration Device (WHF) (Figure 10) is a device developed by the group of Prof Gura and his team [40], that is able to achieve hemofiltration of blood by a semipermeable membrane. Hemofiltration is a modality which, like ultrafiltration, consists of the removal of plasma water (ultrafiltration) and solutes (convection) by an imposed pressure gradient inside the filter, and a replacement of part of this water by reinfusion of physiological solution directly into the extracorporeal circuit. The WHF, like the WAK, is a belt. The patient is connected to the device by a double-lumen venous catheter, coupled to a miniaturized blood pump and two micro-battery pumps for the regulation of the ultrafiltration flow and the anticoagulant infusion. The overall weight of the device is less than 1.5 kg, while the maximum blood flow is about 115 ml/min and ultrafiltration flow ranges from 120 to 288 ml/h. The amount of urea and creatinine (the most important marker for CKD) removed during a treatment with WHF is potentially lower than the one reachable during traditional dialysis treatment: for this reason, the device is more suitable for patients with congestive heart failure.

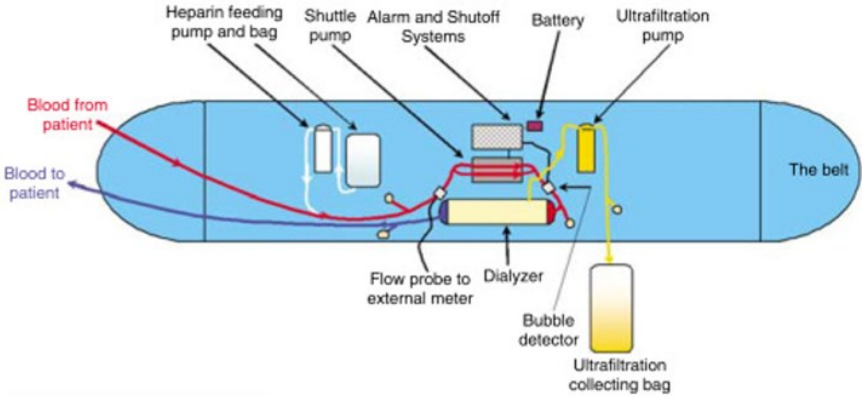


Figure 10. Schematic representation of the WHF

RAD

The RAD is a prototype based on the concept of renal assist device. Humes et al. [41] suggested to replace not only filtrative but also metabolic and endocrinologic functions of the kidney. The RAD (Figure 11) is composed of a filter and hollow-fiber cartridges containing human tubular cells derived from donor organs unsuitable for human transplantation, and has demonstrated promising results in clinical trials in acute kidney failure patients [PMID: 15458454]. However, this device cannot be applied alone for the moment, but it has to be used in parallel with a hemofiltration system, since it cannot remove excess water.

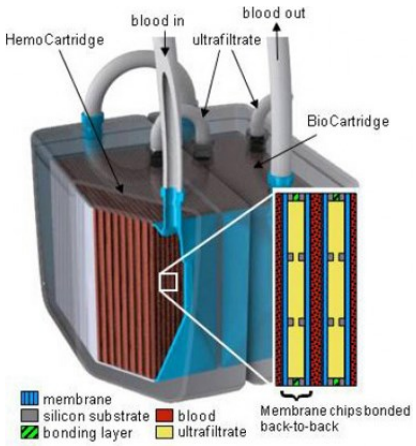


Figure 11. Schematic representation of the RAD

iNEPHRON

Financed by the European community in 2010, and developed by an international consortium of research centers and private companies [42], iNephron (Figure 12) is a small dimensions prototype (10 cm x 6 cm x 4 cm). Blood purification is reached by filters that allow it to separate part of plasma from red blood cells, which is then further filtered to remove small and medium molecular weight

waste molecules. These filters, whose mass is between 30 and 50 g, are based on nanosorbents technology and provide selective absorption capacity of solutes. An integrated system for controlling the treatment and remote monitoring of patients is also provided. iNephron is for the moment only a basic and conceptual prototype which is under development. In the website [42], the developers declare that miniaturization of the device and integration with sensors and control functions are foreseen in a parallel running EU/FP7 project called Nephron+ [43], that is intended to be portable but not wearable. Although iNephron is a promising device, it needs to be further implemented.

Figure 12. Schematic representation of the iNEPHRON and NephronPlus

WAKMAN

Professor Ronco's group developed a conceptual prototype of a wearable device for ultrafiltration able to offer greater mobility to patients: the WAKMAN [44]. The WAKMAN is a wearable ultrafiltration system (Figure 13) based on a miniaturized circuit mounted on a specific jacket that includes a compact and lightweight integrated pump-suction unit. This device can run from 8 to 24 hours and can be easily worn by the patient. Blood flow can be set between 50 and 80 ml/min, while the ultrafiltration flow rate is between 2 and 10ml/min and can be adjusted and personalized according to patients' needs. The device can be carried comfortably in the pocket of the jacket, leaving the patient free to perform much of their daily activities while the treatment is in progress. Compared to conventional peristaltic pumps, a piezoelectric components blood pump is used. However, the WAKMAN is a design exercise introducing some interesting concepts but never translated into a working prototype, and probably difficult to implement in some parts.

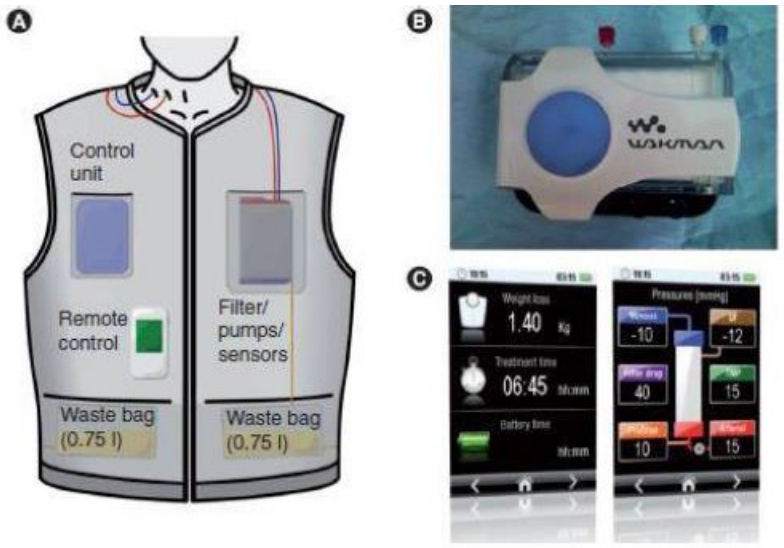


Figure 13. A) **.** Schematic representation of the WAKMAN; B) Intergrated unit pump-hemofilter; C) Remote control display

4. Normative and risk management

4.1 European directive and Standards

The wearable/portable ultrafiltration machine that is intended to be developed falls into the category of medical devices and, consequently, its design must guarantee mandatory requirements defined by European and national legislations. The European Directive defining the essential requirements that any medical device on the European market has to comply with, is the European Directive 93/42/EEC. This directive was then supplemented and amended by Directive 47/2007/EC, which considers also software as medical devices. In Directive 93/42/EEC, first of all it is defined what a medical device is:

Medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
- *investigation, replacement or modification of the anatomy or of a physiological process,*
- *control of conception,*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Two annexes of the Directive are particularly important:

- Annex I, which defines the essential requirements that must be respected to produce, trade and inspect a CE marked medical device,
- Annex IX, which classifies medical devices into four classes; in particular, a wearable and portable device for ultrafiltration falls within class IIb, that includes *all non-invasive devices intended for modifying the biological or chemical composition of blood, other body liquids or other liquids intended for infusion into the body*.

Class IIb devices must be considered separately from the non-contact devices, since they are indirectly invasive and modify substances that will eventually be infused into the body. This definition covers mostly the more sophisticated elements of extracorporeal circulation sets, dialysis

systems and auto transfusion systems as well as devices for extracorporeal treatment of body fluids which may or may not be immediately reintroduced into the body, including, where the patient is not in a closed loop with the device.

One of the most important concepts defined in the directive regarding the design of a medical device, even before the provision of therapeutic or diagnostic efficacy, is that it must be safe: this means to reduce to an acceptable minimum risk the probability of inducing any hazardous situation to the patient or the environment. Thus, before the design phase of any device, and in particular of medical ones, a deep study needs to be carried out in order to perform an appropriate risk management analysis.

Risk management is an efficient and universally recognized method to identify the potential hazardous situations and ensure a sufficient level of safety of biomedical devices. The main aim of this methodology is to quantify, and then, during the production cycle, minimize, the inevitable level of risk related to operations and use of a medical device. In order to respect that, technical standards regarding risks associated with the use of a medical device have been considered. In particular, the standard ISO/IEC 14971 (International Organization for Standardization ISO and International Electrotechnical Commission) is specifically dedicated to the risk management process for medical devices, defining the guidelines to follow during this process. Of course, since the criteria outlined in the standard have a general meaning, they have to be adapted to the particular type of the considered medical device. An important aspect underlined in the standard is the fact that possible risks associated with the device should be analyzed in several ways: the risk should be considered acceptable both on the technical/engineering and clinical or biological levels. It is therefore necessary to face the process in a multi-disciplinary and multi-professional approach, able to analyze the problem from different points of view.

It is necessary to highlight how there are no specific standards treating miniaturized portable/wearable medical devices for extra-corporeal blood ultrafiltration, so the technical standards concerning medical electrical equipment need to be applied and adapted to the particular case.

The risk management process has been performed considering the following standards:

- IEC 60601-1: general harmonized technical standard concerning the safety and effectiveness of medical electrical equipment;
- IEC 60601-1-1: collateral standard concerning safety requirements for medical electrical systems;
- IEC 60601-1-4: collateral standard concerning programmable electrical medical systems;
- IEC 60601-1-6: collateral standard concerning usability of medical electrical equipment;

- IEC 60601-1-8: collateral standard concerning general requirements, tests and guidance for alarm systems in medical electrical equipment;
- IEC 60601-1-11: collateral standard concerning requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment;
- IEC 60601-2-16: collateral standard concerning particular requirements for the safety of haemodialysis, haemodiafiltration and haemofiltration equipment;
- ISO/IEC 12207: technical standard concerning systems and software engineering - software life cycle processes;
- CEI/EN 62366: technical standard concerning the application of usability engineering to medical devices;
- ISO 8637: technical standard concerning specific requirements for cardiovascular implants and artificial organs – haemodialysers, haemodiafilters, haemofilters and haemoconcentrators.

The risk management process has been carried out to comply with the European Directive 93/42/EEC and all the technical standards listed above.

4.2 Risk management

The aim of the risk management process is to identify harms for patients derived from potential hazardous situations and their causes. This process is usually necessary to select all the hardware components devoted to safety for the prototype to be developed.

The clinical risk assessment is based on the device operating in open chain, meaning that no monitoring systems and/or feedback protection are applied. As a next step, after assembling and prototyping the system, other types of risks, specifically related to the use of actuators and sensors, may be considered in addition to the clinical/operational risks.

The categories of risks are:

- hardware
    - mechanical
    - electrical
- software (based on technical standard CEI EN 62304)
- environmental
- physical

- chemical

In Figure 14, a sequencing scheme of the risk management process is reported, according to the technical standard ISO/IEC 14971.

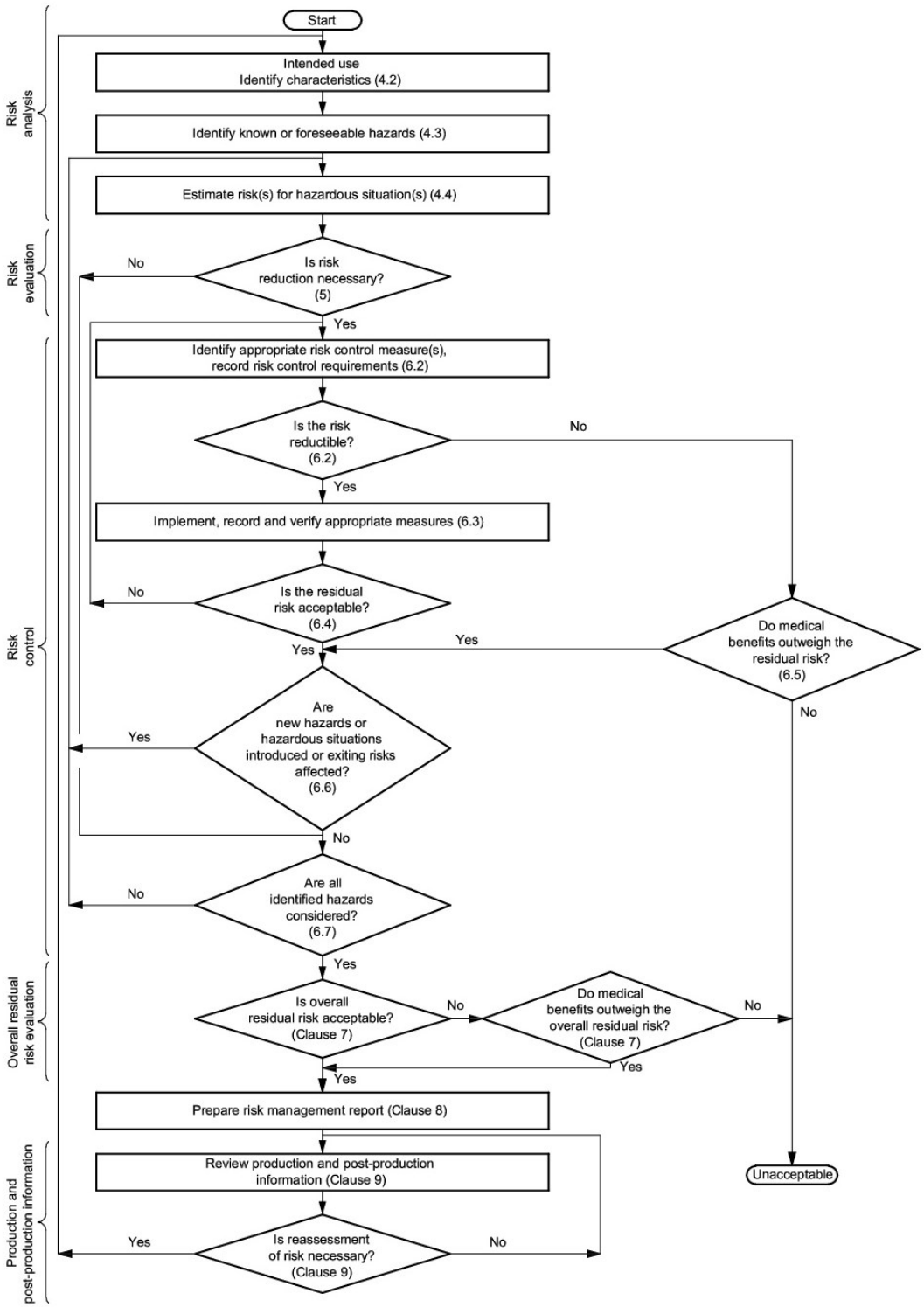


Figure 24: *Overview of risk management activities as applied to medical devices*

As shown in the graph, the key stages of the risk management process are:

- risk analysis;
- risk evaluation;
- risk control;
- implementation and verification of control measures;
- acceptability of residual risk.

According to the terminology adopted in the standard ISO/IEC 14971, designers are requested firstly to identify a list of known and foreseeable hazards, as sources of harm, that are directly associated with the specific medical device. A situation in which people, properties, or the environment are exposed to a hazard is called a hazardous situation. The risk associated with each hazardous situation has to be estimated using literature. Usually, the quantification of the risk results from the product of two components: the severity of the harm, which consists of the consequences of the harm that is generated by each hazard situation, and the probability of occurrence of that harm. If this score for risk quantification is evaluated as too high, a risk reduction is necessary. In this case, risk control measures shall be applied and the related residual risk shall be re-evaluated. This process has to be followed in a recursive way, until the final residual risk is judged acceptable. In order to have a consistent and reproducible method, an appropriate evaluation scale has been identified to define severity, probability, and the resulting risk.

Based on these guidelines, standards (ISO/IEC 14971 and [45]) and literature [46], an assessment of possible harms to the patient deriving from clinical/operational risks, which means only deriving from the clinical use of the WUF, not considering any environmental damage, was done. The list of possible harms is listed in the left column of Table 3. For each harm, the hazardous situations and their causes have been associated through a top down fault free analysis: it is a technique for system safety analysis that starts defining the harms and goes down to define possible causes. The definition of these circumstances allowed filling in Table 3.

Patient harm	Hazardous situation	Hazardous situation causes
Vessel walls damage and thrombosis	Vascular access (catheter) malfunction	Catheter displacement
		Catheter tip touches the vessel wall
		Catheter clotting
		Blood flow rate too high for the catheter
Excessive bleeding	Excessive level of anticoagulant into the blood stream	Excessive continuous administration of anticoagulant
		Excessive bolus administration of anticoagulant
		The concentration of anticoagulant in the solution to be infused is excessive (preparation error)
		The ratio between anticoagulant continuous flow rate and blood flow rate is out of acceptable clinical range
		Error during setting of parameters in the device by the user
Embolism/thrombosis	Air infusion in the extracorporeal circuit	Cracking or rupture of extracorporeal circuit connectors
		Cracking or rupture of the catheter
		Excessive negative pressure in access line
		Incomplete circuit filling during priming phase
Blood loss (1)	Blood coagulation in the extracorporeal circuit	Contact between blood and external surfaces
		Insufficient anticoagulant administration (control error)
		Insufficient anticoagulant bolus administration (control error)
		Insufficient concentration of anticoagulant in the prepared solution to be administered (error in solution preparation)
		Ratio between anticoagulant flow rate and blood flow rate out of acceptable clinical range
		Error during setting of anticoagulation therapy parameters in the device by the user
		Anticoagulant reserve exhausted
		Prolonged treatment interruption: out of battery
		Prolonged treatment interruption: blood pump stopped
		Blood flow rate too slow
		Patient hematocrit too high
		Treatment hematocrit too high: ratio between UF and blood flow rates excessively high

Blood loss (2)	Blood loss in UF compartment	Filter membrane cracking or rupture due to too high transmembrane pressure
Blood loss (3)	Blood loss from extracorporeal circuit	Catheter displacement
		Disconnection of vascular access/lines/filter connectors
		Rupture of vascular access/lines/filter connectors
		Lines/filter rupture: internal pressure too high
		Lines/filter rupture: external mechanical stress (compression, traction, twisting, shearing, vibration)
		Vascular access/lines/filter connectors not properly connected
		External obstruction in access line
		External obstruction in pre-filter line
		External obstruction in return line
Hyperthermia	Blood overheating: heat exchange with the external environment	Environmental temperature too high
		Contact with high temperature fluids
		Contact with high temperature surfaces
		Device combustion
Hypothermia	Blood overcooling: heat exchange with the external environment	Environmental temperature too low
		Contact with low temperature external elements
Hemolysis	Red blood cells rupture	High shear stress: blood viscosity too high
		High shear stress: blood flow rate too high
		Excessive blood pressure: obstruction of vascular access/lines/filter
		Excessively high blood pressure: vascular access/lines/filter clotting
		Hyperthermia
		Mechanical compression stress due to blood pump
		Mechanical shear stress due to blood pump
		Chemical and/or biological residues
Hypervolemia		Error during setting of UF parameters in the device by the user

	The removed plasma water (UF) volume is less than the prescribed one	UF flow rate and/or UF volume removed is lower than prescribed ones: error of treatment process (the UF pump)
		Decreased filter efficiency (e.g. clotting)
		Treatment stop/discontinuation
		Ultrafiltration tank is full
		UF line disconnection
		Rupture of UF line connectors
		Rupture of UF line: excessive inner pressure
		Rupture of UF line: external mechanical stress (compression, traction, twisting, shearing, vibration)
		UF connectors/lines not properly connected
		Rupture of UF tank
Hypovolemia	The removed plasma water volume is more than the prescribed one	Error during setting of UF parameters in the device by the user
		UF flow rate and/or UF volume removed is higher than prescribed ones: error of treatment process (the UF pump)

Table 3. Risk analysis related to the use of the WUF

After having defined the causes possibly leading to harms, it was necessary to quantify the risk that any of these causes may generate during normal treatment with the medical device. The risk's estimation, as explained, can be obtained by the product of two components: severity and probability related to harms. These two factors are usually defined based on the analysis derived from two scales of values. If the result of this product exceeds a risk-tolerance threshold value defined by the designer, it is necessary to reduce the overall risk of a single event through appropriate arrangements. This process has to be repeated until the residual risk level assigned to each harm is acceptable or reaches a level of risk defined as ALARP, (as low as reasonably practicable). "ALARP" identifies a reduced risk that can ensure the maximum level of safety achievable taking into considerations even economic and technical aspects.

The scales of values used in this project to quantify severity and probability of risks are reported in Table 4 and Table 5 [45].

Severity

Level	Assigned score	Generic description
Catastrophic	5	Death
Critical	4	Permanent impairment or life-threatening injury
Serious	3	Injury or impairment requiring professional medical intervention
Minor	2	Temporary injury or impairment not requiring professional medical intervention
Negligible	1	Inconvenience or temporary discomfort; no injury

Table 4. Levels of severity of risk

Probability

Level	Assigned score	Probability of the event
Frequent	5	$\geq 10^{-3}$
Probable	4	$< 10^{-3}$ e $\geq 10^{-4}$
Occasional	3	$< 10^{-4}$ e $\geq 10^{-5}$
Remote	2	$< 10^{-5}$ e $\geq 10^{-6}$
Improbable	1	$< 10^{-6}$

Table 5. Levels of probability of risk

Based on these levels, a cross table has been identified in order to define in a clear and efficient manner the overall risk levels to consider (Table 6).

		Severity				
		Catastrophic	Critical	Serious	Minor	Negligible
Probability	Frequent	B	A	A	A	A
	Probable	B	B	A	A	A
	Occasional	C	B	B	A	A
	Remote	C	B	B	B	A
	Improbable	C	C	C	B	B

Table 6. Definition of risks level (A=unacceptable, B=ALARP (as low as reasonably possible), C=acceptable).

Table 7, that describes all the identified harms and hazardous situations, together with associated levels of risk, has been completed in collaboration with the clinicians of the Department of Nephrology, Dialysis and Transplantation of the San Bortolo Hospital in Vicenza.

HAZARDOUS SITUATION	HAZARDOUS SITUATION CAUSES	SEVERITY LEVEL OF HAZARDOUS SITUATION CAUSE	PROBABILITY OF HAZARDOUS SITUATION CAUSE	RISK ASSESSMENT OF HAZARDOUS SITUATION CAUSE	WORST CASE OF HAZARODUS SITUATION
Vascular access (catheter) malfunction	Catheter displacement	2	2	B	B
	Catheter tip touches the vessel wall	1	3	C	
	Catheter clotting	1	2	C	
	Blood flow rate too high for the catheter	1	1	C	
Excessive level of anticoagulant into the blood stream	Excessive continuous administration of anticoagulant	4	1	B	B
	Excessive bolus administration of anticoagulant		1	B	
	The concentration of anticoagulant in the solution to be infused is excessive (preparation error)		2	B	
	The ratio between anticoagulant continuous flow rate and blood flow rate is out of acceptable clinical range		2	B	
	Error during setting of parameters in the device by the user		2	B	
Air infusion in the extracorporeal circuit	Cracking or rupture of extracorporeal circuit connectors	5	2	A	A
	Cracking or rupture of the catheter		2	A	
	Excessive negative pressure in access line		3	A	
	Incomplete circuit filling during priming phase		3	A	
Blood coagulation in the extracorporeal circuit	Contact between blood and non-self surfaces	3	3	B	B
	Insufficient anticoagulant administration (control error)		1	C	
	Insufficient anticoagulant bolus administration (control error)		1	C	
	Insufficient concentration of anticoagulant in the prepared solution to be administered (error in solution preparation)		1	C	
	Ratio between anticoagulant flow rate and blood flow rate out of acceptable clinical range		1	C	
	Error during setting of anticoagulation therapy parameters in the device by the user		1	C	
	Anticoagulant reserve exhausted		2	B	
	Prolonged treatment interruption: out of battery		2	B	
	Prolonged treatment interruption: blood pump stopped		2	B	
	Blood flow rate too slow	2	1	B	
	Patient hematocrit too high	2	1	B	

	Treatment hematocrit too high: ratio between UF and blood flow rates excessively high	2	1	C	
Blood loss in UF compartment	Filter membrane cracking or rupture due to too high transmembrane pressure	4	2	B	B
Blood loss from extracorporeal circuit	Catheter displacement	5	2	A	A
	Disconnection of vascular access/lines/filter connectors	5	2	A	
	Rupture of vascular access/lines/filter connectors	5	2	A	
	Lines/filter rupture: internal pressure too high	5	2	A	
	Lines/filter rupture: external mechanical stress (compression, traction, twisting, shearing, vibration)	5	1	B	
	Vascular access/lines/filter connectors not properly connected	5	2	A	
	External obstruction in access line	2	3	B	
	External obstruction in pre-filter line	3	3	B	
	External obstruction in return line	3	3	B	
Blood overheating: heat exchange with the external environment	Environmental temperature too high	4	1	B	B
	Contact with high temperature fluids		1	B	
	Contact with high temperature surfaces		2	B	
	Device combustion		1	B	
Blood overcooling: heat exchange with the external environment	Environmental temperature too low	3	3	B	B
	Contact with low temperature external elements		2	B	
Red blood cells rupture	High shear stress: blood viscosity too high	2	3	B	B
	High shear stress: blood flow rate too high		2	B	
	Excessive blood pressure: obstruction of vascular access/lines/filter		4	B	
	Excessively high blood pressure: vascular access/lines/filter clotting		2	B	
	Hyperthermia		2	B	
	Mechanical compression stress due to blood pump		4	B	
	Mechanical shear stress due to blood pump		4	B	
	Chemical and/or biological residues		1	C	
The removed plasma water volume is less than the prescribed one	Error during setting of UF parameters in the device by the user	2	3	B	B
	UF flow rate and/or UF volume removed is lower than prescribed ones: error of treatment process (UF pump)		4	B	
	Decreased filter efficiency (e.g. clotting)		4	B	

	Treatment stop/discontinuation		4	B	
	Ultrafiltration tank is full		3	B	
	UF line disconnection		2	B	
	Rupture of UF line connectors		1	C	
	Rupture of UF line: excessive inner pressure		2	B	
	Rupture of UF line: external mechanical stress (compression, traction, twisting, shearing, vibration)		1	C	
	UF connectors/lines not properly connected		2	B	
	Rupture of UF tank		2	B	
The removed plasma water volume is more than the prescribed one	Error during setting of UF parameters in the device by the user	4	2	B	A
	UF flow rate and/or UF volume removed is higher than prescribed ones: error of treatment process (the UF pump)		3	A	

Table 7. Risk quantification of the causes of hazardous situation

Among the possible causes of hazardous situations, particular attention must be paid on the ones with the highest level of risk (A). In such cases, technological adjustments need to be applied in order to reduce the risk at least from unacceptable (A) to as low as reasonably possible (B).

Table 8 shows how the selected technological adjustments intended to be applied to the WUF (which will be treated in details in the next paragraph) allow reducing the risks of unacceptable hazardous situations (A) to ALARP (B) or even to acceptable (C).

HAZARDOUS SITUATION CAUSES	**RISK ASSESSMENT OF HAZARDOUS SITUATION CAUSE**	**WORST CASE OF HAZARDOUS SITUATION**	**HOW TO DETECT THE CAUSES**	**DETECTION OF HAZARDOUS SITUATION COMPONENTS**	**WORST CASE RISK REDUCTION**
Catheter displacement	B	B	Access/return pressure exceeding lower/upper limit Blood flow exceeding lower limit Access pressure exceeding lower limit	Access and return pressure sensors Blood flowmeter (or blood flow estimation) Access pressure sensors	C
Catheter tip touches the vessel wall	C				
Catheter clotting	C				
Blood flow rate too high for the catheter	C				

Excessive continuous administration of anticoagulant	B	B	Anticoagulant flow rate exceeding upper limit	Anticoagulant flowmeter Anticoagulant administration monitoring system	C
Excessive bolus administration of anticoagulant	B		Anticoagulant bolus exceeding upper limit	Anticoagulant administration monitoring system	
The concentration of anticoagulant in the solution to be infused is excessive (preparation error)	B		Diagnostic analysis		
The ratio between anticoagulant continuous flow rate and blood flow rate is out of acceptable clinical range	B				
Error during setting of parameters in the device by the user	B				
Cracking or rupture of extracorporeal circuit connectors	A	A	Air flow (ml/kg min) exceeding upper limit Air bolus (ml/kg) exceeding upper limit	Air bubble detector	B
Cracking or rupture of the catheter	A				
Excessive negative pressure in access line	A				
Incomplete circuit filling during priming phase	A				
Contact between blood and non-self surfaces	B	B	Pre-filter/return/transmembrane pressures exceeding upper limit	Pre-filter and return pressure sensors	C
Insufficient anticoagulant administration (control error)	C		Anticoagulant flow rate exceeding lower limit	Anticoagulant flowmeter Anticoagulant administration monitoring system	
Insufficient anticoagulant bolus administration (control error)	C		Anticoagulant bolus exceeding lower limit	Anticoagulant administration monitoring system	
Insufficient concentration of anticoagulant in the prepared solution to be administered (error in solution preparation)	C				
Ratio between anticoagulant flow rate and blood flow rate out of acceptable clinical range	C		Pre-filter/return/TMP/drop pressure exceeding upper limit	Access and return pressure sensors	
Error during setting of anticoagulation therapy parameters in the device by the user	C				
Anticoagulant reserve exhausted	B		Anticoagulant flow rate exceeding lower limit	Anticoagulant flowmeter Position sensor (syringe plunger) Anticoagulant administration monitoring system	
Prolonged treatment interruption: out of battery	B		Battery level exceeding lower limit		

Prolonged treatment interruption: blood pump stopped	B		Blood flow and/or blood pump speed equal to zero	Blood line flowmeter Blood pump speed sensor	
Blood flow rate too slow	C		Blood flow exceeding lower limit (non-zero)	Pressure sensors	
Patient hematocrit too high	C		Hematocrit value (IR system) exceeding upper limit	Hematocrit sensor	
Treatment hematocrit too high: ratio between UF and blood flow rates excessively high	C		UF flow over blood flow rate (filtration fraction) exceeding upper limit	Blood line flowmeter UF line flowmeter UF volume monitoring system	
Filter membrane cracking or rupture due to too high transmembrane pressure	B	B	Blood in UF compartment exceeding upper limit	Blood leak detector sensor	C
Catheter displacement	A				
Disconnection of vascular access/lines/filter connectors	A				
Rupture of vascular access/lines/filter connectors	A				
Lines/filter rupture: internal pressure too high	A				
Lines/filter rupture: external mechanical stress (compression, traction, twisting, shearing, vibration)	B	A	Access, Pre-filter/return/UF/TMP/drop pressures exceeding upper limit Humidity	Access, pre-filter, return and UF pressure sensors Flowmeters Humidity sensors	B
Vascular access/lines/filter connectors not properly connected	A				
External obstruction in access line	B				
External obstruction in pre-filter line	B				
External obstruction in return line	B				
Environmental temperature too high	B				
Contact with high temperature fluids	B				
Contact with high temperature surfaces	B	B	Blood temperature exceeding upper limit	Temperature sensor	B
Device combustion	B				

Environmental temperature too low	B	B	Blood temperature exceeding lower limit	Temperature sensor	C
Contact with low temperature external elements	B				
High shear stress: blood viscosity too high	B	B	Diagnostic analysis and/or pressures assessment	Access, pre-filter, return, UF pressure sensors Hematocrit sensor Temperature sensor	B
High shear stress: blood flow rate too high	B				
Excessive blood pressure: obstruction of vascular access/lines/filter	B				
Excessively high blood pressure: vascular access/lines/filter clotting	B		Hematocrit value (IR system) exceeding lower limit		
Hyperthermia	B				
Mechanical compression stress due to blood pump	B				
Mechanical shear stress due to blood pump	B		Diagnostic analysis		
Chemical and/or biological residues	C				
Error during setting of UF parameters in the device by the user	B	B	UF flow rate and/or volume exceeding lower limit	UF volume monitoring system: UF flowmeter Volumetric system Gravimetric system (load cells) Pre-filter return and UF pressure sensor	C
UF flow rate and/or UF volume removed is lower than prescribed ones: error of treatment process (UF pump)	B				
Decreased filter efficiency (e.g. clotting)	B		TMP pressure exceeding upper limit		
Treatment stop/discontinuation	B		Blood flow rate exceeding lower limit		
Ultrafiltration tank is full	B		UF pressure out of range		
UF line disconnection	B		UF pressure out of range		
Rupture of UF line connectors	C		Abnormal pressure values, humidity		
Rupture of UF line: excessive inner pressure	B				
Rupture of UF line: external mechanical	C				

stress (compression, traction, twisting, shearing, vibration)					
UF connectors/lines not properly connected	B				
Rupture of UF tank	B				
Error during setting of UF parameters in the device by the user	B	A	UF flow rate and/or volume exceeding upper limit	UF volume monitoring system: UF flowmeter Volumetric system Gravimetric system (load cells)	B
UF flow rate and/or UF volume removed is higher than prescribed ones: error of treatment process (the UF pump)	A				

Table 8. Parameters to monitor during the treatment e hardware components possibly to be applied in order to reduce the risk associated to the causes of hazardous situations

This analysis allows identifying possible components to equip the wearable/portable system with in order to keep risk to a minimum. In particular, the hardware components which would guarantee a reduction of the overall risk of specific hazardous situations, and then harms, are:

- Air sensor able to read air bubbles in blood line before reinfusion to the patient;
- Blood leak detector able to detect blood loss due to membrane rupture;
- Three pressure sensors to preventively avoid blood loss from the blood circuit due to disconnections or blood coagulation;
- One pressure sensor in the ultrafiltrate line to detect coagulation in the filter potentially leading to blood loss;
- Humidity sensors to detect blood loss;
- Fluid balance monitoring system to check the plasma water volume removed from the patient;
- Temperature sensor to monitor excessive temperature variations;
- A sensor, or a reliable estimation strategy, for monitoring the heparin flow and a sensor detecting when the tank for heparin is empty;
- Hematocrit sensor to measure the hematocrit levels in the extracorporeal circuit;
- System for monitoring blood flow.

This list of components has been further skimmed considering that:

- Risks for hazardous situation, whose related risk is not worse than “ALARP”, should take into account also aspects related to costs, overall dimensions and environment;
- If two or more components have the same function, it has been considered sufficient to apply only one of these components if safety requirements are respected.

In such context, the humidity sensor has the same aim as pressure sensors, which is to detect possible blood loss due to disconnections of the extracorporeal circuit components or blood coagulation. Furthermore, the humidity sensor would be affected by environmental conditions, possibly leading to wrong measurements. For these reasons, no humidity sensor will be adopted.
The hematocrit is the percentage in volume of red blood cells in blood. Since the hematocrit variation along the treatment duration in a standard ultrafiltration therapy has been considered very low, no sensor for detection of hematocrit levels is used in the device presented in this thesis.
Regarding the system for monitoring the blood flow, initially a flowmeter was thought to be used. Anyway, the measurement of blood flow can be both estimated by variations of pressure inside the circuit and measured starting from the velocity of the blood pump, in case such a pump is a volumetric one. Taking also into considerations that a flowmeter would be expensive and quite bulky, it has been decided not to adopt it in the device. A similar reasoning justifies the choice not to adopt a sensor for monitoring the heparin flow which, in case a volumetric pump is employed, can be easily estimated.
Based on this further analysis, the final list of components to be integrated in the wearable device and which can guarantee an adequate level of safety to patients is:

- Air sensor;
- Blood leak detector;
- 4 pressure sensors:
    - Access pressure sensor;
    - Pre-filter pressure sensor;
    - Return pressure sensor;
    - Ultrafiltrate pressure sensor;
- Fluid balance monitoring system;
- A sensor detecting when the tank for heparin is empty;
- Temperature sensor.

It is apparent that the detection of a hazardous situation by itself does not lead to a direct risk reduction associated with it. For this reason, for every hazardous situation, specific responding actions need to be performed. These actions include:

- closure of a clamp (safety valve) placed before the blood returns to the patient;
- stop of the blood pump;
- stop of the ultrafiltration pump;
- acoustic signal when alarms or warnings are detected.

The presence of a clamp is crucial because, when a hazardous situation is detected, it leads to an immediate occlusion of the extracorporeal blood circulation. A clamp must be capable of occluding the circuit through which blood flows, thereby isolating the problem and significantly reducing direct and indirect risk to patients.

5. Components for a wearable device

Based on clinical indications from the staff of the Department of Nephrology, Dialysis and Transplantation of the San Bortolo Hospital of Vicenza and the International Renal Research Institute of Vicenza, and the literature review of existing or proposed prototypes of portable devices as well as conventional treatment machines, it has been possible to identify the requirements that a modern wearable and portable device for extracorporeal ultrafiltration must meet. Subsequently, the most suitable technologies for the components considered essential for the development of the WUF have been selected.

As mentioned, in general the WUF must provide extracorporeal circulation of blood and ultrafiltrate removal by means of pumps. Clearly, the device should be wearable, wireless and independent from the electrical power outlet at least for periods lasting long enough not to pose serious limitations to patients' usual mobility habits. The WUF is intended to be used for continuous ultrafiltration therapy, i.e. 24 hours a day: in such a condition, the apparatus may consume large amounts of energy which imposes that adequate energy sources are available and a careful design of components so as to guarantee relevant energy savings. In addition to such requirements, miniaturization, ergonomics, and low weight are obviously of paramount importance and need to be taken into account during all the design phases.

Going into details, for the specific treatment considered, the requested blood flow is about 50 ml/min. It is essential that the vascular access adopted avoids infections and clots formation; it is also necessary that connection and disconnection are easy to perform. The extracorporeal circulation has to be made of anti-thrombogenic materials and have a low priming volume. The circuit must be provided with adequate safety measures for the patient. The filter must be small in size, about one-tenth of normal filters used in standard ultrafiltration therapies. The membranes of the filter must be non-thrombogenic, or at least as low as possible, in order to minimize the risk of coagulation.

The device must be able to remove an amount of ultrafiltrate volume similar to one physiologically removed from the kidneys. The removal of excess fluid will result in a better control of hypertension. The volume to be removed is then between 1.5 and 2 liters in 24 hours (or even less). The therapy allows also to eliminate substances such as sodium, thereby helping to overcome some dietary limitations of the patient.

When blood encounters artificial materials, the coagulation system of blood is immediately activated, inducing the coagulation cascade. In order to reduce this phenomenon during the extracorporeal blood circulation, a controlled and continuous infusion of anticoagulation drugs, such as heparin, has to be administered into the circuit. The estimated heparin flow is between 1 and 2.5 ml/h.

In order to allow patient to wear the device and to walk without interfering with daily activities, it must have a light and ergonomic design.
Finally, the device should be designed to be run autonomously and monitored remotely by medical staff. Indeed, the device controller should not only allow setting up the therapy and running it, but should also allow performing a continuous or on-demand data logging for monitoring purposes. The prescription of operative parameters and treatment data visualization must be easily accessible through a comprehensive software interface too.

Clearly, for a wearable/portable device it is necessary to include in the design only what is strictly necessary. As previously stressed, some of the components that have been integrated in the system have been chosen among those available commercially. A specific initial effort has been devoted to define which of them could be:

- Disposables (replaced after each treatment), which are preferable for hygienic reasons;
- Not disposables (not replaced after each treatment), for economic reasons.

A comprehensive seek on the market of such off-the-shelf components has been carried out, limiting the exploration to components manufactured in Italy or manufactured but international companies with Italian distributors in order to meet the strict requirements imposed by the administrative leader of the “RAP” project. After the identification of all the possible components suitable for the project, the selection of the best ones has been based on clinical, technical and economic evaluations. On the other hand, for some “critical” components it has been necessary to perform specific and thorough investigations because either they were not commercially available or not enough studied in literature. After such investigations, described later in this chapter, it has been determined whether these components needed to be adopted, if they could be selected among off-the-shelf products or if they should be customized or even designed specifically for this application.

5.1 General scheme of the extracorporeal circuit

Considering the basic requirements previously stated and results from the risk management analysis, it has been possible to define the general scheme of the WUF to be developed. It is represented in Figure 15.

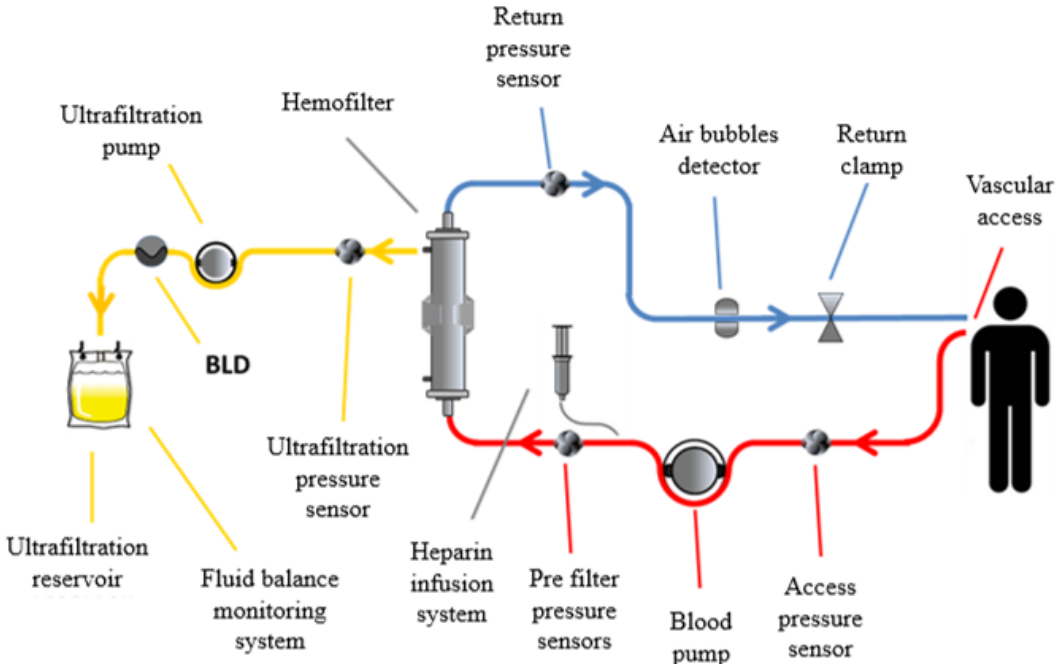


Figure 15. General scheme of the WUF

Each component shown in the scheme will be described and analyzed in details in the following paragraphs, justifying its choice and selection.

5.2 Off-the-shelf components: requirements and selection

The analysis and choice of the off-the-shelf components of the WUF have been carried out applying a methodological approach consisting of the following phases:

- functional analysis of each component;
- definition of specifications to be met;
- identification of available technologies;
- identification of the components available in the market that integrate the identified technologies and that meet design specifications.

Off-the-shelf hydraulic components will be first described, then off-the-shelf electric and electronic components, including sensors end controllers, will be discussed. The components will be presented in the following order:

- Off-the-shelf hydraulic components
- Off-the-shelf sensors
- Off-the-shelf controllers
- Off-the-shelf additional electric and electronic devices (boards and sensor conditioning system)

5.2.1 Off-the shelf hydraulic components

The off-the-shelf hydraulic include the vascular access, the hemofilter, tubes and ultrafiltration pump.

Vascular access

The vascular access is the device through which blood is extracted and then reinfused into the patient. In general, vascular accesses can be classified as temporary or permanent. The temporary ones are mainly used for patients suffering from acute kidney injury or for patients with chronic kidney disease waiting for permanent access; the permanent ones are instead specifically used for patients undergoing dialysis treatments continually. Since the aim of the WUF is to treat patients in a continuous form, temporary accesses will not be described. The main permanent vascular accesses are arteriovenous fistula (AVF), arteriovenous graft and central venous catheter (CVC).

The AVF is the most used permanent vascular access type for extracorporeal treatments (such as hemodialysis). In order to provide an extracorporeal blood flow high enough to perform blood

purification, a surgical anastomosis between a vein and an artery is made. Usually, it is applied in peripheral vessels in arms (Figure 16).

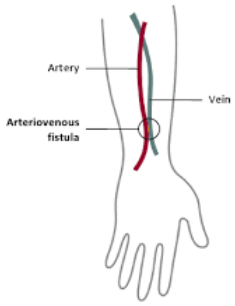


Figure 16. Schematic example of an arterio-venous fistula

The arterio-venous graft consists of a prothesis surgically connected with the artery and the vein (Figure 17). The most used material is Polytetrafluoroethylene (PTFE). This type of vascular access is usually applied when an AVF cannot be carried out in the patient's arm.

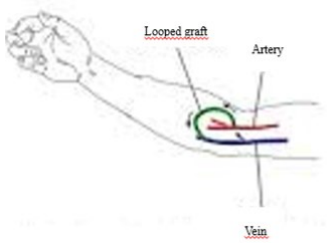


Figure 17. Schematic example of an arterio-venous graft

Fistulas (AVF and graft) are applied in the arm and would not be the best solution for a WUF, since they would not allow freedom of movement and to perform normal daily activities for patients.

For these reasons, the central venous catheter (CVC) has been considered the best solution (Figure 18).

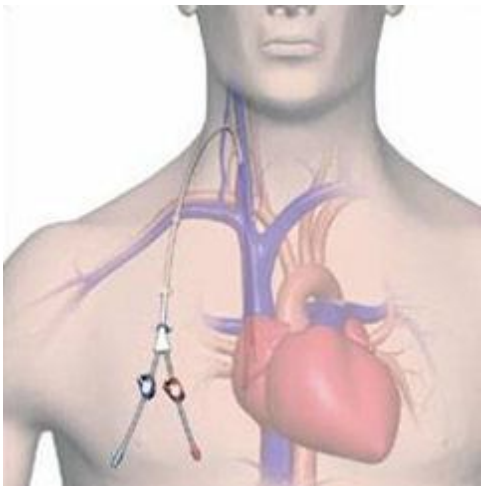


Figure 18. Central venous catheter positioned in jugular vein

A catheter is inserted through the skin into a large vein (jugular, femoral or subclavian). The catheter is then threaded through this vein until it reaches a large vein near the heart. The type of catheter used in blood purification therapies is "dual-lumen": in the proximal part (the part remaining outside of the skin, the so-called exit side), two ports (red and blue colored) are present, one for extraction and the other one for reinfusion of blood to the same vein of patients. Different designs of dual lumen catheter have been developed by different companies. In particular, different cross sections are represented in Figure 19.

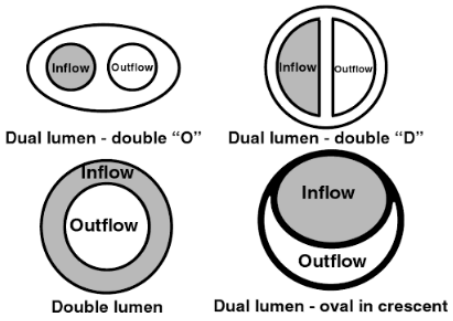


Figure 19. Design examples of dual lumen catheters

The most used configuration is the double "D" dual lumen, since it allows a good hemodynamics inside the catheter.

Particular attention has been paid on the definition of the minimum size of the catheter. In particular, based on the WUF prescribed blood flow, the length and the diameter of the channels have been determined for this specific aim. The details are discussed in Appendix A. A double "D" lumen

catheter (Figure 20), positioned in the jugular vein, with a length of 19 cm and a lumen of 10 French, corresponding to an external diameter of 3.34 mm, has been chosen.

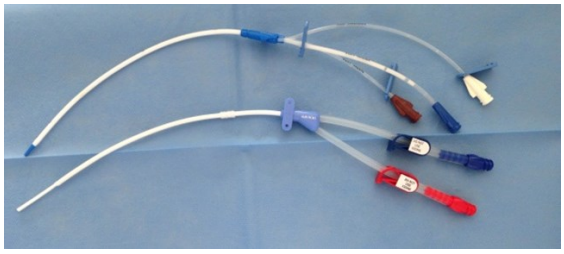


Figure 20. Selected dual lumen catheter for the WUF

Hemofilter

The importance of the hemofilter in performing the ultrafiltration therapy has been already stated. An ideal hemofilter for a WUF must have the following features:

- high biocompatibility;
- inner membrane with an appropriate ultrafiltration coefficient;
- good ratio between exchanging surface and total volume;
- small dimensions;
- limited priming volume;
- minimum production costs.

The most important characteristic of a hemofilter is biocompatibility. A filter can be considered biocompatible if its use does not have any adverse clinical effect on a patient such as headache, nausea, anxiety, pruritus, leukocyte variation, complement activation (complex of proteins responsible for the immune system) or granulocytes activation. In particular, the hemofilter to be applied must ensure hemocompatibility, complying with the standard UNI EN ISO 10993-4 which regulates *in vitro* and *in vivo* tests for this type of biomedical devices and provides tests related to thrombosis, coagulation, platelet function, hematological and immunological parameters.
The ultrafiltration coefficient (Kuf) is an important parameter for the choice of the hemofilter and indicates the amount of maximum ultrafiltrate volume potentially removable by the hemofilter. More precisely, it indicates how much volume of ultrafiltrate fluid can be removed from blood in an hour by applying a transmembrane pressure of 1 mmHg. Based on the basic requirements stated before, in order to ultrafiltrate a maximum of 2 l per day (corresponding to almost 85 ml/h), and assuming a

TMP of 100 mmHg, the minimum ultrafiltration coefficient requested to the hemofilter for the WUF is Kuf = 1 ml/h/mmHg.

It seems intuitive that a high ratio between exchanging surfaces (determined by the whole area of the fibers constituting the membrane inside the hemofilter) and volume, maximizes the efficiency of the device in terms of removing water, although maintaining restrained the overall size.

Finally, the priming volume (volume of blood contained in the hemofilter) should not be excessively high in order to reduce potential risks of blood loss.

Based on these requirements, the selection of the appropriate disposable hemofilter has been carried out. In particular, the selected hemofilter has been designed by an industrial partner (Medica S. p. A., Medolla, Modena, Italy) starting from a commercial device initially targeting pediatric treatments. The reduced dimensions of the filter allow a low priming volume and guarantee good ergonomics, although the requested permeability parameters are still enough for the WUF. The characteristics of the selected hemofilter are summarized in Table 9, while Figure 21 shows the hemofilter.

Surface area	0.15 m^2
Membrane material	Polysulfone
Cut-off	50000 Da
Fiber internal diameter	250 µm
Fiber external diameter	350 µm
Fiber thickness	50 µm
Fiber length	127 mm
Number of fibers	1700
Priming volume	10 ml
Maximum TMP	500 mmHg
Potting material	Polyurethane
Housing material	Polycarbonate / Copolyester
Ultrafiltration coefficient	3 ml/h/mmHg

Table 9. Characteristics of the hemofilter

Figure 21. Selected hemofilter for the WUF

Tubes

The tubes (or pipes or lines) of the extracorporeal circuit are the disposable components which come directly in contact with blood. Tubes have to be made of hemo-compatible material and have to interact with the not disposable components of the device. One important requirement is that these tubes must allow a low priming volume (the whole blood volume contained in the extracorporeal blood line). Consequently, the inner and outer diameter needs to be selected taking into account these aspects.

The tubes are typically made of polyvinylchloride (PVC), although even other biocompatible materials such as silicone or polyurethane rubber (depending on the application) can be applied. The cost of this component is generally low, so the reuse is not considered economically viable. In addition to the tubes coming in contact with the blood (blood line), there is an additional line leading the ultrafiltrate from the exit site of the filter to the tank (ultrafiltrate line): this part of tubes does not need to meet strict requirements in terms of hemo-compatibility.

The bloodline can be divided into: access line and return line.

The access line is the part of tubing from the patient's vascular access to the hemofilter. It also considers the part of tube connecting the actuator for infusion of heparin with the main blood circuit.

The return line is the line that connects the hemofilter to the patient's vascular access.

The connections with the hemofilter of access and return lines have to be of luer-lock type. This type of connections, regulated by the standard ISO 8637-2 and characterized by threaded components, allows a safety block of the joints between the tubes and the hemofilter, preventing potential disconnections.

Based on all these considerations, the dimensions and materials selected for the extracorporeal circuit of the WUF are represented by a CAD design in Figure 22.

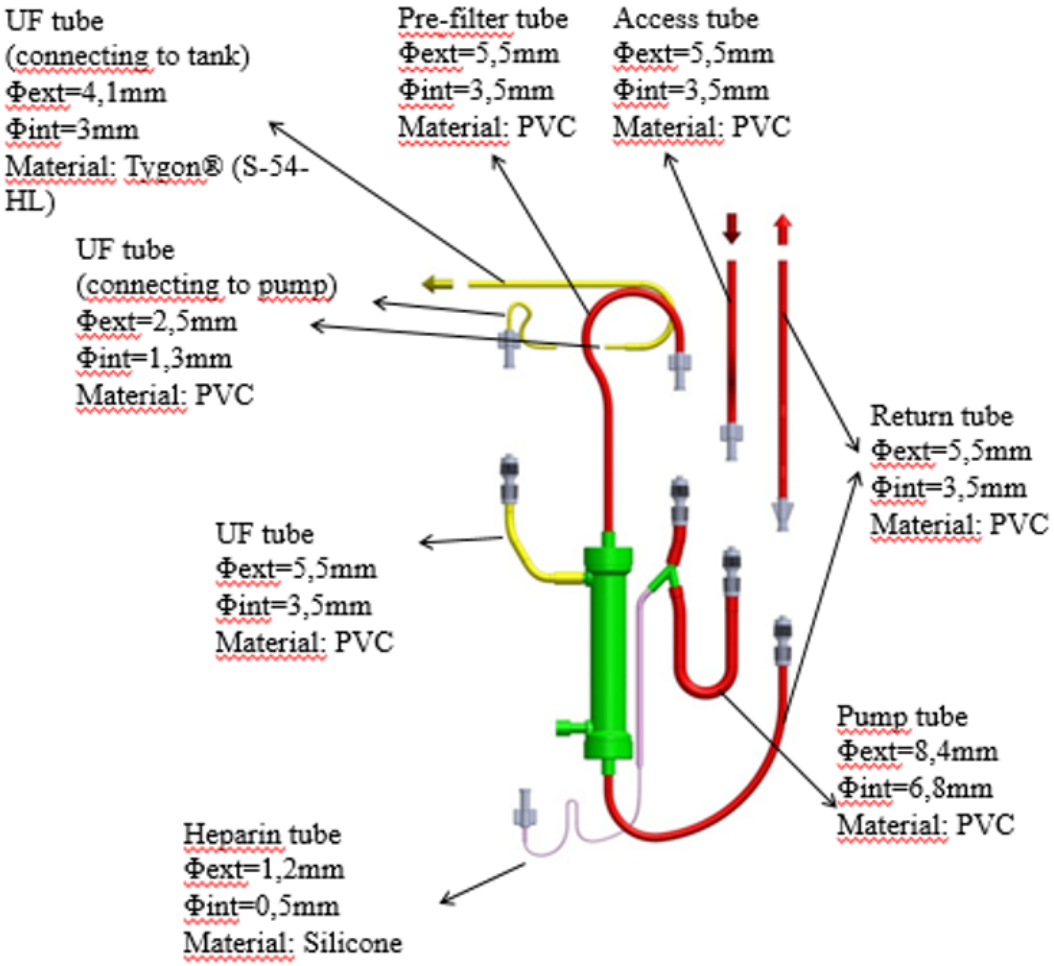


Figure 22. CAD representation of tubes selected for the WUF

Ultrafiltration pump

The ultrafiltration pump is the pump used to make ultrafiltrate flow. The requirements that a UF pump must guarantee in order to be applied in a wearable/portable device are:

- It should be compact, small, and light
- It should have a few moving parts in order to assure reliability;
- It does not need to have biocompatibility characteristics (as in the case of the blood pump) but it must be sterile (in case of a slight UF backflow, avoiding any bio-chemical hazard);
- It should avoid backflow of ultrafiltration liquid, therefore it is necessary to ensure that the ultrafiltration pump is occlusive or to use non-return valves;
- It must ensure adequate flow of ultrafiltration: based on the requirements previously stated, the ultrafiltration flow range may vary between 1 and 7 ml/min;
- It must ensure an accurate control of the set value of flow rate since the excessive or reduced removal of plasma water from a patient may have consequences related to physiological

hemodynamic instability; there are no precise data in literature on these maximum limits allowed for devices like the WUF. However, taking into consideration the standard IEC60601-2-16, concerning hemodialysis machines for chronic patients (where, however, the applied flow rates are much higher and therefore not fully coherent with those of miniaturized devices), it should be guaranteed that:

a) the NET FLUID REMOVAL (weight loss over duration) must be within ± 0.1 l/h of the set point, and

b) the target NET FLUID REMOVAL is to be kept within ± 400 ml at any time during the treatment;

- It should be silent and introduce negligible mechanical vibrations;
- It should guarantee low energy consumption and high efficiency;
- It should have a good cost/effectiveness ratio.

Based on these specific requirements, a wide range of pump typologies has been investigated. Two types of pump were found suitable:

- Diaphragm pumps
- Peristaltic pumps

Diaphragm or membrane pumps exploit the combination of the reciprocating action of a diaphragm and suitable valves to pump the fluid. On the contrary, peristaltic pumps (further described later, for the blood pump application) are based on alternating compression and relaxation of a tube to draw the fluid into it. Compression and relaxation are imposed by a rotating roller passing along the length of tube. The main difference, in terms of applicability, between these two types of pump is related to the fact that first ones have to be disposables, since there is direct contact between the fluid and the main structure of the pump, while the second ones may not be disposable since the tube is the only part contaminated by the ultrafiltrate.

Since peristaltic pumps are always driven by a rotating motor, they cannot achieve relevant levels of miniaturization. A disposable diaphragm MEMS micropump using piezoelectric actuators has then be selected (Figure 23). The pump is the mp6 micropump manufactured by Bartels Mikrotechnik.

The functional principle of the MEMS micropump is based on a piezoelectric diaphragm in combination with passive check valves. A piezo ceramic plate mounted on a coated brass membrane is deformed when voltage is applied. By the resulting down stroke, liquid (e.g. ultrafiltrate) is being

displaced out of the pump chamber below. The check valves on both sides of the pump chamber define the direction flow.

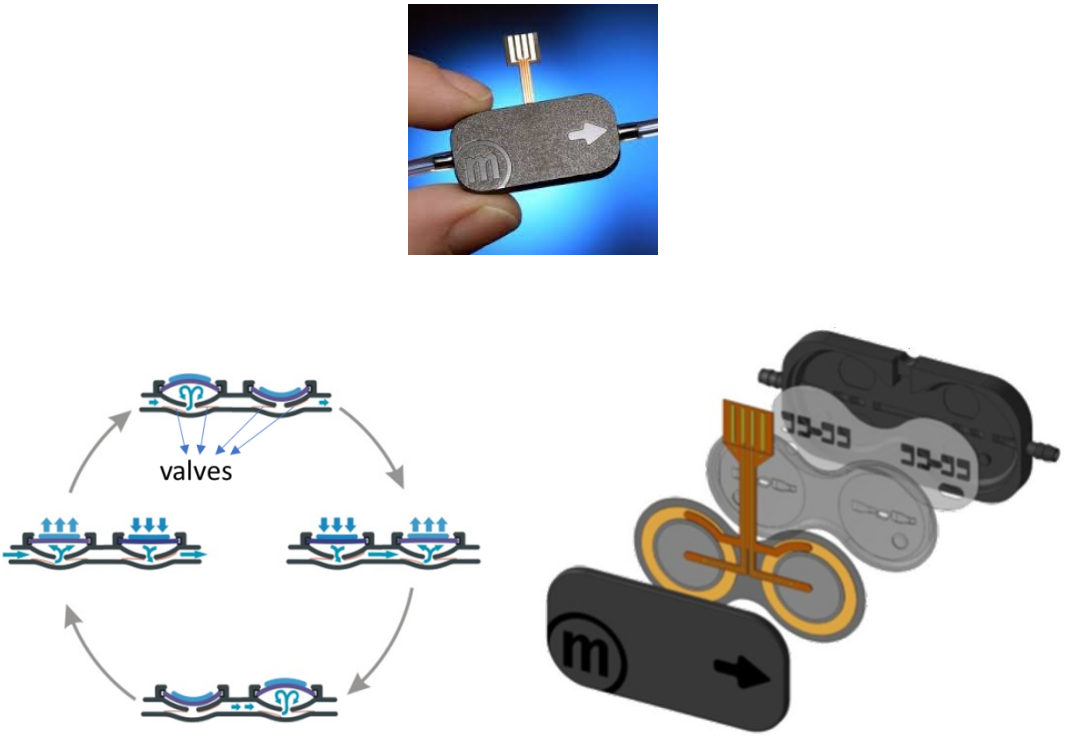


Figure 23. Selected ultrafiltrate pressure for the WUF

The ultrafiltration flow that the disposable reciprocating membrane pump is able to generate is a function of the voltage, shape and frequency of the control signal. Voltage (up to 250Vpp) determines the height of the deflection of the piezoelectric actuators while the frequency affects the number of deflections. By varying the frequency (range 1 – 300 Hz), together with the shape of the signal (e.g. rectangular or sinusoidal waves), it is possible to obtain different flows. A rectangular signal returns higher flows (maximum 7 ml/min), while a sinusoidal wave minimizes the pump noise.

The characteristics of the pump are summarized in Table 10.

Maximum pressure	450 mmHg
Dimensions	30 x 15 x 3.8 mm
Weight	2 g
Material in contact with ultrafiltrate	Polyphenylsulfone
Power consumption	< 200mW
Life time	5000 h

Table 10. Technical characteristics of the selected ultrafiltration pump

5.2.2 Off-the-shelf sensors

Among off-the-shelf sensors there are pressure sensors, the air sensor, the blood leak detector sensor and the temperature sensor.

Pressure sensors

As it has been stated previously, during the risk management analysis, pressure sensors are fundamental components that must guarantee a continuous measurement of the relative pressure levels in the circuit in order to avoid any hazardous situation due to blood loss. In particular, pressure sensors need to be placed:

- in the access line (in order to measure the so called "access pressure"): this value is negative because the sensor has to be placed upstream of the pump, where there is blood suction, to monitor any hazardous situation possibly leading to blood loss in this part of the circuit. The pressure acceptable range in adult machines ranges from -500 mmHg to 0 mmHg, depending on the clinical condition of the catheter. The monitoring of the access pressure is performed to check the clinical situation of the catheter and to detect if access tubes are well connected or obstructed.
- in the prefilter line (where the so called “pre-filter pressure” is measured): this value is positive because the sensor has to be placed downstream of the pump (but upstream of the hemofilter). The acceptable pressure range in adult machines ranges from 0 mmHg to +500 mmHg. This pressure sensor is applied in order to detect if there is any obstruction in the hemofilter due to coagulation, clotting or clogging.
- in the return line (where the "return pressure" is measured): this value is positive because the sensor has to be placed downstream of the pump (and downstream of the hemofilter). The acceptable pressure range in adult machines ranges from 0 mmHg to +500 mmHg. The monitoring of the return pressure is performed to check the clinical situation of the catheter and to detect if return tubes are well connected or obstructed.
- in the ultrafiltrate line (in order to measure the “ultrafiltrate pressure”): this value is positive during the first part of the treatment, since the membrane inside the hemofilter is clean and not obstructed by phenomena like clotting or clogging. When the pores of the membrane start becoming occluded, this pressure first starts decreasing and then becomes negative. The acceptable pressure range in adult machines ranges from -500 mmHg to +500 mmHg. This pressure sensor is applied in order to detect if there is any obstruction in the hemofilter due to clogging inside the pores of the fibers.

The use of disposable MEMS devices instead of standard pressure sensors used in hospital machines allows to miniaturize the whole system (Figure 24).

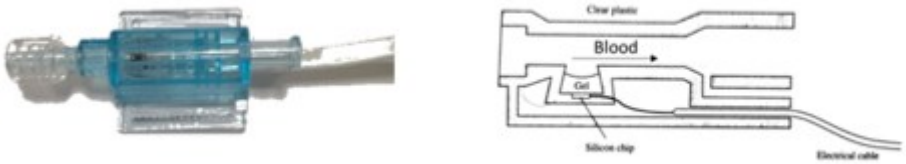


Figure 24. Selected pressure sensors for the WUF

The sensors chosen are Argon Standalone DTX Plus™ manufactured by Argon Medical Devices. The blood pressure detection system inside the sensor is based on a silicon chip applied on a diaphragm, where piezo-resistive elements or extensometers in Wheatstone Bridge configuration are placed. The sensor power supply is connected to the bridge to generate an excitation voltage. A current meter is also connected to determine the pressure exerted by the fluid. When no voltage is applied to the strain gauge, the Wheatstone Bridge is in balance and no electrical current flows through the amperemeter. However, when a load exerted by the fluid is applied to the pressure gauge, there is a variation in the resistance of the strain gauge, which in turn causes a change in the output voltage of the Wheatstone Bridge that is directly proportional to the amount of fluid pressure that causes the element bending. The electrical connections of the MEMS are protected from the liquid by an elastic silicone gel. This gel provides electrical insulation by preventing any electrical shock from the sensor to the patient and vice versa.

Air sensor

For the WUF, an air bubbles detector must be applied before blood is reinfused into the patient. In case of air detection, the control system must immediately stop the pumps in order to avoid any air infusion. Different technologies have been proposed in order to detect air in plastic tubes of extracorporeal circulations. In particular, they are:

- Optical sensors
- Capacitive sensors
- Ultrasound sensors

The earliest air bubbles detectors were optical. They consisted of a light source which triggered a photocell situated on the opposite side of the tube. The cell did not react if blood obstructed the light path. Anyway, this device was not so sensitive and could not react if the light path was obstructed by fibrin deposits on the inner wall of the circuit.
The capacitive technology is based on the difference in electrical impedance between fluid and air. Fundamentally, capacitors whose capacities differ significantly (even 80 times) between fluid and air are used. The capacity is measured by plates placed outside the tube. These plates are connected to a bridge. The bridge must be carefully balanced giving a zero output, or a set threshold, when only the fluid flows through the tube. This method of detection is however subject to errors due to the low detection threshold (it is very difficult to detect a bubble of 1mm of diameter determining a variation of capacity of about 1 pF), and requires complex and expensive precision electronics. Furthermore, a frequent calibration is required.

The most used MEMS technology for detection of air bubbles is based on ultrasounds (Figure 25).

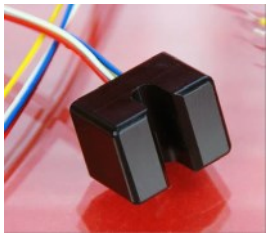


Figure 25. Selected air sensor for the WUF

The ultrasonic approach is based on the great difference between acoustic impedance between liquid and air. The velocity varies from 331 m/sec in air to 1570 m/sec in blood. Furthermore, it is not dependent on the concentration, opacity and color of the fluid. Pulse-type ultrasound sensors detect the presence of air or liquid based on the velocity or transit time of the received signal. Ultrasound sensors contain integral piezoelectric crystals which utilize high-frequency acoustic energy (resonance frequency from 1 to 3 MHz, generally next to 2.25 MHz). The receiver crystal vibrates based on ultrasonic vibrations received from the transmitter crystal, and generates an electric signal. Following each pulse, the electronics checks whether a return signal is received within a specific window of time, which corresponds to the time that the wave takes to pass through the liquid-filled tubing. Only signals received within this temporal window indicate that there is fluid and not air. Signals which have been interrupted by air will not be received within this window.

Based on its advantages the technology adopted in the WUF is the ultrasonic one. The selected non-disposable device, the Sonocheck ABD-07 manufactured by Sonotec, has a U-shaped body able to accommodate the tube where blood flows: in the opposing arms of the U, the two piezoelectric

transducers (transmitter and receiver) are positioned. Furthermore, the air sensor device generates a control signal that can be employed to check whether the tube is correctly positioned in the device. The amplitude of this signal is at a low level if the tube is not positioned in the sensor, at a high level if the tube is properly positioned and fluid is flowing, at a medium level if the tube is properly positioned but air is detected.

The standard IEC60601-2-16 declares that the maximum allowed air infusion limit per unit of time is 0.03 ml/(kg min), while as bolus infusion, the limit is 0.1 ml/kg. The air sensor has to be inserted in the return line, possibly in a position far from the blood reinfusion to the patient in order to preventively avoid air infusion. Typically, an air removal system is present in the extracorporeal circuit and is placed immediately before the air sensor. It will be proved in Section 5.3.2 that it makes sense not to introduce such a system in the designed portable device.

Blood leak detector sensor

Another important condition to monitor during the treatment is to test if the fibers inside the hemofilter are not broken, which may lead to possible blood losses from the blood compartment to the ultrafiltrate compartment. This can be caused by an excessive pressure exerted on the fibers. With reference to the standard IEC60601-2-16, the maximum acceptable blood flow lost must be less than 0.35 ml/min, considering a hematocrit value of 32%. In order to immediately detect this hazardous situation, a sensor can be placed directly in this part of the extracorporeal circuit. This sensor is called Blood Leak Detector (BLD). The leading technology is the optical one.

The selected non-disposable BLD is an optical sensor (Figure 26). It is based on the optical detection of the light that passes through the ultrafiltrate tube. A decrease in the amount of light passing through the tube indicates the presence of hemoglobin in the ultrafiltrate and therefore, most likely, a break in the filter membrane. The BLD sensor is made of:

- a light source (light emitting diode - LED) that generates, through an optical path, a beam having a wavelength ranging between 800 nm and 930 nm (infrared)
- a light detector (photodiode) which receives the beam,
- a case, made of plastic, with a slot suitable to fit a tube between the light source and the light detector.

The light absorption of the oxygenated and non-hydrogenated hemoglobin is almost in a range of wavelengths of between 800 nm and 930 nm. The narrow emission spectrum, together with the use of an enclosed housing, allows the BLD not to be substantially affected by environmental light. As

for the output, the sensor generates a voltage that is proportional to the intensity of the light energy coming from the LED and hitting the photodiode: if blood flows into the optical path, the light intensity decreases and, if it is lower than a set threshold, the hazardous situation can be detected.

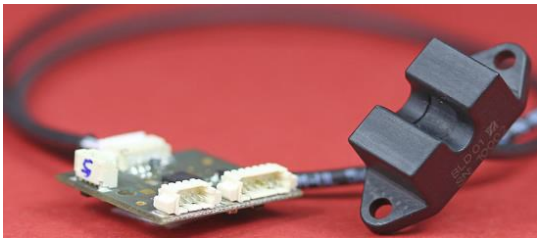


Figure 26. Selected blood leak detector sensor for the WUF

Temperature sensor

In order to detect if the temperature in the extracorporeal circuit is too low (possibly leading to hypothermia) or too high (possibly leading to hyperthermia), a temperature sensor has been adopted. The sensor has been placed close to the pre-filter line. The selected analog temperature sensor is the module LM35D (Figure 27). The presence of a temperature sensor also allows implementing a cooling strategy for the WUF by simply managing a fan. Several miniaturized, silent, energy efficient and cheap fans can be found in electronics catalogs, being extensively used in pc's and notebooks. For this reason, the fan chosen is not shown here.

Figure 27. Selected temperature sensor for the WUF

The temperature sensor has a measuring range between 0 and 100°C. The voltage supply is between 4 and 30 V, output voltage between 0 V and 6 V.

5.2.3 Off-the-shelf microcontrollers

In order to identify and select the most suitable hardware components for the control system, the main technical requirements have been initially identified based on:

- clinical specifications and functionalities expected for the WUF, as indicated by the medical staff of the hospital;
- analysis and comparison of off-the-shelf control systems applied for other electro-medical devices used for hemodialysis and ultrafiltration;
- indications deriving from the standards regulating the control system requirements for electro-medical devices.

The current standard IEC 60601-1 concerning electro-medical devices expressly declares that the control system of such devices must be accomplished with a redundant logic. It means that the overall system must be designed considering the use of two microcontrollers working in parallel: if a malfunction of the main controller may potentially cause a hazardous situation and, consequently, a risk for the patient, the use of the second one allows to immediately detect the problem, switching the device into a safe mode. This requirement represents a specific commitment in the design of the WUF, although the use of two controllers working in parallel determines an increase in size, higher power consumption and higher complexity of the software and control logic that has to be implemented. All these drawbacks could be effectively addressed by designing and developing a customized control architecture, which is however beyond the scope of this project.

In order to find an optimal solution able to combine the above-mentioned requirements with the need for providing adequate flexibility to the WUF controller (in order to make it usable even in changing working conditions or improved future versions of the prototype), it has been decided to design the control electronics just adopting commercially available programmable hardware platforms for physical computing. Indeed, such solutions are certainly suitable for a preliminary project, but may present some limitations in an industrialized device. In that case, if necessary, customized boards replicating the same control logic can be developed straightforwardly. The aforementioned commercially available platforms usually integrate a microcontroller on which a dedicated development environment is pre-installed and can be connected directly, or through suitable conditioning modules to sensors and actuators. Software programming is often simplified thanks to the use of high level standard languages. Specific development kits further simplify debugging and testing software programs. Different off-the-shelf integrated programmable hardware platforms have been evaluated and compared (some examples are Arduino, Raspberry PI, Beagleboard, Freescale, Texas Instruments MSP430), in order to identify the ones guarantying adequate standards of reliability and scalability. Clearly, some of the above listed platforms are just microcontrollers (e.g. Arduino) while other ones are microcomputers (e.g. Raspberry). The formers have improved capabilities to manage sensors and actuators by numerous digital and analog input and output (I/O)

ports, the latter usually give the possibility to generate more complex GUI's (graphical user interfaces) and provide more computational power but usually have a very limited number of I/O ports.

One relevant aspect that has been taken into account in the selection of the hardware platforms was the possibility to easily integrate them into an electronic circuit board to which sensors, actuators and drivers would be connected.

Based on the peculiar features of the WUF, it has been decided to use separate hardware platforms to control all the devices involved in the extracorporeal ultrafiltration therapy and to manage the GUI and data logging. In particular:

- the hardware platforms that monitor the ultrafiltration process must ensure real time operations and must be able to handle serious or anomalous situations requiring an immediate suspension of the treatment in order to avoid any risk for the patient; two identical but independent microcontrollers working redundantly are used to this purpose;
- that hardware platform managing the GUI, the initial set-up of the treatment (by a physician or an experienced nurse), remote monitoring during therapy and data logging locally or through the internet is a single microcontroller. No redundant control is required to this purpose.

Therefore, the WUF control architecture is based on 2 microcontrollers and 1 microprocessor that need to work independently but synergistically, in order to coordinate the whole machine cycle of the WUF. The comparison with other electro-medical devices has shown that such an architecture is used frequently since it guarantees patients' safety without excessively complicating the device electronics.

Namely, the microcontrollers used are those belonging to the Arduino Mega platform (Figure 28). In particular, two Arduino Mega kits have to work in parallel in order to implement a redundant logic: the first one (the so-called control system) controls the ultrafiltration process of the WUF, the second one (the so-called protective system) performs appropriate redundant control routines. Arduino Mega consists of a stackable board of dimensions 102 x 53 mm, which is based on a 16 MHz ATMEL ATmega2560 CPU with 256 kb of memory. It has 54 digital I/O ports, 14 of which provide PWM outputs, and 16 analog inputs. The power consumption of each board is very low (estimated in a range between 100 and 200 mW in working conditions) in relation to the skills of computing and data processing that the development kit is able to offer.

Figure 28. Arduino Mega platform: the selected off-the-shelf microcontroller for the control of the ultrafiltration process of the WUF

As for the management of the GUI, the initial set-up, monitoring and data logging, an embedded microcomputer with an extremely reduced footprint has been adopted. Specifically, the single board computer Raspberry PI 3 model B (Figure 29), based on ARM processor, has been selected. The board, of dimensions 85 x 56 x 17mm, is equipped with a CPU 7 1.2GHz Broadcom BCM2387, 4 x USB 2.0 ports, 40 pin extended GPIO (Serial, I2C, SPI), Micro SD slot for the operating system and data storage and 1Gb of RAM memory. It hosts a Linux-based operating systems.

Figure 29. Raspberry PI 3 model B platform: the selected off-the-shelf microcomputer for the management of GUI and data logging of the WUF

During the therapy, the interface between the device and the patient is based on a LCD touch screen monitor Nextion LCD (Figure 30) through which the microcontrollers can communicate warning messages or emergency situations that can be easily resolved independently by the patient. Examples of such situations are a temperature out of the prescribed range, low battery power or a full ultrafitration tank.

Figure 30. Selected LCD monitor for the WUF

The LCD screen has been used also to communicate the current state of the device, so if the therapy is in progress, whether in start-up mode or even when the therapy is over. During the therapy, the monitor provides real-time information on the battery charge status and the quantity of ultrafiltrate removed. The touch screen also allows to pause or permanently stop the treatment.

5.2.4 Electric and electronic devices (boards and sensor conditioning system)

The relevant number of off-the-shelf electric and electronic components of the WUF, combined with a few customized ones which will be discussed later, has made it necessary to develop customized electronic boards simplifying the wiring of all such components and the conditioning of sensor signals. The development of the electronic boards has been carried out by a team of engineers involved in the RAP project given the peculiar expertise necessary for designing and commissioning printed circuit boards (PCBs).

In particular, the set of PCBs has been specifically designed and realized in order to integrate both disposables and non-disposable components needing signal conditioning (sensors) or driver circuits (pumps and electro-mechanical clamp). The design of the electric and electronic circuitry has been conceptualized and realized taking into account that:

- the miniaturization and compactness of PCBs are important requirements for the overall design of the WUF;
- disposable components needing a conditioning circuitry or driver circuit have to be easily connected with the relative PCBs;
- connections of electric cables with the PCBs should be practical and functional.

Based on these considerations, four main PCBs have been designed and realized. They are:

- the main PCB where the two microcontrollers have also been integrated;

- a power board for driving the motors of the blood pump, the heparin pump, and the clamp;
- a signal condition PCB for pressure sensors;
- a PCB for the driver of the UF pump.

The main PCB, with the main components and conductive tracks, is represented in Figure 31.

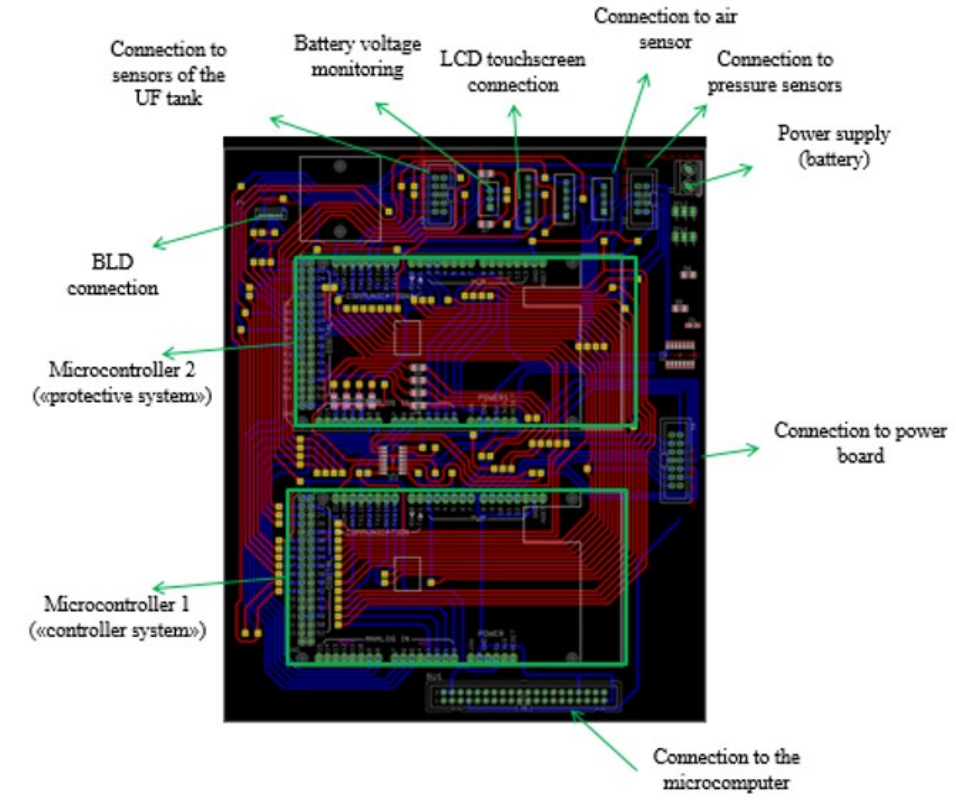


Figure 31. General scheme of the main PCB of the WUF

The power board is represented in Figure 32.

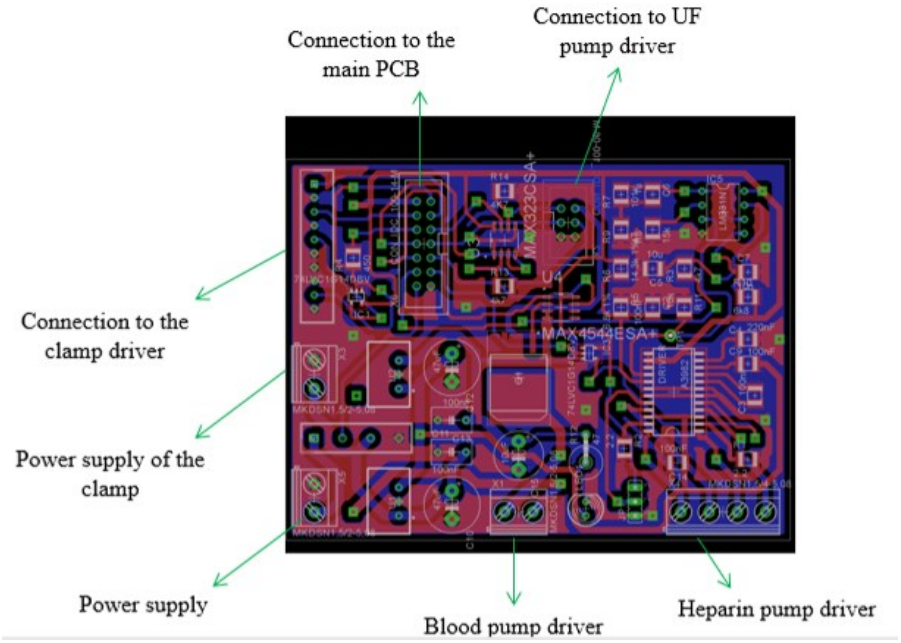


Figure 32. General scheme of the power board of the WUF

As previously stated, disposable components like pressure sensors and the ultrafiltration pump need to be easily connected to dedicated PCBs. The PCB for the conditioning of the electric signals from pressure sensors is shown in Figure 33, while the one driving the UF pump is shown in Figure 34.

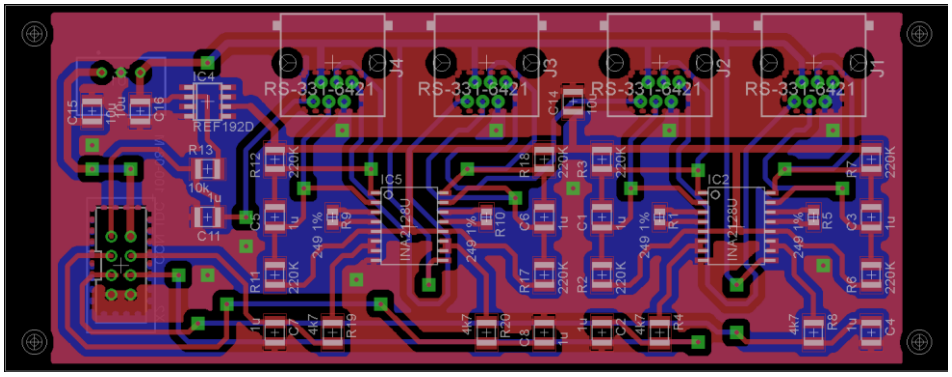


Figure 33. PCB for signal condition of pressure sensors

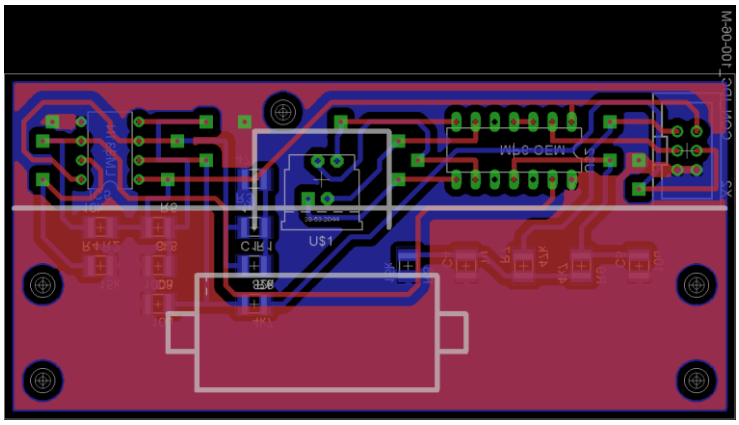


Figure 34. PCB for driving the UF pump

5.3 Critical components: requirements, selection and design

As stated, the critical components needed a specific investigation. They are:

- Blood pump
- Air removal system
- Heparin infusion system
- Electro-mechanical clamp
- Ultrafiltrate collection and volume measurement system

5.3.1 Blood pump

The blood pump is the core of the system. It allows the circulation of blood in the extracorporeal circuit. The requirements that the blood pump must meet are:

- not to exert excessive mechanical stress possibly leading to rupture of red blood cells: it means that it must ensure a reduced hemolysis and reduced cytotoxicity. This requirement, that can be stated as hemo-compatibility, is probably the most important;
- miniaturization, compactness and lightness;
- minimal contact area and duration of contact between blood and moving parts: these factors are both relevant in the determination of the hemolysis rate;

- to ensure an adequate blood flow: the chosen value for the WUF is 50 ml/min, in order to perform an extracorporeal ultrafiltration treatment extended throughout the day. This value guarantees an adequate shear rate value along the membranes through which blood flows, in order to reduce the contact time between blood and thrombogenic material and consequently to reduce coagulating phenomena. Furthermore, the chosen value is coherent with the desired filtration fraction, that is the percentage ratio between the ultrafiltration flow and the blood flow; from literature, such a relationship cannot exceed a value of approximately 30%, otherwise it is easier to promote blood coagulation within the filter;
- not to induce blood overheating;
- not to cause too much noise and relevant mechanical vibrations;
- to assure low energy consumption;
- to have a good cost/effectiveness ratio.

Based on these requirements, the most suitable available technologies have been identified. Generally speaking, the blood pumps that can be used in an ultrafiltration device can be divided into positive displacement pumps and dynamic pumps [47].

A dynamic pump produces a head and a flow by increasing the velocity of the liquid through the machine with the help of the rotating vane impeller. None of the dynamic pumps can have a separate case such as flexible tubing because all the dynamic pumps need a connection between the outside and the inside of the case of fluid (e.g. a shaft that provides centrifugal force). The direct contact with the blood and the pump moving parts could lead to possible infection and blood clotting problems. Consequently, dynamic pumps can only be employed if they are introduced in the design as disposable devices. These pumps have the advantage that they do not need valves, that may lead to hemolysis; on the contrary, the flow and the efficiency of these pumps usually decrease when the output pressure increases. Often, these pumps need to be primed, that means to be initially filled with fluid to start operating.

The main types of dynamic pumps are:

- Centrifugal pumps (Figure 35): these pumps are based on the effect of centrifugal force on a fluid;
- Axial pumps.

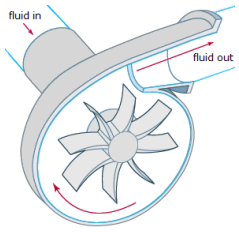


Figure 35. Schematic example of a centrifugal pump

Positive displacement pumps are constant flow devices and make blood move by trapping a fixed amount of blood and forcing (displacing) that trapped volume into a discharge pipe or discharge system. Two main kinds of forces push the fluid in pumps. One is the translational force, which is applied in the translational direction of the flow, and the other is the normal force, which is applied to the normal direction of the flow. All positive displacement pumps operate by combining these two forces.

The main feature of these pumps is that the flow rate is constant for each operating cycle and it does not depend on the discharge pressure, but only on the number of cycles performed in the unit of time. Positive displacement pumps can be further classified according to the actuator used to move the fluid. They can be defined as:

- rotary: when the actuator is coupled with a rotating motor;
- alternatives: when the actuator is moved with an alternate motion.

The main types of rotary pumps are gear pumps, lobe pumps and peristaltic pumps. Peristaltic pumps are the most employed in the medical field (Figure 36): they are based on alternating compression and relaxation of the tube drawing the fluid into it. A rotating roller passes along the length of the tube totally compressing it and creating a seal between suction and discharge side of the pump. Upon restitution of the tube a strong vacuum is formed drawing the fluid into the pump. The fluid to be pumped does not come into contact with any moving parts and is totally contained within the extruded tube.

Figure 36. Schematic example of a peristaltic pump

The main types of alternative pump are:

- plunger or piston pumps: in which the volume variation is obtained by alternating sliding of a piston in a cylinder;
- diaphragm or membrane pumps: combining the reciprocating action of a diaphragm and suitable valves on either side of the diaphragm to pump the fluid.

Among positive displacement pumps and dynamic pumps, the two types of pumps most employed in extracorporeal blood circulation devices are centrifugal pumps and peristaltic pumps.
As previously stressed centrifugal pumps need to be disposable and theoretically their overall cost can be higher. Furthermore, when considering a possible application to the WUF, since the surface coming in contact with blood is quite wide and the blood flow desired relatively low (50 ml/min), risks related to blood clotting are high. Nevertheless, this type of pump guarantees continuous flows (no pulse, thus less localized shear stress), and good energy efficiency, and have therefore be considered a possible option.
Peristaltic pumps are the ones currently used in hospital dialysis machines. They have the big advantage to guarantee an indirect contact between the rotor and blood (the physical interface is the tube). On the other hand, they can be bulky (mainly as a consequence of the motor and gearbox size) and are less energy efficient.
After an extensive research of possible candidates within these two categories of pumps, and especially among the peristaltic ones, the following off-the shelf centrifugal and peristaltic pumps have been selected (Figure 37):

- Peristaltic pump Welco WPX1;
- Centrifugal pump RS M400-S180.

Figure 37. Preliminary selected peristaltic and centrifugal pumps for the WUF

The main characteristics of these pumps are summarized in Table 11.

	Welco WPX1	**RS M400-S180**
Pump type	Peristaltic	Centrifugal
Dimensions	46 x 49 x 96 mm	L=41x 26 x 25 mm
Weight	132 g	33 g
Voltage	8 to 24 Vdc	12 Vdc
Power consumption	7,2 W	6 W
Max flow	175 ml/min	2800 ml/min

Table 11. Main technical characteristics of selected blood pumps

Considering the initial requirements reported at the beginning of this paragraph, the most important characteristic that these pumps must comply with is the hemo-compatibility. No data or analyses are made available by the pump manufacturers, in this sense these components are critical and deserve a specific investigation, which has been carried out in collaboration with the clinicians of the hospital. Hemo-compatibility has been evaluated in terms of hemolysis and cytotoxicity. Hemolysis is the phenomenon of red blood cell rupture due to mechanical stress, resulting in the release of free hemoglobin, the iron-containing oxygen-transport metalloprotein in the red blood cells, into extracellular space. Cytotoxicity assesses the potential harmful effect on blood cells that come into direct contact with the materials of the pumps.

Since there are no specific standards complying with the methodology for the evaluation of the hemolysis in specific circulators for hemodialysis, the ASTM F1841-97 standard has been considered. This standard deals with in vitro testing methods for the evaluation of hemolysis in continuous-flow blood pumps, specifically suitable for extracorporeal oxygenation devices. Hemolysis results obtained using the pump of a continuous renal replacement therapy standard machine have also been collected and considered a reasonable benchmark, since the pump employed in such a machine has already obtained the CE mark and hence its hemolytic values should be within a range of safety.

For each of the three experiments carried out, 530 ml of blood from healthy donors were used. The initial hematocrit level was between 34% and 38%. During the whole experiment, blood temperature was kept constant at 36°C by a magnetic stirrer with a heating plate. According to the standard ASTM F1841-97, the treatment duration has been 6 hours, sampling at every hour. The setup of the experiment for each pump is represented in Figure 38.

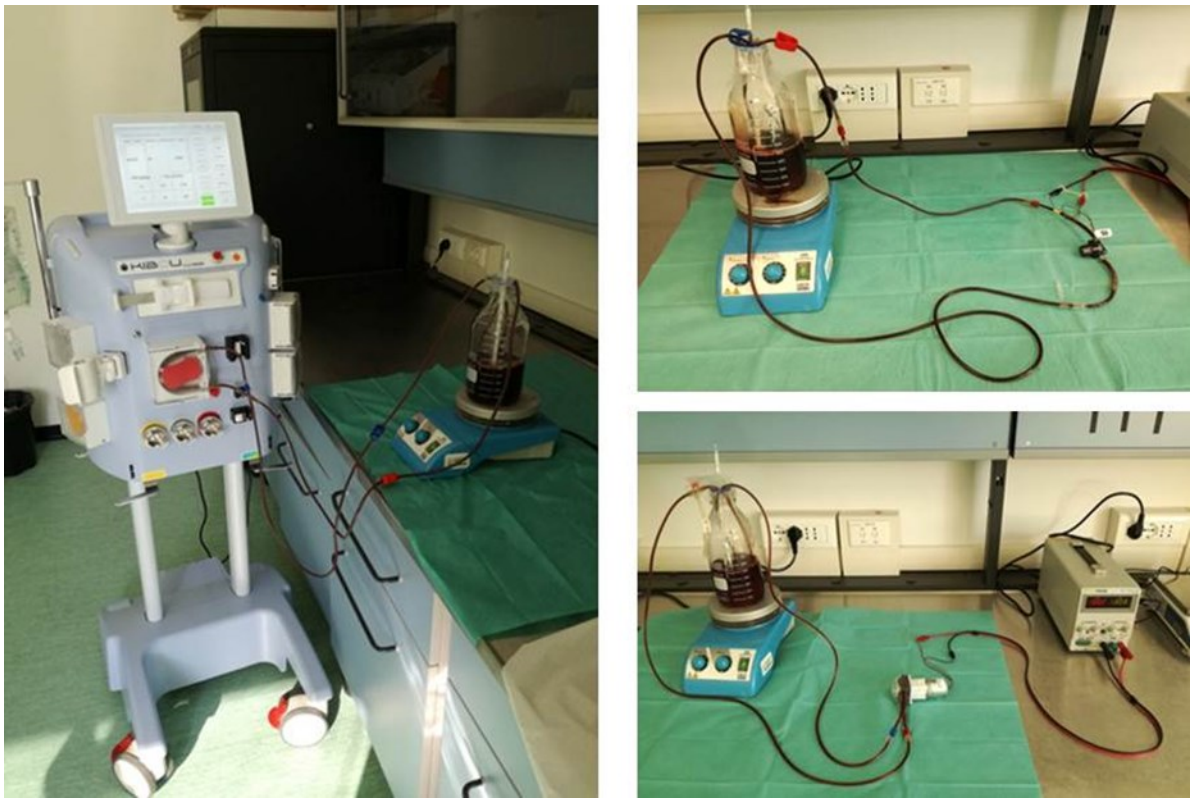


Figure 38. Set up of the in vitro experiment for the three pumps (benchmark pump, centrifugal pump and peristaltic pump).

Free hemoglobin concentration has been measured for each sample. This measurement has been carried out using a "point of care" system (Hemocue, Angelholm, Sweden). A parallel analysis of the same samples was also carried out in the Central LAB of the Vicenza hospital, where a spectrophotometric method has been used to determine discrete ranging levels of free hemoglobin concentrations. For each sample, the measurements obtained with the two methodologies matched.
The value of hemolysis was calculated through a normalized hemolysis index:

$$N.I.H = \Delta freeHB \cdot V \cdot \frac{100-HCT}{100} \cdot \frac{100}{Q \cdot t}$$

where N.I.H. is expressed in g/100l, ΔfreeHB (g/l) represents the difference in free hemoglobin concentration between the sampling time point considered and the baseline, V (l) is the volume of the circuit, HCT the hematocrit, Q (ml/min) is the blood flow rate, t (min) is the time interval.
The test has been carried out at a blood flow of 50 ml/min for each pump.
Results are shown in the two graphs of Figure 39 and in Tables 12 and 13.

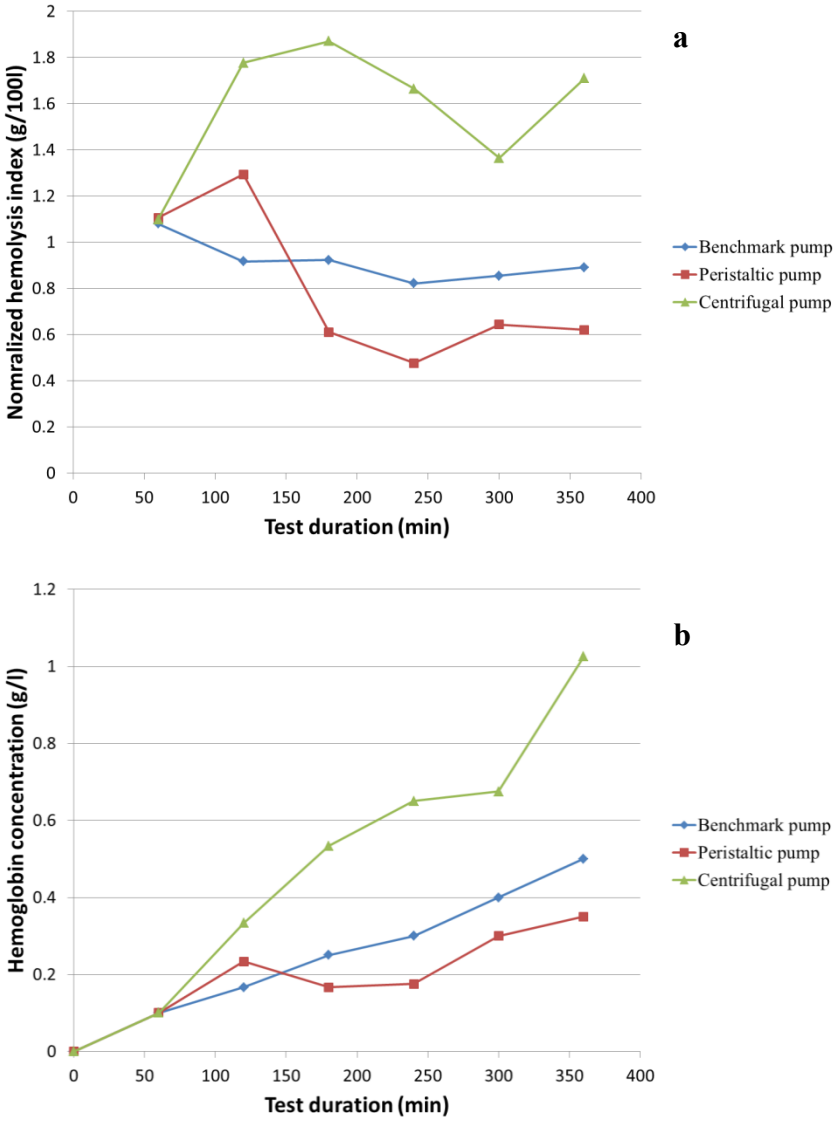


Figure 39. Results of in vitro hemolysis tests. The subplots a and b represent the normalized index of hemolysis (N.I.H.) and hemoglobin concentration respectively.

N.I.H. (g/100 l)	Test duration (min)						
	0	60	120	180	240	300	360
Benchmark pump		1.08	0.92	0.92	0.82	0.85	0.89
Peristaltic pump		1.11	1.29	0.61	0.48	0.64	0.62
Centrifugal pump		1.10	1.78	1.87	1.67	1.36	1.71

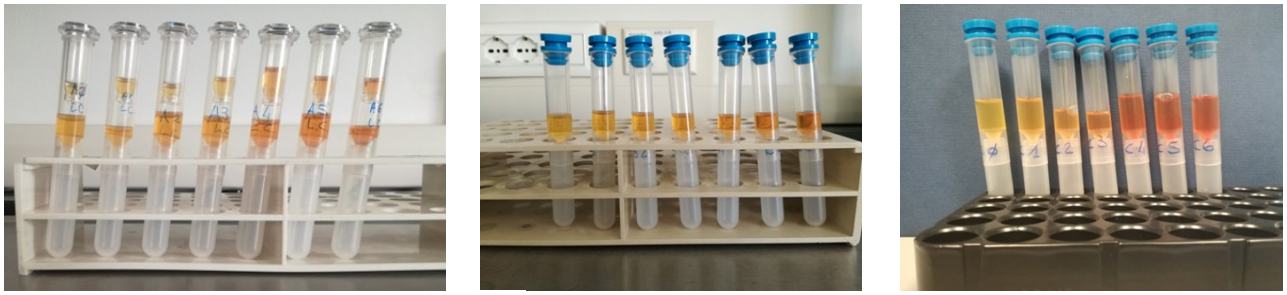
Table 12. Results of Normalized Index of Hemolysis using the 3 pumps

Free hemoglobin concentration (g/l)	Test duration (min)						
	0	60	120	180	240	300	360
Benchmark pump	0.00	0.01	0.02	0.03	0.03	0.04	0.05
Peristaltic pump	0.00	0.01	0.02	0.02	0.02	0.03	0.04
Centrifugal pump	0.00	0.01	0.03	0.05	0.07	0.07	0.10

Table 13. Results of free hemoglobin concentration using the 3 pumps

N.I.H. and free hemoglobin concentration values of the selected miniaturized peristaltic pump (in red) are comparable to the ones of the benchmark pump (in blue), while the centrifugal pump (in green), after two hours of experiment, determined values approximately twice higher than the benchmark pump.

These results have been confirmed also by a basic colorimetric evaluation of the samples referred to the three pumps (Figure 40). The higher presence of hemoglobin in the samples taken during the in vitro test performed with the centrifugal pump with respect to the ones performed with the other two peristaltic pumps is evident.



a **b** **c**

Figure 40. Colorimetric evaluation of hemoglobin concentration in samples taken during tests with the benchmark pump (a), peristaltic pump (b) and centrifugal pump (c).

As for the cytotoxicity test, blood samples were taken after 3 and 6 hours from the start of the test and then centrifuged to obtain plasma. A particular cell line of blood, U937-line monocytes, was incubated for 48 hours with the plasma samples. At the end of the 48 hours, differences in viability and necrosis (cell death for non-natural causes) of the incubated monocytes were evaluated through a flow cytometer.

The results of the induced cytotoxicity test are shown in the following charts. In the histograms (Figure 41), normalized Δ% values with respect to baseline are represented.

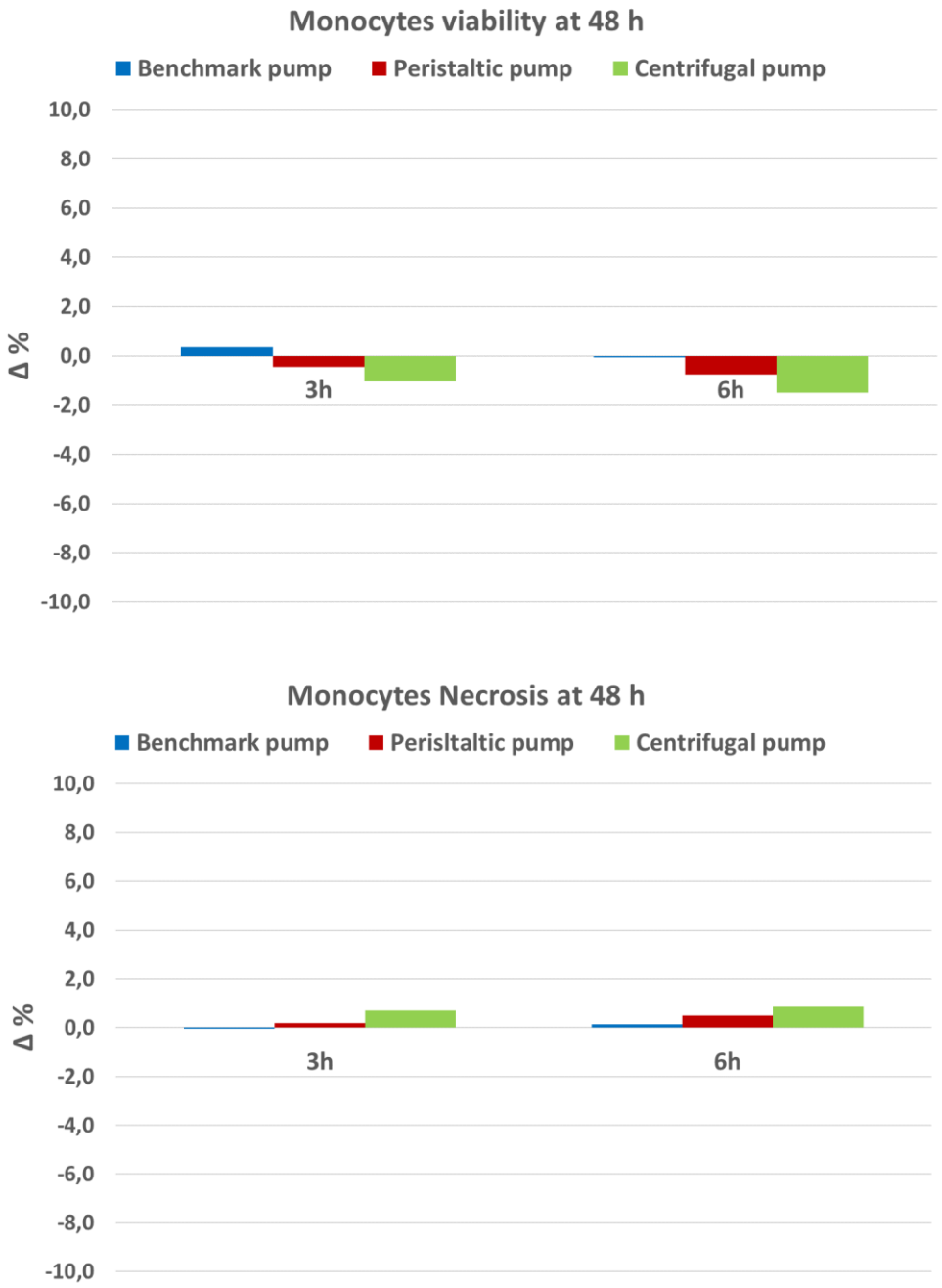


Figure 41. Monocytes viability and necrosis after 48 h of incubation with blood coming in contact with the 3 pumps

To properly interpret the results, it is necessary to consider that variations below 5% are not significant. From the results obtained after 48 hours of incubation, it is possible to notice that the cell behavior is homogeneous and within a low variability between the three considered pumps (values between ± 2%). We can therefore conclude that the three considered pumps induce negligible cytotoxicity.

In conclusion, these experiments revealed that the centrifugal pump, despite generating acceptable cytotoxicity values, induces hemolysis levels which were considered too high and suggested to discard it for the WUF application. The peristaltic pump has been selected for the WUF prototype.

5.3.2 Air removal system

Air infusion into the circuit is considered one of the most dangerous hazard situations for patients during extracorporeal blood purification therapies performed with continuous renal replacement therapy and ultrafiltration machines.

According to standard IEC 60601-2-16 (2012), safety conditions are guaranteed if:

- continuous air infusion is less than 0.03 ml/(kg·min);
- infusion of air bolus is less than 0.1 ml/kg.

For a patient weighing 50 kg, the average volume and flow that can be infused in order to be within the safety limits set by the standards are respectively:

- Continuous infusion of air < 1.5 ml/min;
- infusion of air bolus is less than 5 ml.

Currently, the risk of embolism due to air infusion into the patient's circulatory systems is avoided by an air removal chamber placed upstream the return vascular access. However, air bubble chambers induce blood/air interface and stagnation of blood, often leading to clotting and, consequently, to risk of blood loss from the patient. In literature, there are lacks of specific studies and data describing in detail the causes of air infusion and the severity of such events. A better understanding of the phenomenon could however stimulate the design and development of alternative bubble removal systems overcoming the limitations of air removal chambers and opening new perspectives in the field of portable/wearable devices for extracorporeal renal replacement therapies.

In standard hemodialysis machines, the air removal system is a disposable chamber, integrated in the disposable extracorporeal circuit, which carries out air removal by gravity effect. This system cannot be applied in the WUF because the verticality of the chamber cannot be always ensured. Since there is no study evaluating how severe this problem is, an investigation has been carried out in the hospital. The aim was to experimentally evaluate the air infused and the prevalence of the possible causes of air infusion during a standard therapy performed in hospital.

Seven representative extracorporeal treatments performed on critically ill patients in the Intensive Care Unit of the hospital, have been investigated. On average, the treatment duration was of 24 hours. The modality was continuous veno-venous hemofiltration (CVVH) in pre-dilution mode. The therapy is similar to extracorporeal ultrafiltration. The representative scheme of a CVVH modality is shown in Figure 42: contrary to extracorporeal ultrafiltration modality, it provides an infusion of physiological solution (purple line) in order to replace the plasma water removed by ultrafiltration. The infusion can be carried out before (pre-infusion) or after (post infusion) the hemofilter.

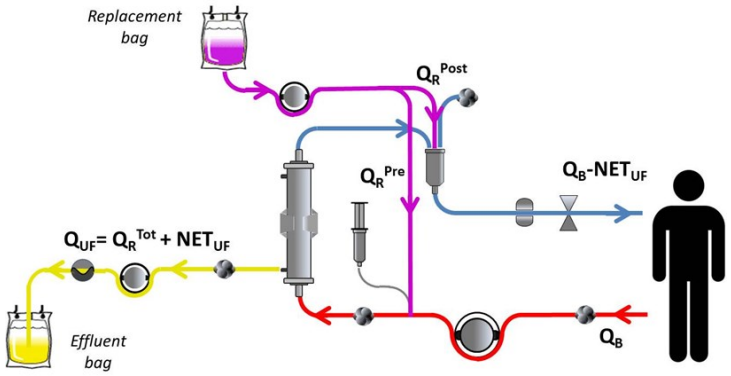


Figure 42. Scheme of Continuous Veno-Venous hemofiltration (CVVH)

Blood flow rate (206 ml/min ± 13.4ml/min) and infusion flow rate (2900 ml/h ± 741.6) were variable based on clinical prescription. An external ultrasonic air bubble detector sensor identical to the one selected for the WUF and described previously, has been placed immediately upstream the air removal chamber in the return line (Figure 43). Digital data acquisition and processing were performed through the platform NI Compact DAQ and a dedicated software program written using NI Labview® 10.0.1. The treatment data logs have been collected from the CRRT machine at the end of each session in order to correlate the air infusion events detected by the sensor with the phases of the therapy session.

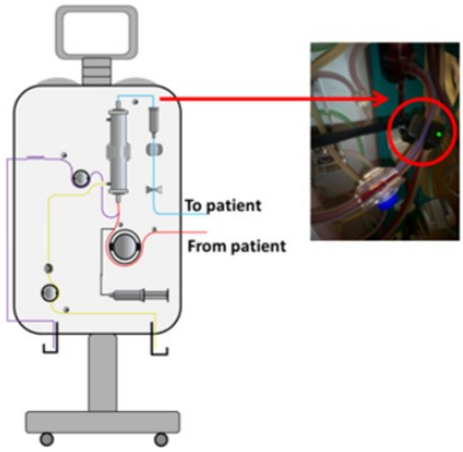


Figure 43. Experimental set up of the experiment: an air sensor has been placed immediately before the air removal system in a standard machine for extracorporeal therapies

In general, during the investigated extracorporeal sessions, air presence inside pipes was quite infrequent and strictly related to specific and temporary events (initial priming step, incomplete priming, bag change, vascular access malfunctions). The total infusion of air, excluding the priming phase, was on average 0.001% of the total volume of treated blood, so completely negligible. In 5 out of the 7 treatments, no air has been detected during the whole session. Figure 44 shows the number and duration of air events recorded during the worst-case session, i.e. the session when the maximum number of events was registered. Most of the air presence results enclosed to the priming step (Figure 44-a): this is obvious, since it is the aim of the priming procedure removing air from the circuit. During the real treatment, in normal conditions, air presence is detected in conjunction with particular events. Figure 44-b represents the number and duration of events of air detection during the treatment in which the maximum number of events has been measured.

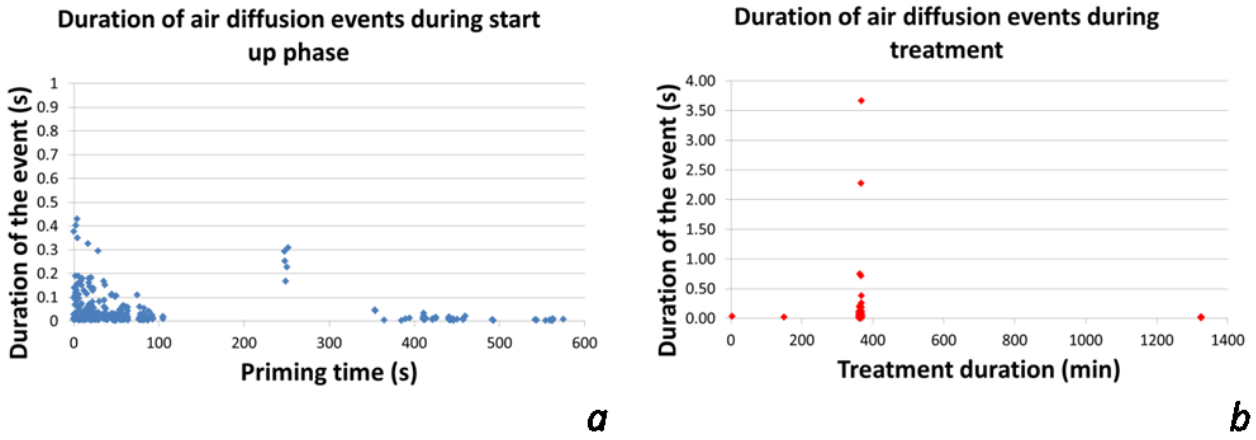


Figure 44. Duration of air events during priming (a) and treatment (b) recorded during the treatment in which the maximum number of events has been registered.

The peak visible in Figure 44-b represents air detection consequent to an event of infusion bag change procedure. This event, in an extracorporeal ultrafiltration therapy, does not have to be performed and consequently, events of air infusion due to this cause are inherently avoided. Table 14 summarizes the total number of events that were associated to air detection during all the seven real treatments (excluding the priming steps).

Cause of air infusion	Number of events	% over total number of events
Incomplete priming	3	22%
Bag change	7	50%
Catheter mispositioning	2	14%
Other causes	2	14%

Table 14. Overall prevalence of detected causes of air infusion during treatment

It can be noticed that half of the events causing air inflation inside the circuit is due to the bag change procedures. However, in absence of peculiar events, air presence can be considered negligible. Furthermore, the air infusion flow, estimated in 2.9 ml/treatment in the worst case, was much lower than the safety limits specified in the standard IEC 60601-2-16. Based on these experimental data collected during seven distinct CVVH treatments, it is possible to conclude that the total volume of air inflation during an ultrafiltration treatment is generally low.
Finally, these results suggest that the risk related to eliminating air removal systems in portable/wearable devices is not as high as usually assumed, especially in those devices where direct infusion of physiological solutions into the circuit are not applied.

Consequently, no specific device for eliminating air has been designed for the WUF: in case excessive air was detected inside the extracorporeal circuit, an electromechanical safety clamp would close the circuit and stop air bubbles before they are infused into the patient. The experimental results discussed above prove that this should be a rather infrequent event.

These results have been published in the posters session of the Congress of the European Society for Artificial Organs (ESAO) 2016, in Warsaw [48].

5.3.3 Heparin infusion system

In general, blood extracorporeal treatments are made possible thanks to the anticoagulation therapy directly administered into the circuit. If blood comes in contact with non-hemocompatible surfaces of the circuit, the coagulation cascade starts soon, leading to formation of clots inside the circuit (especially in the hemofilter) and with the potential risk of losing patient's blood of the patient.

Two main types of anticoagulation therapies can be administered during a blood extracorporeal treatment: the systemic and the regional ones. Nowadays, the regional anticoagulation therapy, performed with citrate, prevents the coagulation of blood by chelating calcium directly in the circuit and theoretically no infusion of anticoagulant drugs into the patient is determined. However, the application of the regional anticoagulation therapy with citrate in a wearable system is not easy to make, because the continuous infusion of relatively high flows of citrate (between 500 to 2000 ml/h) requires big reservoirs and two further pumps, one for citrate itself and one for the replacement of calcium.

The use of heparin as an anticoagulation drug seems to fit better the requirements for the WUF. Low molecular weight heparin can be infused as bolus directly into the circuit immediately after the start of the therapy. However, a slow but continuous infusion of unfractionated heparin diluted with physiological solution during the whole 24-hours-treatment allows maintaining anti-coagulated the blood for a longer period. It has therefore been considered necessary to adopt a system able to automatically perform a continuous infusion of such anticoagulant.

The quantity of heparin to be infused during an extracorporeal blood ultrafiltration therapy depends on the total blood volume of the patient and thus, on his weight. However, considering an average clinical prescription, almost 1000 International Units (U.I.) of unfractionated heparin need to be continuously infused every hour into the circuit immediately before the hemofilter. Usually, a solution consisting of 25000 U.I. (5 ml) of heparin diluted in 45 ml of physiological solution is created, in order to avoid excessive infusion of the anticoagulant drug into the patient in case of low precision of the infusing systems. Based on these considerations, the flow range that a heparin infusion system should assure in the WUF is between 0 and 2 ml/h (steps of 0.5 ml/h). A high accuracy would be needed. Moreover, if the treatment is intended to be performed for 24 hours, a reservoir/tank of at least 50 ml would be necessary.

Standard infusion pumps used in hospital machines are based on stepper or DC motors that drive the piston of a syringe to move the heparin plunger forward. These systems (Figure 45) cannot be adopted in the WUF, since they are massive, bulky and difficult to interface with the device controller.

Figure 45. Example of massive and bulky heparin infusion system adopted in standard hospital machines

Consequently, a dedicated system for continuous heparin infusion, equipped with a sensor detecting when the heparin tank is empty, has been conceived, designed and prototyped. It is based on the application of a micro-peristaltic pump able to infuse the drug in a range between 0 and 2 ml/h: such a design has allowed achieving a very satisfactory level of miniaturization and lightness. Since this system is being patented, no further details can be provided in this paragraph.

5.3.4 Electro-mechanical clamp

When a hazardous situation is detected in the blood extracorporeal circuit, it should lead to an immediate occlusion of the extracorporeal blood circulation. In devices for blood extracorporeal circulation used in hospitals, this task is performed by an automatic pinch valve, usually referred to as “clamp”. A clamp must be capable of occluding the disposable circuit through which blood flows, thereby isolating the problem and significantly reducing direct and indirect risk to patients. Furthermore, a clamp should operate normally closed, i.e. it should automatically close the circuit whenever no actuation power is available, in order to cope with possible power supply or actuator failures. Commercially available safety clamps are usually unsuitable to portable/wearable devices being large, heavy and high-power consuming, additionally, their not negligible power losses generally lead to high operation temperatures.

Within the PhD project, two designs have been developed. Since at the beginning of the project the blood pump was still to be chosen, the requirement was to occlude both access and return tubes in case of selection of a centrifugal pump. A first electro-clamp prototype has been therefore developed to satisfy such a strict design requirement embedding a high safety margin. Indeed, the requiring pinching force to be applied was higher with respect to the one necessary to occlude only the return tube as required whenever an occlusive peristaltic pump is adopted.

Since the final design of the WUF includes a peristaltic pump, a second clamp prototype has been developed with a different architecture, that is more compact than the first one. The second prototype

is intended to be patented, and therefore the design of just the first electromechanical clamp will be described.

All the design specifications to be met by the clamp must ensure the essential goal of achieving maximum safety to avoid any possible hazardous situation. The correct operation of the device is the normally closed one. This feature is commonly achieved using a spring preload, which can be counteracted by an electric actuator. Since the clamp should not get in contact with blood, the flow is regulated by pinching the tube into which blood flows. The analysis of the commercially available solutions has highlighted that a clamp to be used with 4.2 mm-diameter PVC tube requires at least 4.2 W to keep blood flowing. Such a power consumption is unsuitable for a wearable battery-operated device. Indeed, an ultrafiltration treatment usually lasts up to 24 hours, thus a 100 Wh battery capacity would be required just to power the safety clamp. This power capacity implies using batteries weighting between 500 g and 1 kg, according to the average power density of off-the-shelf lithium-ion batteries [49]. Both the weight and the generated heat are too high to provide a comfortable solution. To reduce both the battery weight and heat generation, the maximum power consumption is imposed to be lower than 1 W as a design specification to be met in the present project.

Preliminary tests have shown that the chosen 4.2 mm-diameter tube requires a maximum pinch force approximately equal to 25 N in the typical range of tube materials and dimensions. By choosing a safety factor equal to 2, the force that need to be exerted by the clamp should be at least equal to 50 N. This choice might allow adapting the clamp to a configuration in which both the inlet and outlet tubes need to be pinched by a single device. The clamping force should be provided by the spring preload alone, since the desired tube occlusion should be performed without the aid of the actuator. Such a force must be provided for a clamp displacement that is at least equal to the size of the internal tube diameter, which is 2.6 mm in the system under investigation. For safety requirements, the maximum blood flow considered for the design of the clamp has been considered equal to 70 ml/min and not 50 ml/min as previously described. In such a condition, the linear speed of the blood is equal to 0.224 m/s. Thus, blood flow should be stopped within 0.67 s if the distance between the last safety sensor and the patient's vascular access is at least equal to 150 mm, as chosen in the layout of the system. Finally, if a safety factor of 10 is used in this situation to improve safety, the design target is to ensure a complete occlusion with 67 ms from the detection of the fault.

In accordance with these specifications, the prototype of the clamp has been designed. It is based on a multi-loop articulated mechanism.

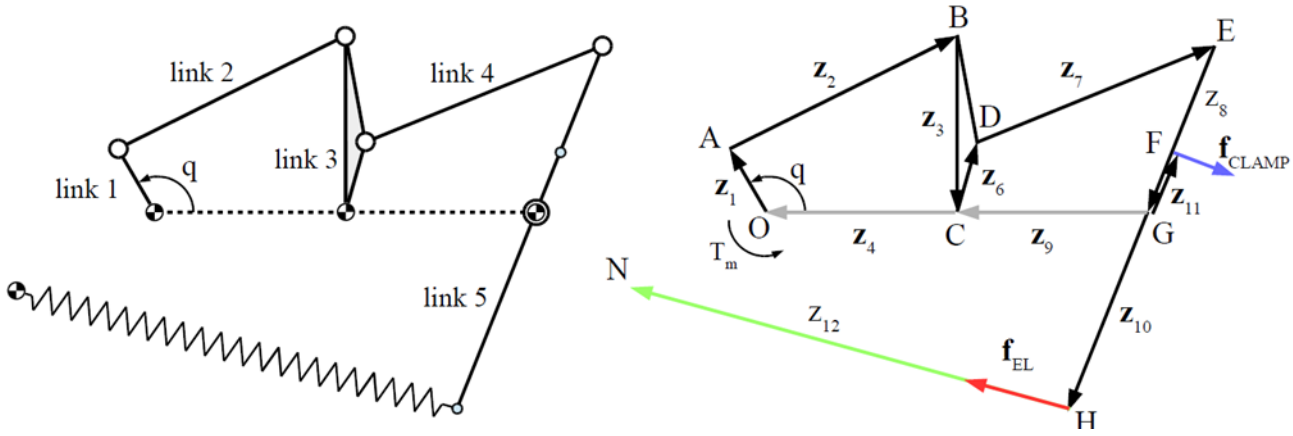


Figure 46. Kinematic scheme and external forces exerted on the clamp mechanism

According to the kinematic scheme in Figure 46, the mechanism is defined as the cascade of two four-bar linkages. The coupling between the two four-bar mechanisms is provided by the ternary link 3. The choice of an articulated design is motivated by the need to achieve high force advantage, thus requiring a reduced size actuator. A careful design of articulated mechanisms, moreover, allows to reduce to a minimum the overall size of the device. The preliminary CAD design, shown in Figure 47, shows that the mechanism can be fit almost entirely within the footprint of the actuator. The design avoids the use of prismatic joints to comply with the manufacturing limitations imposed by the rapid-prototyping machine used to produce a working sample of the device.

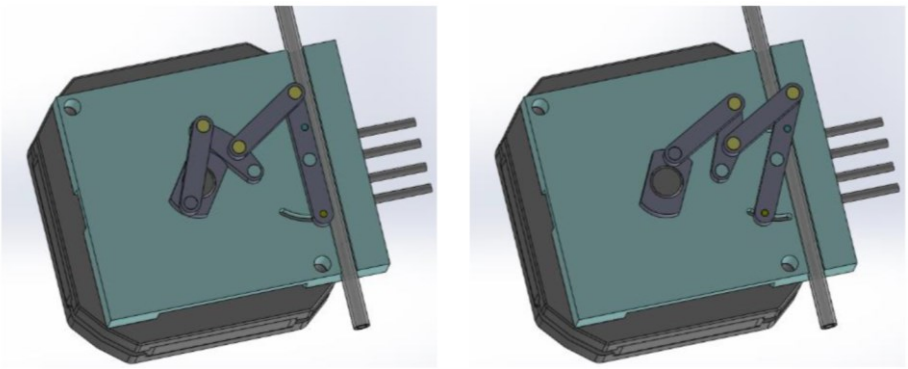


Figure 47. CAD design of the clamp, open (a) and closed (b) configurations

Figure 47 shows the mechanism in the closed configuration. The spring is hosted between the ground link (shown in light blue) and the electric motor. According to the kinematic scheme of Fig 40, the motor provides torque T_m about joint O and drives link 1 directly. No reduction gear has been introduced in the design to reduce the number of elements of the mechanism and to ensure back-

drivability of the mechanism. Back-drivability is essential for the correct operation of the device and is the capability of the force exerted by the spring to overcome the motor detent torque and the resistant force opposed by the tube and promptly move the mechanism in case of need. The fixed end of the spring is located at point *N*, while the other end is connected to link 5 at point *M*. The choice of the spring ad its location must ensure an adequate magnitude of the force f_{CLAMP} exerted on the tube where blood flows. Tube pinching is provided by a small size metal pin located at point *C* on link 5. Spring preload is, during normal operation, counteracted by the counter-clockwise torque exerted by the motor, which is amplified by the closed kinematic chain.

According to the main design goals stated before, the design of the mechanism must be optimized to accomplish a minimization of the motor size, as well as of the overall size of the device. The design procedure has involved the definition of the length of the links, of the joint positions and of the spring parameters. The goal of the optimization is the minimization of the maximum torque that the motor should provide to open the mechanism. The motor torque, which depends on the value of the independent coordinate q, is evaluated within the usable workspace *Q*, which is defined as the range of the angular rotation of the driving link 1 between the open and the closed configurations.

The achievement of a feasible design as the result of a numerical optimization technique is ensured by defining some constraints. The first constraint is set on the displacement of the pinching element: it must be ensured that the overall displacement of point *C* is adequate to produce a displacement that is at least equal to the inner diameter of the tube, i.e. 2.6 mm. Additionally, the force exerted on the tube, denoted f_{CLAMP} in Figure 46, must be higher than 50 N. These two constraints require a careful trade-off: a larger displacement of point C is achieved by reducing the ratio between the lengths z_3 and z_6, as well as the ratio between z_8 and z_6, as well as with the increase of the length z_{11}. However, these changes in turn have the negative effect of reducing the force advantage.

The equilibrium equations for the mechanism can be inferred through the principle of virtual works in all the pinching configurations. When the motor is switched off, the sole external forces acting on the mechanism are the spring pull $\boldsymbol{f}_{EL}$ and the clamping force $\boldsymbol{f}_{CLAMP}$. The resulting static equilibrium is therefore:

$$\begin{bmatrix} f_{EL}^{x} & f_{EL}^{y} \end{bmatrix} \begin{bmatrix} \dfrac{\partial x_M}{\partial q} \\ \dfrac{\partial y_M}{\partial q} \end{bmatrix} + \begin{bmatrix} f_{CLAMP}^{x} & f_{CLAMP}^{y} \end{bmatrix} \begin{bmatrix} \dfrac{\partial x_C}{\partial q} \\ \dfrac{\partial y_C}{\partial q} \end{bmatrix} = 0 \qquad (1)$$

Equation (1) includes the sensitivity coefficients of the cartesian positions of points *C* and *H*, which can be evaluated as:

$$\frac{\partial x_C}{\partial q} = z_{11}\sin(\varphi_{11})\frac{\partial \varphi_8}{\partial q} \tag{2}$$

$$\frac{\partial y_C}{\partial q} = -z_{11}\cos(\varphi_{11})\frac{\partial \varphi_8}{\partial q} \tag{3}$$

$$\frac{\partial x_M}{\partial q} = -z_{10}\sin(\varphi_8)\frac{\partial \varphi_8}{\partial q} \tag{4}$$

$$\frac{\partial y_M}{\partial q} = z_{10}\cos(\varphi_8)\frac{\partial \varphi_8}{\partial q} \tag{5}$$

In Equations (2-5), and throughout the whole section, the angles φ_i (i=1,…,12) denote the absolute angular position of vectors z_i. The computation of Equations (2-5) requires evaluating the following sensitivity coefficient:

$$\frac{\partial \varphi_8}{\partial q} = \frac{z_1 z_6}{z_3 z_8}\frac{\sin(q-\varphi_2)}{\sin(\varphi_2-\varphi_3)}\frac{\sin(\varphi_6-\varphi_7)}{\sin(\varphi_7-\varphi_8)} \tag{6}$$

Equation (1) will be included in the optimization routine to ensure a sufficiently large occlusion force, thus allowing for the achievement of a proper spring design.

The actuator effort in the open configuration is evaluated by including the effects of the torque generated by the motor, T_m, and the spring pull. The small force due to the interaction with the tube in this phase is reasonably neglected. The resulting static equilibrium equation is:

$$[f_{EL}^{x} \quad f_{EL}^{y}] \begin{bmatrix} \frac{\partial x_M}{\partial q} \\ \frac{\partial y_M}{\partial q} \end{bmatrix} + T_m = 0 \tag{7}$$

Although all the design parameters of the mechanism have a strong influence on its performances, the large number of variables suggests including just a subset of them within the optimization parameters vector. Indeed, the effectiveness and the convergence of a nonlinear constrained optimization routine is easily jeopardized by large scale problems [50]. Therefore, the number of optimization parameters has been kept to a minimum by performing a preliminary design of the mechanism, which has involved the choice of the lengths of the links of the two cascaded four-bar mechanisms. Such a preliminary design has been carried out considering that the mechanical advantage is directly proportional, among the others, to the ratios of the link lengths z_3/z_1, z_6/z_8 as shown in Eq. (6), as well as the ratio z_8/z_{11}, which appear in the sensitivity coefficients of Equations (2-5). These ratios have therefore been set to be as high as possible, considering also the trade-off between getting high force magnification and assuring an adequate displacement at point *C*, and while avoiding interference or collisions.

The effects of the other geometrical parameters included in the design have a less straightforward interpretation and therefore their optimal values will be computed through the numerical optimization. The numerical optimization routine therefore includes the following design parameter vector:

$$\boldsymbol{x} = [x_N, y_N, L_0, z_{10}, \gamma_{36}] \tag{8}$$

Parameters z_{10}, L_0, x_N and y_N set the features of the spring-loading mechanism to be optimized, being L_0 the free length of the spring. Moreover, the constant angle between vectors $\boldsymbol{z}_3$ and $\boldsymbol{z}_6$, denoted γ_{36}, is to be determined through the optimization routine as well. This parameter has a strong influence on the performance of the mechanism, since it affects both the absolute value of the sensitivity coefficient $\partial\varphi_8/\partial q$ and the overall displacement of the contact point C, as shown in Figure 48 and Figure 49.

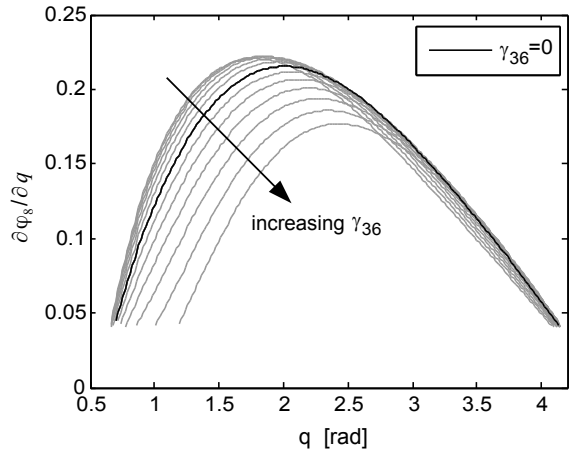


Figure 48. Sensitivity coefficient $\partial\varphi_8/\partial q$ vs q with different choices of γ_{36} in the $\pm\pi/6$ range

Figure 48 shows how $\partial\varphi_8/\partial q$ is affected by γ_{36} in the range $\pm\pi/6$ rad. Results are reported for the usable workspace Q, which is defined as the subset of the whole workspace for which $\partial\varphi_8/\partial q$ is adequately far from singularity to assure back-drivability, and that the torque needed to counteract the spring pull always takes positive values. Such a threshold has been chosen equal to 0.04. Figure 48 reveals that larger values of γ_{36} lead to higher force magnification.

Figure 49 shows the total displacement of the contact point C against γ_{36}. The results reveal that larger values of γ_{36} reduce the amplitude of the displacement of the pinching element, up to the point that the displacement of point C is too small to produce a full tube occlusion. The most suitable value of γ_{36} must therefore result from a careful trade-off between these two opposite effects. Such a feature will be ensured through the solution of the optimization routine.

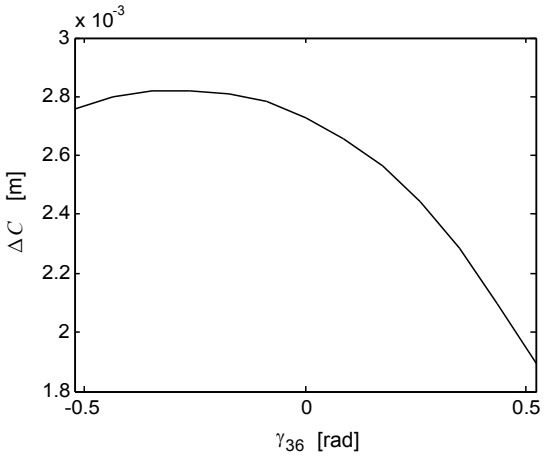


Figure 49. Maximum displacement of point C vs. γ_{36}

The stiffness of the spring has been chosen by evaluating the trade-off between the overall size and the needed stiffness, considering that the latter should provide adequately large forces with small displacements.

The resulting optimization procedure produces an optimal choice of the five parameters included in vector $\boldsymbol{x}$ that minimizes the scalar cost function J defined as follows:

$$J = \min_{q \in Q} \max T_m(q, \boldsymbol{x}) \tag{9}$$

The cost function J of Eq. (9) is chosen to minimize the peak value of the torque that the motor must exert to counteract the spring pull throughout the whole usable workspace. Such a motor torque can be computed according to the equilibrium of Eq. (7). The choice of a "minmax" cost function is chosen to minimize the size of the motor, given the peculiar use of the clamp which consists in keeping the clamp open, i.e. with negligible exerted torque, for most of the time. Hence, the most critical motor parameter is the maximum torque.

The need for a feasible optimal design requires to include into the optimization routine some constraints, that result in nonlinear constraints:

$$f_{CLAMP} \geq 50 \tag{10a}$$

$$\Delta C \geq 2.6 \tag{10b}$$

$$y_N \leq -5 \tag{10c}$$

The first constraint ensures that the clamping force is sufficient to produce a full occlusion of the tube, and is evaluated according to Equation (1). The constraint of Equation (10b) is set to ensure a sufficiently large displacement of point C throughout the workspace Q. Such a displacement is set to be at least equal to the inner diameter of the tube.

The third constraint is chosen to ensure that there is no interference between the fixed end of the spring, located at point N, and the shaft of the motor.

The design optimization has been performed by using a pattern search method based on the simplex algorithm. The outcome of the minimization procedure has been compared with the result of a genetic algorithm procedure [51], which has produced the same results, thus corroborating the convergence of the optimization. The parameters of the optimized design are shown in Table 15. The table lists also the position of the fixed revolute joints, the link lengths, the spring stiffness k and the spring free length L_0.

O = [0;0] mm	D = [8.5; 0] mm	H = [17;0] mm
N = [-14;-5] mm	z_1= 4 mm	z_2= 12 mm
z_3= 10 mm	z_6= 4 mm	z_7= 12 mm
z_8= 10 mm	z_{10}= 8.5 mm	z_{11}= 5.3 mm
γ_{36}= 0.2187 rad	k = 3000 N/m	L_0= 16 mm

Table 15. Optimal design parameters

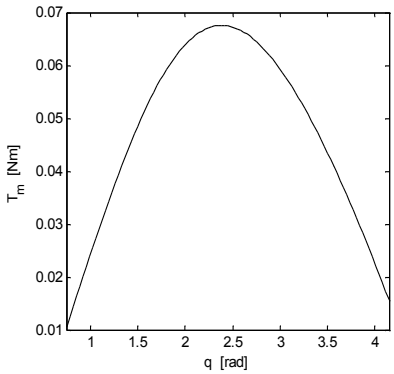


Figure 50. Motor torque T_m vs independent coordinate q

The resulting motor torque is represented in Figure 50 for all the configurations within the usable workspace Q. The small peak torque needed to achieve the equilibrium allows for the use of a relatively small size motor with no gearboxes.

The clamping force is shown in Figure 51. It also complies with the design specifications, since it is larger than 50 N for every configuration within the usable workspace Q. The clamp is completely closed for $q = 0.7429$ rad, for which the force exerted on the tube is equal to 50 N. Such a configuration is equilibrated by a minimum value of the motor torque T_m, according to Figure 50, since link 1 and 2 are almost aligned. The fully open configuration corresponds to $q = 4.153$ rad: in this configuration, the motor must produce a torque that is roughly equal to 0.015 Nm. Such a small value ensures a reduced power consumption in the normal operation of the device.

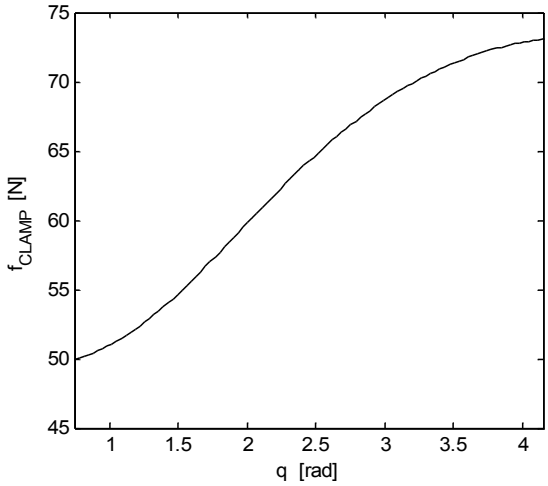


Figure 51. Clamping force f_{CLAMP} vs independent coordinate q

The position analysis of the mechanism is sketched in Figure 52, which shows the configurations of the mechanism for ten equally spaced crank positions within the usable workspace Q. The figure shows that link 1 and 2 are close to the alignment for both the open and the closed configuration.

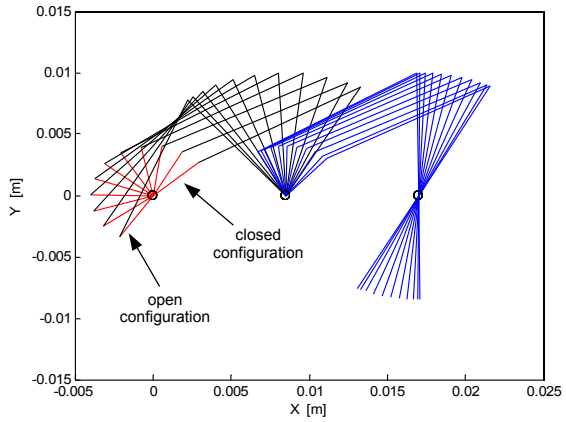


Figure 52. Mechanism displacement throughout the workspace Q

The actual displacement of the clamping point for the optimized design is shown in Figure 53. Such a plot shows that the total displacement of the point C is equal to 2.6 mm, and is therefore adequately large to produce a full occlusion of the blood-carrying tube. This feature has been enforced by the nonlinear constraint of Equation (10b).

Given the required, a pancake Sanyo Denki stepper motor has been chosen. Such a motor can provide a continuous holding torque equal to 83 mNm when operated using 24 V DC power supply. The choice of a stepper motor is motivated by the common unavailability of slim profile DC motors. The advantages of the reduced space occupation of a stepper motor comes at the cost of a less simple drive

circuit, that is required to provide the correct current at each phase of the motor. The motor can provide the needed torque to keep the clamp in the open position with a power consumption that is estimated to be nominally equal to 143 mW (i.e. without considering the power losses of the driving circuit and the efficiency loss due to the heating of the motor). This value satisfies the design specification of 1 W.

In order to verify that the complete closure of the pipe is obtained within the required maximum time, the dynamic response of the mechanism is investigated through forward dynamic analysis. This analysis is needed to evaluate whether the system can avoid the injection of an air bubble into the patient's circulating system by occluding the pipe in a sufficiently small amount of time.

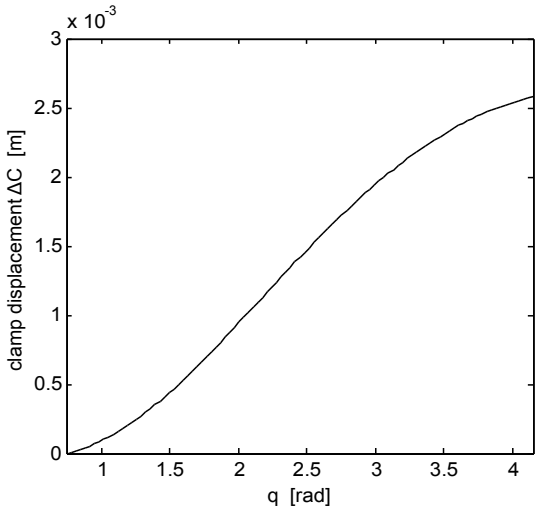


Figure 53. Clamp displacement vs independent coordinate q.

The system dynamics has been therefore modelled by accounting for the spring force, the inertial contribution of the motor shaft, and by representing the tube resistant force as a constant term $f_{tube} = 25$ N. Additionally, the detent torque T_d (i.e. the torque required to rotate the motor shaft with no current applied to the windings) of the stepper motor has explicitly considered in the evaluation and estimated as 1/10 of the motor holding torque, as it often happens in commercial motors. Such a value has been also experimentally verified through direct measurements on a motor sample. Other sources of friction, such as the friction at the joints, are neglected. Indeed, it is reasonable assuming that friction at the joint can be kept small by introducing suitable joint clearance. Such a clearance does not affect significantly the motion of the mechanism, given the presence of spring preload. In order to consider a worst-case scenario, an overall constant inertia J_{tot} equal to twice the motor one has been considered (J_{tot}= $0.03 \cdot 10^{-4}$ kgm^2). The approximated dynamic model during the spring-induced motion can therefore be written as:

$$J_{tot}\ddot{q}(t) = f_{EL}^{x}\frac{\partial x_M}{\partial q} + f_{EL}^{y}\frac{\partial y_M}{\partial q} - T_d - f_{tube}\frac{\partial x_C}{\partial q} \tag{11}$$

Equation (11) has been integrated from the initial conditions $q = 4.153$ rad and $\dot{q} = 0$ rad/s. The solution of the forward dynamics highlights that the complete pipe obstruction, which happens when $q = 0.7429$ rad, is achieved after just 49 ms. Considering that the speed of blood along the tubes is roughly equal to 0.224 m/s and that the response time of the blood detector sensor is equal to 100 ms, air bubbles can only travel 33 mm after their detection. Therefore, to assure that air bubbles could be stopped even before reaching the clamp, a reasonable distance between the bubble detector and the clamp should be approximately 50 mm to include further safety margins.

A prototype of the clamp presented and discussed above has been manufactured mainly by additive manufacturing technology. The prototype is shown in Figure 54. In the picture the clamp is shown occluding a single tube. The prototype has proved the expected good characteristics in terms of miniaturization and power consumption, also in comparison with commercially available clamping devices for medical use. However, a couple of relevant motivations have justified discontinuing the development of such a clamp mechanism and launching a new project (carried out in parallel with the doctoral one) for investigating the possibility of adopting a completely different approach to clamp design. Such a project has delivered a successful device, which is not discussed here for patentability reasons. The motivations which have suggested suspending the development of the clamp presented in this section are:

1. the final selection of a volumetric and occlusive peristaltic pump for blood circulation has determined a reduction in terms of required clamping force: only a single tube needs to be occluded rather than two.
2. the 3D printing manufacturing technology, which was the sole initially available, has shown some considerable drawbacks in terms of dimensional accuracy and robustness of the miniaturized links of the multibody.

Admittedly, the design presented is still relevant because immediately employable in case a not occlusive pump was employed in a future development of the WUF. As for the limits of the 3D printing technology, they can all be overcome by just manufacturing the mechanism links using the more traditional subtractive technology.

The clamp design proposed in this section has also been published in the proceedings of the *International Conference of IFTOMM Italy* in Vicenza [52], and then selected for publication in the *International Journal of Mechanics and Control*.

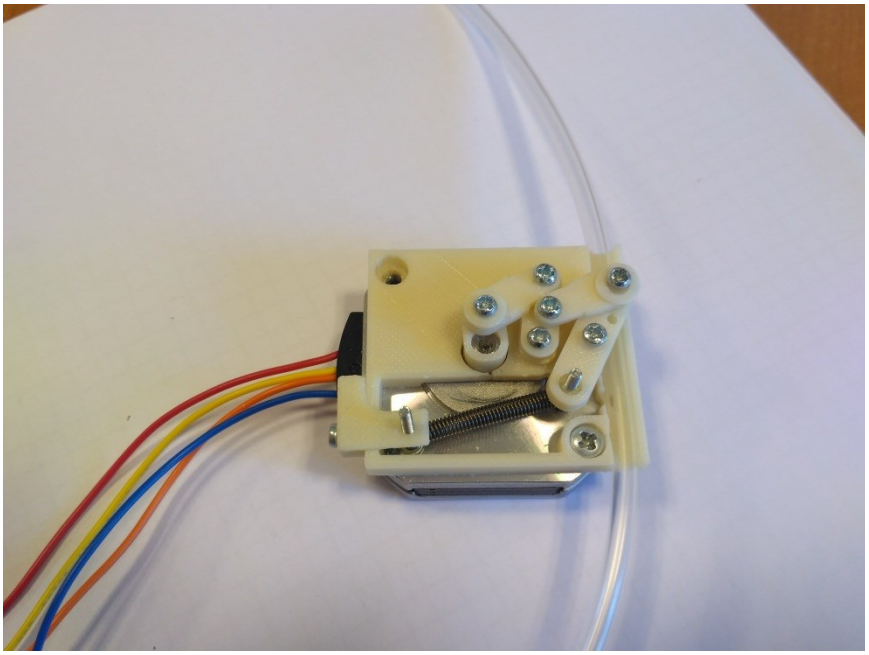


Figure 54. Prototype of an electromechanical clamp suitable to the WUF.

5.3.5 Ultrafiltrate collection and volume measurement system

The standard IEC60601-2-16, although it refers to chronic hemodialysis treatments, defines specific requirements on the control of hourly amount of ultrafiltrate to remove. It states that:
a) the net fluid removal (decrease in time) must be within ±0.1 l/h with respect to the set point based on clinical prescription;
b) the target net fluid removal is to be kept within ± 400 ml at any time during the treatment.

It is therefore necessary to have a feedback control of the amount of ultrafiltrate removed from the patient, in order to avoid either excessive or reduced water extraction during the therapy. Such measurements are needed by the control system to regulate the ultrafiltration pump and keep the ultrafiltration flow as constant as possible throughout the therapy. Standard ultrafiltration machines collect ultrafiltrate into bags whose weight is measured by load cells (gravimetric method). However, this approach could be unreliable in a wearable device, since the measurement can be affected by changes in bag orientation end by the continuous oscillations induced by patient's gait. To overcome

this problem, miniaturized flowmeters may be employed, since they allow keeping size and weight to a minimum, but in general they are extremely expensive.

An effort towards designing disposable devices for measuring the ultrafiltrate volume is being made by a few companies.

In this project, a completely novel approach combining level and acceleration sensors directly integrated in a suitable ultrafiltration tank has been developed. However, since this system is being patented, no further details can be provided in this paragraph.

5.4 Battery pack

After having defined all the hardware components of the device, the overall power consumption has been estimated to select an appropriate battery as power source (Table 16).

Components	Estimated power consumption (W)
Ultrafiltration pump	0.2
Pressure sensors and electrical circuits	1 - 2.5
Blood pump	7.2
Safety Clamp	2 - 4
2 Arduino microcontrollers	0.5
1 Raspberry microcomputer	1 - 2.5
Other components (e.g. display, heparin infusion system)	< 1
TOTAL	**12.4 - 17.9**

Table 16. Summary of estimated power consumptions of the main components of the WUF

In the worst case, the total power consumption is estimated about 18 W.
In order to simplify battery management, it has been decided to use a power bank device that can be easily, effectively, and quickly recharged without stopping the therapy. The selected power bank battery is Powerbank XTPower XT-20000QC2.
The characteristics and technical data of such device are summarized in Table 17.

Battery type	Lithium-Ionen
Capacity	20400mAh (3,7V) / 75,5Wh
Connections	1x USB Standard Output 1x USB Q2 Output 1x DC Socket (OUTPUT/INPUT) 1x Micro-USB socket (INPUT)
Input	1 x USB 5V 2.1A max. 1 x DC Socket 13-20V 3A max. / 30W max.
Output	1 x USB 5V 2.1A 1 x USB QC2 5V/2.1A 9V/2A 12V/2A
DC Socket	12V/16.5V/19V/20V/24V 50 Watt continuous / 65 Watt max.
Dimensions	174 x 78 x 21.5 mm
Weight	450g

Table 17. Technical data of the power bank unit selected for the WUF

The full charge stored in the battery, can assure a duration of battery-operated therapy ranging between 4 (worst case) and 6 (best case). For patients, such a battery life is far enough to guarantee performing many daily activities, such as commuting, leisure and playful activities (e.g. walking outdoors), or long-distance travels. In the last case the possibility of recharging the battery by just plugging into a standard electrical outlet greatly simplifies the WUF operations and extends its range of use.

6. Control Architecture

The control architecture applied for the WUF prototype is shown in Figure 55. The architecture has been carefully designed to meet both the restrictive requirements imposed by the application (the development of a miniaturized, energy efficient and wearable device which could be monitored remotely) and those imposed by the directives and by the need to minimize risk for patients. As shown in Figure 55, the architecture includes two main sections that have been named “program application section” and “device control section”. The selected microcomputer and the two microcontrollers can successfully implement such an architecture.

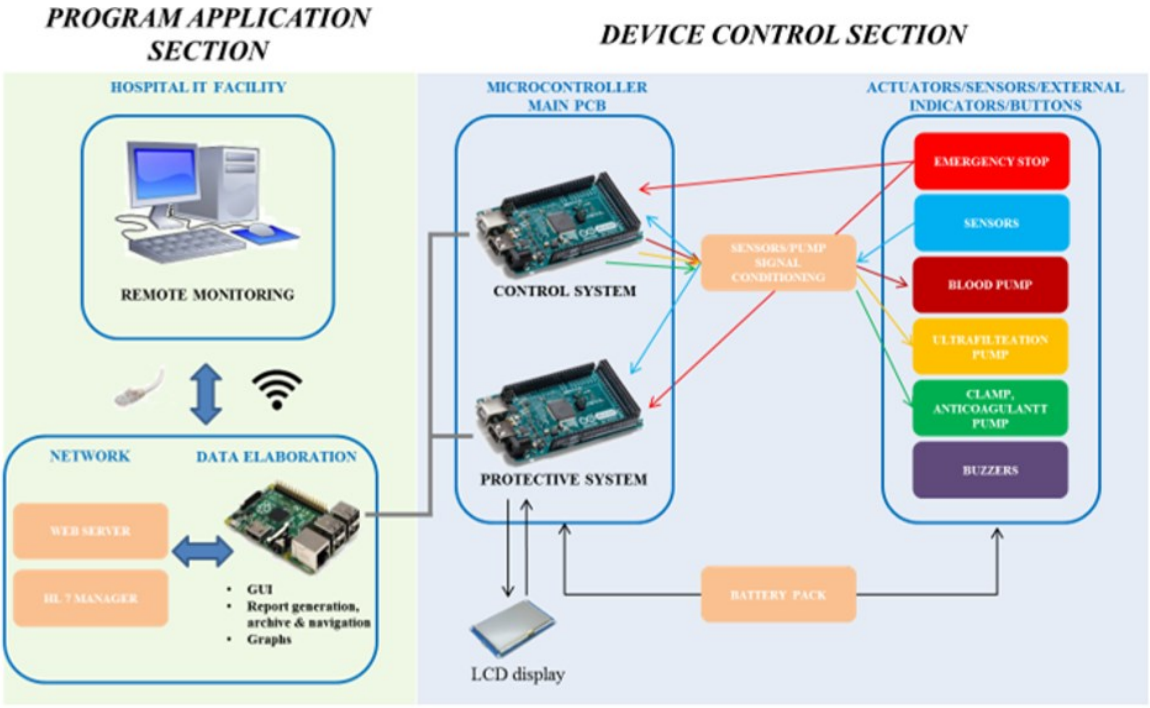


Figure 55. WUF control architecture

The main tasks of the program application section are:

- to set up the device on the basis of the treatment parameters,
- to manage network communication,
- to collect and sort therapy data,
- to show the clinical treatment information using a GUI during the whole treatment, supporting remote monitoring.

The microcomputer Raspberry PI 3 model B can perform all these tasks. Based on the peculiar field of application of the WUF, it has been chosen to make it possible to check therapy data and download reports and charts, in three ways:

- by opening a specific web page on the web server installed in the microcomputer through a generic internet-like connection;
- by visualizing the GUI running on the microcomputer from a remote terminal through VNC connection;
- by using HL7 transmission protocol, to exchange data with the hospital information system.

HL7 (Health Level 7, standard ISO 16527) is a specific standard protocol for exchanging information between medical applications. This standard defines a format for the transmission of health-related information.

The device control section, instead, receives the reference commands from the GUI (and hence from the program application section) or from the touchscreen monitor, reads the feedback signals from the transducers, and basically suitably drives the actuators of the pumps to perform the therapy. It also returns information on the status of the system (pressure values, amount of UF removed, etc.) to the GUI via USB connection. The two miniaturized microcontrollers (Arduino Mega) can manage this process in real-time: a dual parallel safety-loop has been designed in order to implement redundancy control. The two microcontrollers must read the signals measured by the transducers and detect potential non-compliant situations.

More in details, the control system implemented in one of the two Arduino Mega completely manages the ultrafiltration therapy. The control system reads signals from the sensors and provide the correct set point to the pumps. Data are transmitted at pre-set intervals to the microcomputer that stores them in a data log file, allowing a complete monitoring of the therapy.

In the second Arduino Mega (the “protective” one), the protection system has been implemented: such a microcontroller reads the signals from the sensors.

The firmware with which the two microcontrollers have been programmed has the task of cyclically scanning the ports to which the devices are connected, processing data and saving them into a special 60 Byte array. In case of out of range measures or mismatches between the measures read by the 2 microcontrollers, the safety procedure, requiring the treatment interruption by stopping the pumps and the closure of the safety electro-mechanical clamp, is activated. At the same time, one bit of the communication array is set at a high logical level in order to immediately communicate the current status and to display the alarm information on the GUI. Furthermore, the protective microcontroller is connected with the LCD touchscreen through which the patient can immediately understand the status of the therapy as well. The safety procedure can be activated even manually through an emergency stop button and any alarm or warning detected by the system is signaled through a buzzer. In order to further improve the overall system safety, a watchdog hardware component has been applied to check the microcomputer status continuously.

As for the programming languages chosen for the GUI, they are C++ and Python because of their versatility and software portability. With reference to the web environment, PHP, HTML and MySQL have been selected for the onboard web server: they allow encryption of patients' data and the possible scheduling of backup copies of all the device data, which are also downloadable through remote terminal via FTP server.
As for the programming languages chosen for the GUI, they are C++ and Python because of their versatility and software portability. With reference to the web environment, PHP, HTML and MySQL have been selected for the onboard web server: they allow encryption of patients' data and the possible scheduling of backup copies of all the device data, which are also downloadable through remote terminal via FTP server.

The control architecture proposed in this section, together with a general conceptual design of the WUF, has also been published in the proceedings of the *International Conference of IFTOMM Italy* in Vicenza [53].

7. Control logic

An accurate definition of the control logic has been carried out for the overall ultrafiltration therapy to be performed with the WUF. As previously explained the two microcontrollers and the microcomputer perform different tasks. In particular, the safe control of the device pumps and actuators is carried out by the two Arduino Mega microcontrollers which must also acquire and process sensor signals as well as detect and manage possible hazardous situations. The control logic has been developed based on clinical requirements, risk analysis, and after investigating thoroughly the behavior and the performances of some standard and reliable extracorporeal blood ultrafiltration machines in hospital.

The control logic has been structured in three main operational phases to be performed with the WUF. They are:

- Setup phase;
- Therapy phase;
- Termination phase.

All these phases have been translated into software programs running on the microcontrollers and the microcomputer. Each phase has been further divided into relevant clinical procedures, reflecting requirements arisen from the risk analysis, and technical steps to be executed. The GUI has been developed in order to allow hospital staff to manage and monitor the state and progression of the therapy from the beginning to the end.
The scheme describing the main control logic is represented in Figure 56.

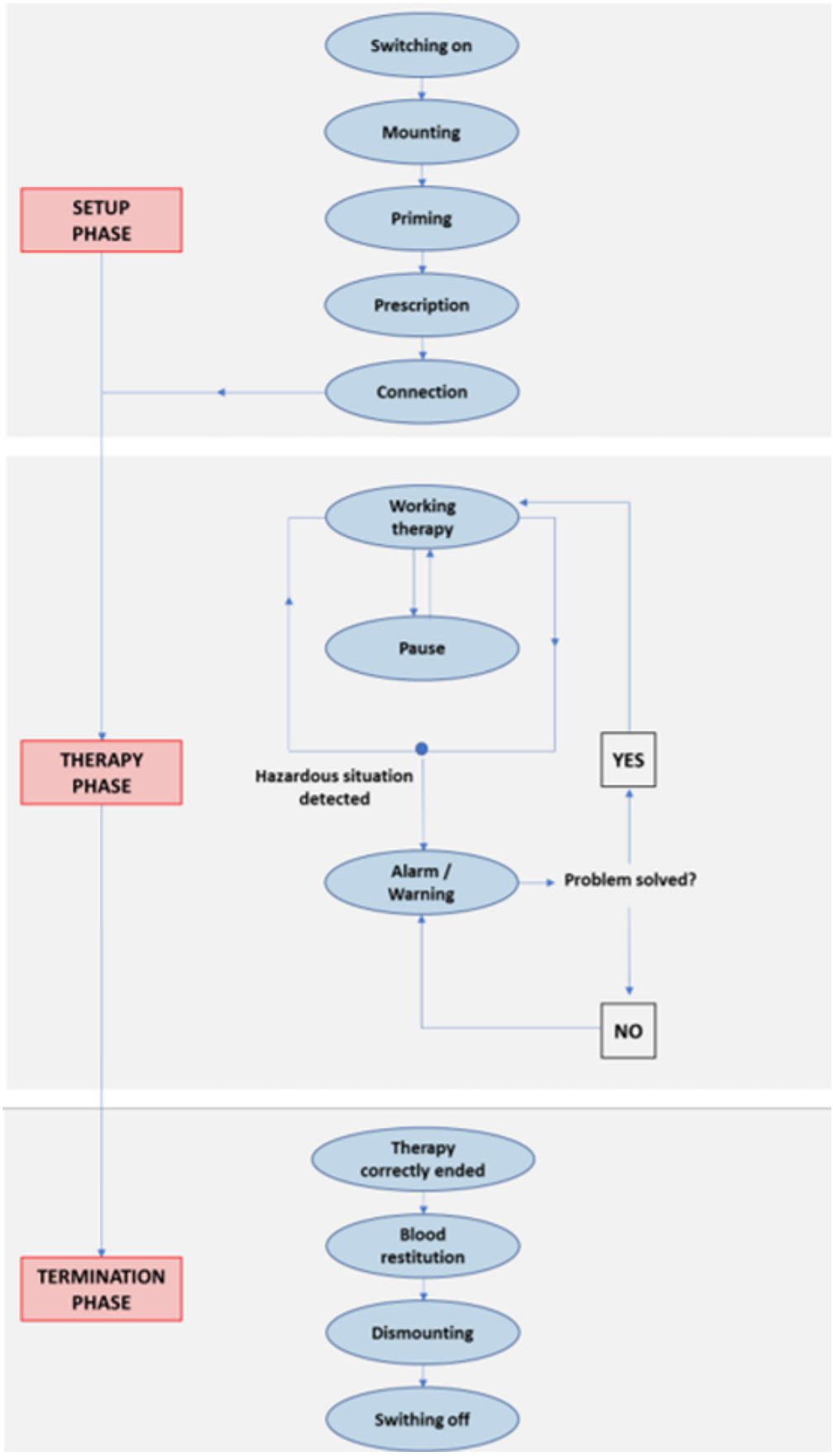


Figure 56. The main scheme describing the control logic of the WUF

7.1 Setup phase

The setup phase consists of the following clinical procedures:

- Switching on of the device;
- Mounting of the disposable components on the non-disposable panel;
- Priming of the extracorporeal circuit;
- Prescription of the therapy;
- Connection to the patient.

The switching on of the device is the first step of the setup phase. During this state, the system verifies the communication between the two microcontrollers and the microcomputer. If the communication test is passed and the user authorizes the start the therapy by the GUI (Figure 57), the system enters the mounting procedure.

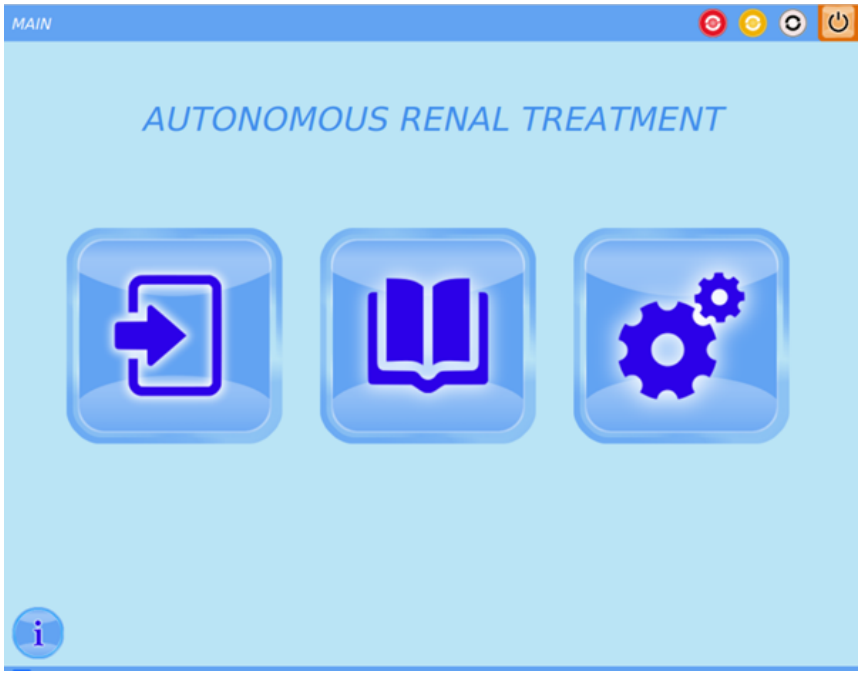


Figure 57. Main screen of GUI after the switching on of the device

The mounting procedure consists in preparing the device with all its physical components. Such a procedure needs to be performed in hospital by a trained nurse. The peculiar design of the WUF drastically simplifies such a procedure, since, as it will be described in the next chapter, all single use components are grouped in a single panel which can easily hooked to and unhooked from the non-disposable panel of the WUF, which is fixed to a rigid frame. During the mounting procedure all the pumps are stopped and the clamp is kept open to allow the mounting of the tubes. The possibility to

proceed to the next step (priming procedure) is assured by either the GUI of the microcomputer or a button displayed in the touchscreen monitor.

The priming is the most important procedure to be performed in the setup up phase. The priming is performed in order to fill the extracorporeal circuit with physiologic solution, remove all the air from the circuit, deposit some heparin along the inner surfaces of the hemofilter and tubes, and check if the circuit and the sensor have been well connected.
In particular, the technical steps performed during the priming procedure are:

1. To command the clamp to an open state configuration.
2. To set the velocity of the blood pump at 50 ml/min, with the UF pump switched off, for a duration of 4 minutes. After 2 minutes from the starting of this step, the heparin pump is set at 2 ml/h (33 μl/min). This step allows the prefilling of the blood compartment of the extracorporeal circuit and of the hemofilter.
3. To verify the correct connection of the disposable pressure sensors. This step is considered passed if at least 3 consecutive measures of each pressure sensor are collected and are non-zero.
4. To verify if the blood flow rate (50 ml/min) is correct. In order to do this, pressure measurements are collected to estimate the blood pump velocity. More details on such an estimation process are provided below, since it is used in the treatment routine too.
5. To fill the ultrafiltration compartment. In order to do this, the electro-mechanical clamp is closed and the blood pump is set at 50 ml/min until the ultrafiltrate tank starts to detect water.
6. To open the electro-mechanical clamp, to set the blood pump at 50 ml/min and the ultrafiltration pump at 7 ml/min. The duration of this step is 1 minute. At the same time, pressure measurements from all the sensors are collected. This step is performed in order to start to fill the arrays of pressures measurements necessary to be applied in the next step.
7. To close the electro-mechanical clamp, to stop the pumps (both the blood and UF ones) and to close a manual clamp placed in the ultrafiltration circuit. This operation can be performed by the touchscreen monitor.
8. To confirm by the touchscreen monitor that the clamp in the UF line has been manually closed by pressing the corresponding button.
9. To carry out the pressurization test in order to verify that there are no leakages in the extracorporeal circuit. The blood pump is set at 50 ml/min with the electro-mechanical clamp in the blood line and the manual clamp in the ultrafiltrate line that are closed. Sensor

signals, whose sample rate is at a frequency of 20 Hz, as it will be explained later, are low-pass filtered by a 16-tap moving average (see APPENDIX B). As soon as one among the pre-filter pressure, return pressure or ultrafiltrate pressure reaches the value of 300 mmHg, the blood pump is stopped. After 2 seconds, the three moving average pressure values are compared: if the difference between these is less than 40 mmHg for at least 5 seconds, the test is passed. If none of these pressures reaches the value of 300 mmHg in a period longer than 10 seconds from the start of the test, or if the comparison between at least two of the three moving average pressure measures is higher than 40 mmHg for the first 5 seconds, an alarm on the touchscreen monitor appears and the pressurization test needs to be repeated.

10. To open the electromechanical clamp, to set up the blood flow, the UF flow and the heparin flow at 50 ml/min, 7 ml/min and 2 ml/h respectively. This step is performed for 3 minutes.
11. To perform the self-test of the air bubble detector, to calibrate and perform the self-test of the BLD sensor, to check the temperature sensor.
12. To check the status of the microcomputer by the watchdog in the protective microcontroller.

Part of the priming procedure represented in the GUI is shown in Figure 58.

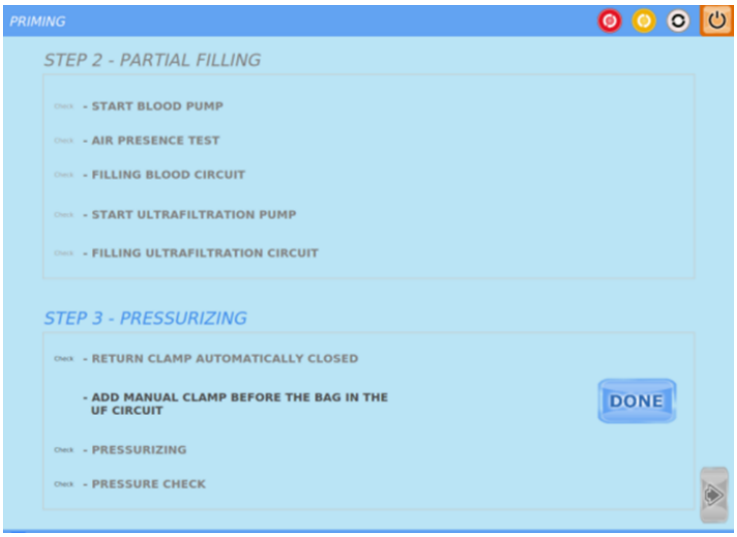


Figure 58. Sample screen of part of the priming procedure in the GUI

It is necessary to stress that, during some steps, a continuous check on pressures inside the circuit is performed. In particular, the moving average low-pass filter is applied to access pressure, pre-filter pressure and return pressure in the above steps 2, 4, 6 and 10. The allowable range of access pressure has been set between -300 mmHg and +50 mmHg. The allowable range of pre-filter pressure and

return pressure has been set between -50 mmHg and +300 mmHg. The moving average low-pass filter is applied to UF pressure in steps 6 and 10. The allowable range of UF pressure has been set between -300 mmHg and +300 mmHg.

The next procedure is related the accurate therapy prescription. The parameters to be set are:

- The blood flow rate;
- The ultrafiltration flow rate and the target ultrafiltrate volume to be removed during the overall treatment session; alternatively, it is possible to set the ultrafiltration flow rate and the treatment duration, or the target ultrafiltrate volume to be removed during the overall treatment session and the treatment duration;
- The heparin flow rate (it can be disabled) or the volume of heparin bolus and periods of infusion.

Finally, the connection procedure is carried out by connecting the access line and return line directly to the catheter of the patient.

Before entering the therapy phase, it is necessary to confirm the choice manually by both the GUI and the touchscreen.

7.2 Therapy phase

The second operational phase is the one corresponding to the ultrafiltration therapy.

The first procedure to be performed is blood circulation. Indeed, before starting with the ultrafiltration, it is important to fill the extracorporeal circuit with the patient's blood without removing water. This procedure is performed for 3 minutes.

After the blood circulation procedure, the ultrafiltration treatment starts. The main page of the therapy phase visualized in the screen is shown in Figure 59.

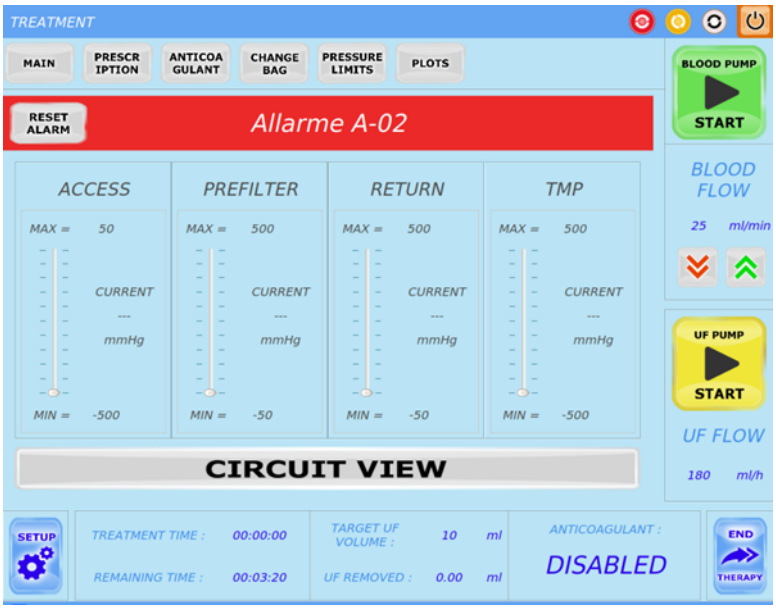


Figure 59. Sample screen during the therapy phase in the GUI

The main loop of the therapy phase manages the following operations:

- To command blood pump, ultrafiltration pump and heparin pump based on clinical prescription;
- To read and manage all the signals coming from the sensors. The management of the sensor implies, for example, the periodic launch of the self-test (air bubble detector sensor and BLD) and of the test for correct reading (pressure sensors). In particular, the sensors are:
    - Pressure sensors;
    - Air bubble detector sensor;
    - BLD sensor;
    - Temperature sensor;
    - Sensors for measuring the ultrafiltrate volume;
    - Sensors for measuring if the heparin tank is empty;
- To command the electro-mechanical clamp if a hazardous situation is detected;
- To manage and to verify the communication between the microcontrollers and the microcomputers;

If a hazardous situation is detected, the device automatically enters the state of alarm. In this state, the device automatically reacts by stopping the pumps and occluding the clamp based on the type of alarm and its risk. The alarm can be reset: if the problem is solved, the therapy can be carried on, otherwise the system re-enters the state of alarm. Table 18 shows the list of alarms detectable with the WUF and expedients that the device carries out in order to avoid any harm to the patient.

Alarm	Actions to be adopted
Access pressure error (difference in the signals acquired by the two microcontrollers)	To stop all the pumps and to close the clamp
Access pressure lock (Access pressure is not measured correctly)	To stop all the pumps and to close the clamp
Access pressure below lower limit	To stop all the pumps and to close the clamp
Access pressure above upper limit	To stop all the pumps and to close the clamp
Air detection	To stop all the pumps and to close the clamp
Air detection test error (self-test not passed)	To stop all the pumps and to close the clamp
Anomaly on the clamp power supply circuit	To stop all the pumps and to close the clamp
BLD installation error (self-test not passed)	To stop all the pumps and to close the clamp
Blood Leak Detector error (difference in the signals acquired by the two microcontrollers)	To stop all the pumps and to close the clamp
Blood leakage	To stop all the pumps and to close the clamp
Blood pump not stopped when it should be	To stop all the pumps and to close the clamp
Blood pump speed error	To stop all the pumps and to close the clamp
Blood pump stopped when it should not be	Warning in the screen appears
Clamp is not closed when it should be	To stop all the pumps
Clamp is not opened when it should be	To stop all the pumps and to close the clamp
Excessive Volume variance (the difference between expected Volume loss and real Volume loss is too high)	To stop the ultrafiltrate pump
Heparin reservoir is empty	To stop all the pumps and to close the clamp
Low battery voltage	To stop all the pumps and to close the clamp
Microcomputer error	To stop all the pumps and to close the clamp
Microcontroller 1 (controller system) error	To stop all the pumps and to close the clamp
Microcontroller 2 (protective system) error	To stop all the pumps and to close the clamp

Parameters out of range	
Pre-filter pressure error (difference in the signals acquired by the two microcontrollers)	To stop all the pumps and to close the clamp
Pre-filter pressure lock (Pre-filter pressure is not measured correctly)	To stop all the pumps and to close the clamp
Pre-filter pressure below lower limit	To stop all the pumps and to close the clamp
Return pressure error (difference in the signals acquired by the two microcontrollers)	To stop all the pumps and to close the clamp
Return pressure lock (Return pressure is not measured correctly)	To stop all the pumps and to close the clamp
Return pressure below lower limit	To stop all the pumps and to close the clamp
Temperature below lower limit	To stop all the pumps and to close the clamp
Temperature above intermediate limit	To switch on a cooling fan
Temperature above upper limit	To stop all the pumps and to close the clamp
Temperature error (difference in the signals acquired by the two microcontrollers)	To stop all the pumps and to close the clamp
TMP above upper limit	To stop all the pumps and to close the clamp
UF pressure lock (UF pressure is not measured correctly)	To stop all the pumps and to close the clamp
UF pressure below lower limit	To stop all the pumps and to close the clamp
UF tank full	To stop the ultrafiltrate pump
Ultrafiltrate pressure error (difference in the signals acquired by the two microcontrollers)	To stop all the pumps and to close the clamp
User interface error	To stop all the pumps and to close the clamp
Volume of removed ultrafiltrate error (difference in the signals acquired by the two microcontrollers)	To stop all the pumps and to close the clamp
Volume of removed ultrafiltrate has exceeded the safety limit	To stop the ultrafiltrate pump

Table 18. List of alarms detectable by the WUF

In particular, the following alarms:

- Blood pump not stopped when it should be
- Blood pump speed error
- Blood pump stopped when it should not be

needed a specific investigation to understand how to detect the actual blood pump speed (and consequently the blood flow) not using any specific sensor for a direct measurement. As stated before, the blood flow can be estimated by variations of pressure inside the circuit and measured starting from the velocity of the blood pump.

During the therapy phase, another state can be selected: the pause one. In this temporary state, the pumps are switched off. By pressing a button on the touch screen monitor or directly by the GUI, it is possible to resume the therapy.

Another important procedure is the one to empty the ultrafiltrate tank. This procedure can be set directly from the therapy page in the GUI (or in the touchscreen monitor) by pressing the specific key "CHANGE BAG" (Figure 60).

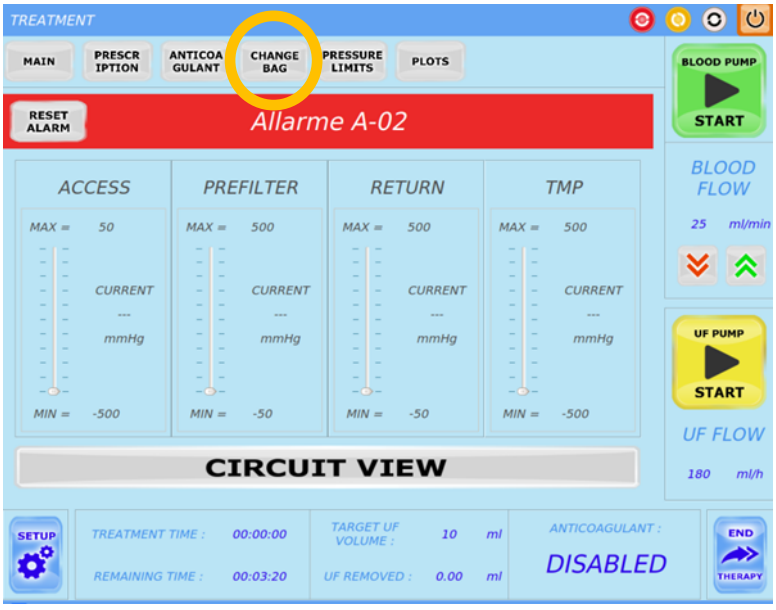


Figure 60. Key for the procedure of ultrafiltrate bag change/ tank emptying in the GUI

In this state, the UF pump is stopped, while the other pumps (blood and heparin) and all the sensors in the blood extracorporeal circuit continue to work normally. Once the procedure has been completed, the therapy can be carried on.

7.3 Termination phase

When the therapy is finished, the user can press in the GUI the key “End therapy” (see on the bottom-right corner of Figure 60): all pumps are stopped and the termination phase starts. It is important to remark that this phase must be performed in the hospital with a trained nurse that has to perform all the needed operations, in the proper order, which is listed and guided by the GUI.
The first procedure of the termination phase is blood reinfusion into the patient. To do this, the access line needs to be disconnected from the catheter and connected to a physiological solution (Figure 61).

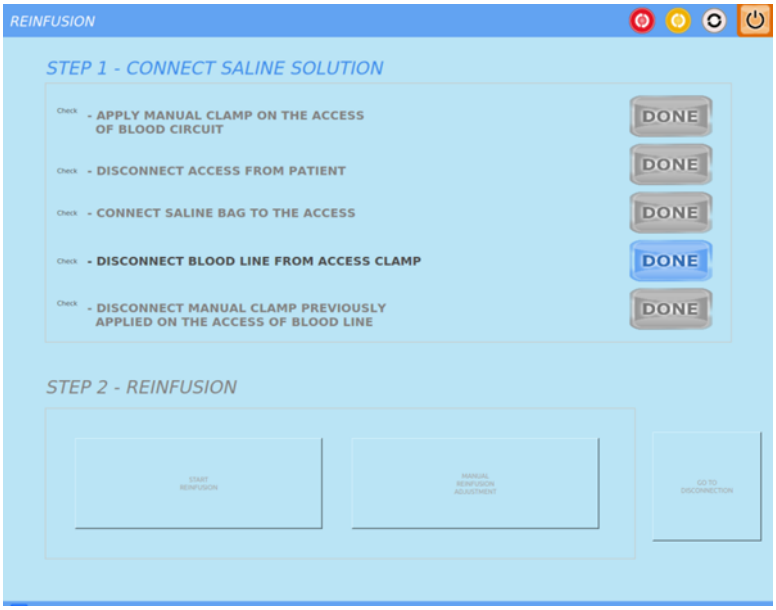


Figure 61. Blood reinfusion procedure represented in the GUI

During the blood reinfusion procedure, the device activates the blood pump at 50 ml/min for 30 seconds (the priming volume of the extracorporeal circuit is almost 20 ml), while all the measures coming from sensors are continuously checked. Additionally, there is the possibility to re-infuse more volume by pressing a specific key in the GUI (“Manual reinfusion adjustment”).

After having reinfused the blood to the patient, the blood pump is stopped and the return tube can be disconnected from the catheter. The device enters the dismounting procedure. After opening the electro-mechanical clamp, it is possible to easily remove the panel disposable components from the non-disposable one.

Finally, the device can be switched off.

8. Design of the device

The WUF layout has to be designed meeting the following specific requirements:

- Satisfactory ergonomics when worn
- Low weight and compact dimensions
- Ease of movement for the patient during daily activities
- Comfort for the patient even when sitting or lying (possibly providing the possibility of continuing the therapy without wearing the device)
- Easiness in assembly and dismounting disposable components
- Easiness in reaching not disposable component for maintenance
- Stability of the device when not worn (for temporary or continuous needs)

Based on these considerations and analysis of previous proposals from the literature, three main layout proposals have been taken into account. They are (see Figure 62 for example of the first two layout proposals):

- Belt-like device (horizontal arrangement);
- Jacket device (frontal arrangement);
- Backpack device (rear and vertical arrangement).

Figure 62. Layout proposal for the WUF: belt-like and jacket.

As for the belt-like device, if on the one hand it allows an immediate visual evaluation of any problems during the treatment, on the other it limits the possibility of movement for the patient, reducing the number of daily activities that may be carried out comfortably. Moreover, such a layout

result scarcely convenient to use when not worn (for example, because the patient is lying in bed or sitting in an office).

Similar considerations can also be applied for a jacket or a gilet layout: although the predominant vertical positioning of the components ensures an ordered and clear arrangement, the encumbrance for the patient is high and the usability of the device certainly limited.

It is also important to point out that both the above-mentioned solutions may cause embarrassment in presence of other people, being extremely apparent. Additionally, the necessary replacement of disposable components at the beginning of the therapy may be made difficult by the disperse component arrangement, resulting in long setup preparations for healthcare nurses.

Generally speaking, the WUF layout has to be designed with the aim of optimizing component positioning while keeping the device overall size to a minimum in terms of width, height and depth. For example, the peristaltic pump selected for blood circulation is characterized by a significant depth. In order to simplify the fitting of tubes in the pump rotor, it is certainly better arranging the pump orthogonal to the plane in which the other hydraulic components are positioned. This suggests abandoning a fully planar layout (such as those characterizing a sling or a belt), and preferring spatial arrangements exploiting all the volume in the three dimensions (i.e. a box-like displacements). In particular, in order to overcome the limits of the layout proposals previously described and in accordance with the requirements defined above, an innovative solution has been conceived for the layout of the WUF: a backpack/trolley design combined with a multi-layer displacement of components effectively collected into separate panels in accordance with their use and features.

Figure 63 represents an initial conceptual idea of the WUF and clarifies such a concept of a multilayers approach in box-like design.

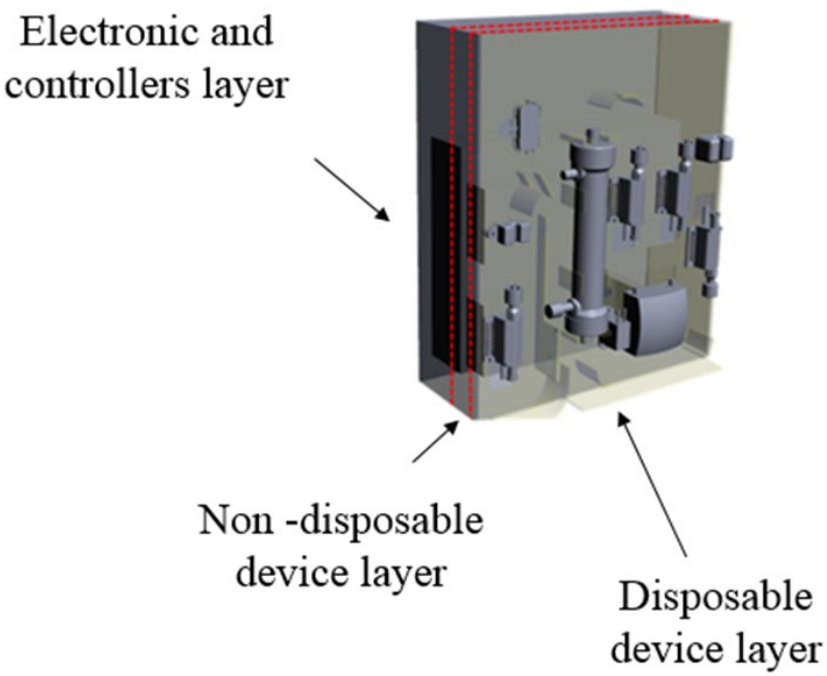


Figure 63. Conceptual layout introducing a box-like multi-layer design

The box-like design fits well a backpack or a trolley, both guaranteeing good ergonomics and high levels of transportability of the device. In particular the chosen design allows:

- to increase, thanks to the depth of the box, the available space for the arrangement of components;
- to provide a good separation between disposable and non-disposable devices (by stacked 2D panels);
- to ensure comfortable setup and disconnection operations;
- to simplify the positioning of the battery pack and of the ultrafiltrate tank;
- to extend usage opportunities: the trolley configuration can as comfortable as the backpack one and certainly preferable in case of lying patients;
- to avoid embarrassment for patients, since the device can be well hidden during the treatment, inside an anonymous and compact backpack or trolley;
- to simplify the measurement and the discharge of the extracted ultrafiltrate, thanks to the possibility to design a tank which can be kept almost vertical.

It is clear that the adoption of a backpack imposes a high level of safety in case of alarm, since no immediate visual inspection is possible. However, the risk analysis previously carried out and the adopted safety measures can be considered enough to ensure safety even with such a layout.

The multi-layer layout proposed in this thesis has been translated into an arrangement of component into in three vertical parallel panels:

- an internal and protected panel (the closest to patients' shoulders) houses the electric and electronic components of the device including the three controllers,
- an intermediate panel houses the non-disposable components (e.g. peristaltic pump, air sensor, blood leak detector),
- an external panel houses all the disposable components of the device (and hence the entire circuit) and can be easily hooked to or unhooked from the intermediate respectively at the beginning or the end of the therapy.

Through such a design there is the possibility to fully exploit the depth of the backpack (reasonably over 80 mm), and especially the space between the "electronic panel" and the "non-disposable" one, to include bulky components, as for example the peristaltic pump and the microcontrollers, without creating discomfort or limitations in the patient's movement.
Figure 64 shows a 3D CAD view of the device, showing, in particular the non-disposable panel, the disposable one, the top cover of the device (housing the battery, a touchscreen monitor and a self-locking red emergency stop push button), and the instrumented UF tank, which, again, smartly exploits the depth of the box-like design. The UF tank is big enough to collect two liters of ultrafiltrate, and therefore should not be emptied during the treatment. However, both for safety and comfort reasons, the tank it is equipped with a drain on the bottom. As for the box cover, it should be noticed that the touchscreen monitor can be placed in a movable case (not shown in the picture) which can be easily unlock from the cover and fastened to the backpack shoulder, hence becoming visible and usable along the whole therapy.
The overall dimensions of the box are 405 x 300 x 140 mm and the estimated weight is less than 7 kg: 5 kg of the device itself plus up to 2 kg of ultrafiltrate collected in the tank.
Figure 64 also makes apparent that the multi-layer design drastically simplifies the change of the disposable components which are all collected on a single panel. Such a panel is the most external one and hence it is easily accessible when the backpack (see Figure 64) or the trolley are open. This allows keeping the duration of patients' stays at the hospital to a minimum when a therapy is over and a new one is started. As a consequence, hospitalization costs are also kept to a minimum.

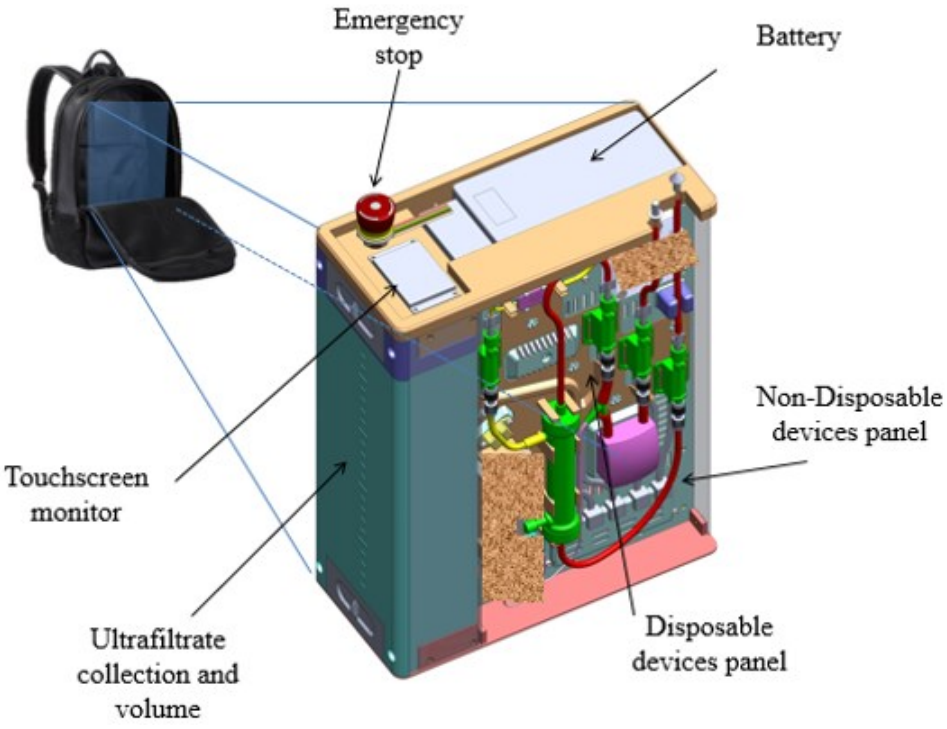


Figure 64. Final layout proposal for the WUF

It is worth underling that in the design of both the non-disposable and the disposable panels, some constraints must be taken into consideration:

- the 4 pressure sensors must be placed in specific positions in the extracorporeal circuit:
  - Access line
  - Pre-filter line
  - Return line
  - Ultrafiltrate line
- the electro-mechanical clamp must be placed immediately before the blood returns to patient;
- the heparin system must allow the heparin infusion before the blood enters into the hemofilter;
- the ultrafiltration pump must allow filling the UF tank from the top.

Figure 65 shows the CAD sketch of the "disposable panel" and the prototype of the panel manufactured using additive technology by an 3NTR A2v2 3D printer. In both the CAD sketch and the prototype picture, part of the heparin infusion system is masked since a verification of patentability is currently being made**.**

The "non-disposable panel", instead, has been equipped with components on both sides. In Figure 66, the CAD sketch and the prototype of the frontal side are shown. In both the images, part of the heparin infusion system and the electro-mechanical clamp which has been developed in parallel with the one presented in Section 5.3.4 are masked for reasons of patentability. Louvers have been adopted

to guarantee natural and forced air circulation, especially in the areas where possibilities of overheating are higher (e.g. close to the blood pump and the electro-mechanical clamp). The panel is fixed to the main body (or in other words the frame) of the box by several screws on the perimeter. The connection between the “non-disposable panel” and the “disposable” one is obtained by several snap joints which simplify assembling and disassembling procedures.

Figure 67 shows the CAD sketch of the reverse side of the “non-disposable panel”. The power board descripted in Section 5.2.4 is fixed just next to the motor of the blood pump. The motor of electro-mechanical clamp is masked again for reasons of patentability. The PCB for the conditioning of the electric signals from pressure sensors and the one driving the UF pump have also been adapted on the back of this panel.

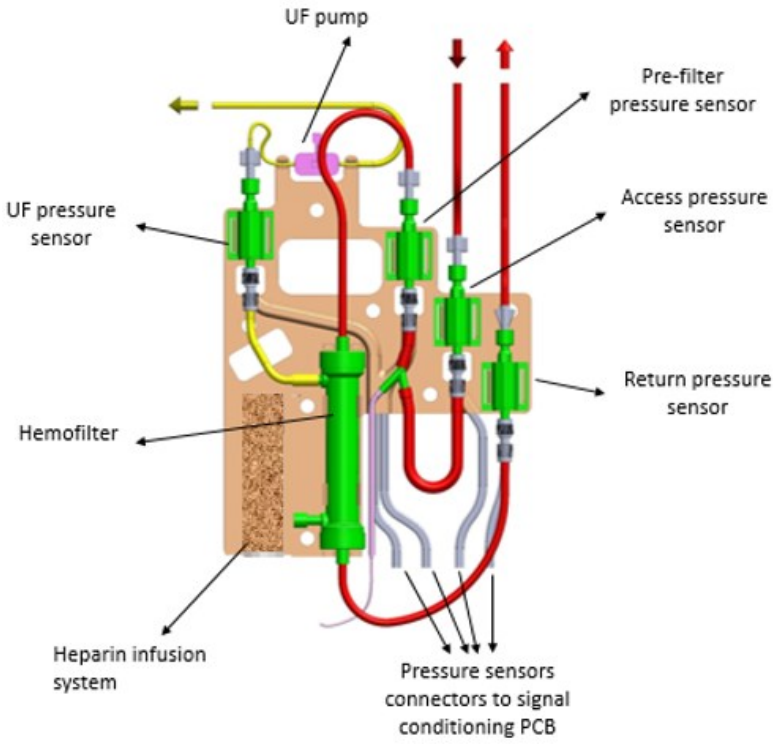
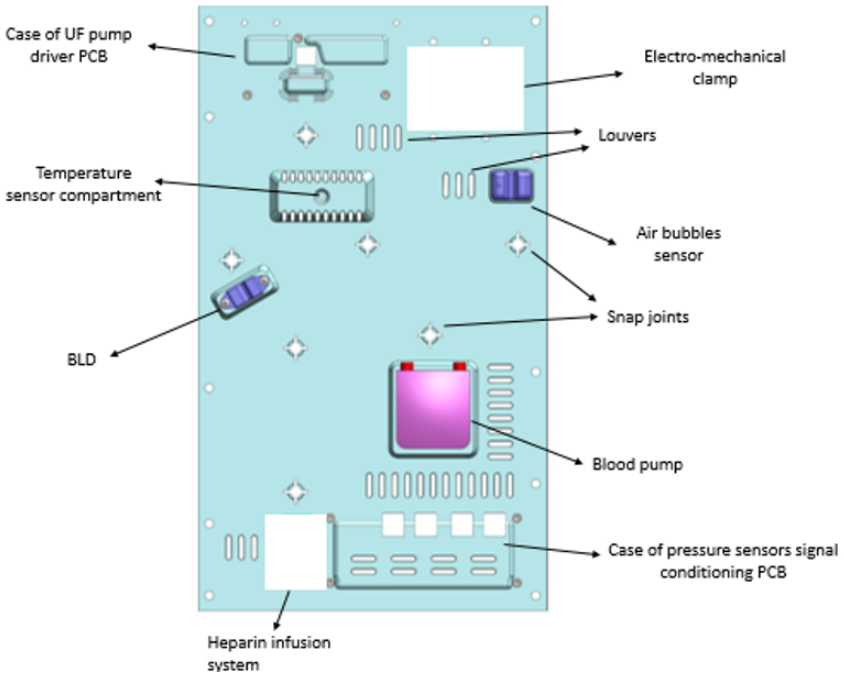


Figure 65. Disposable panel and components



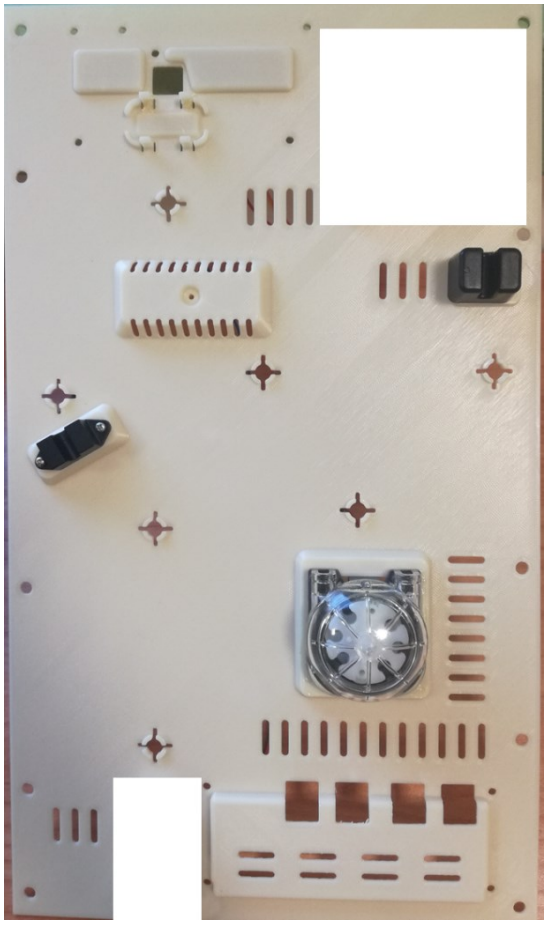


Figure 66. Non-disposable panel and components

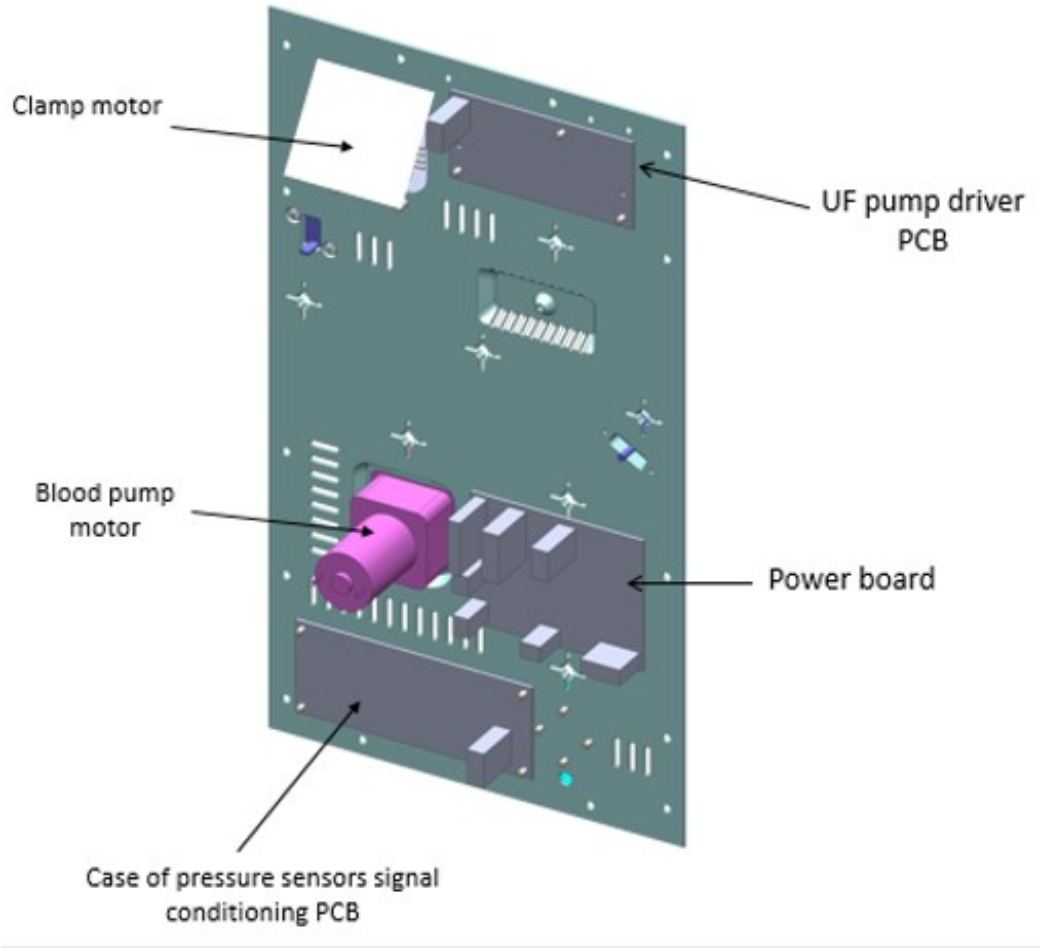
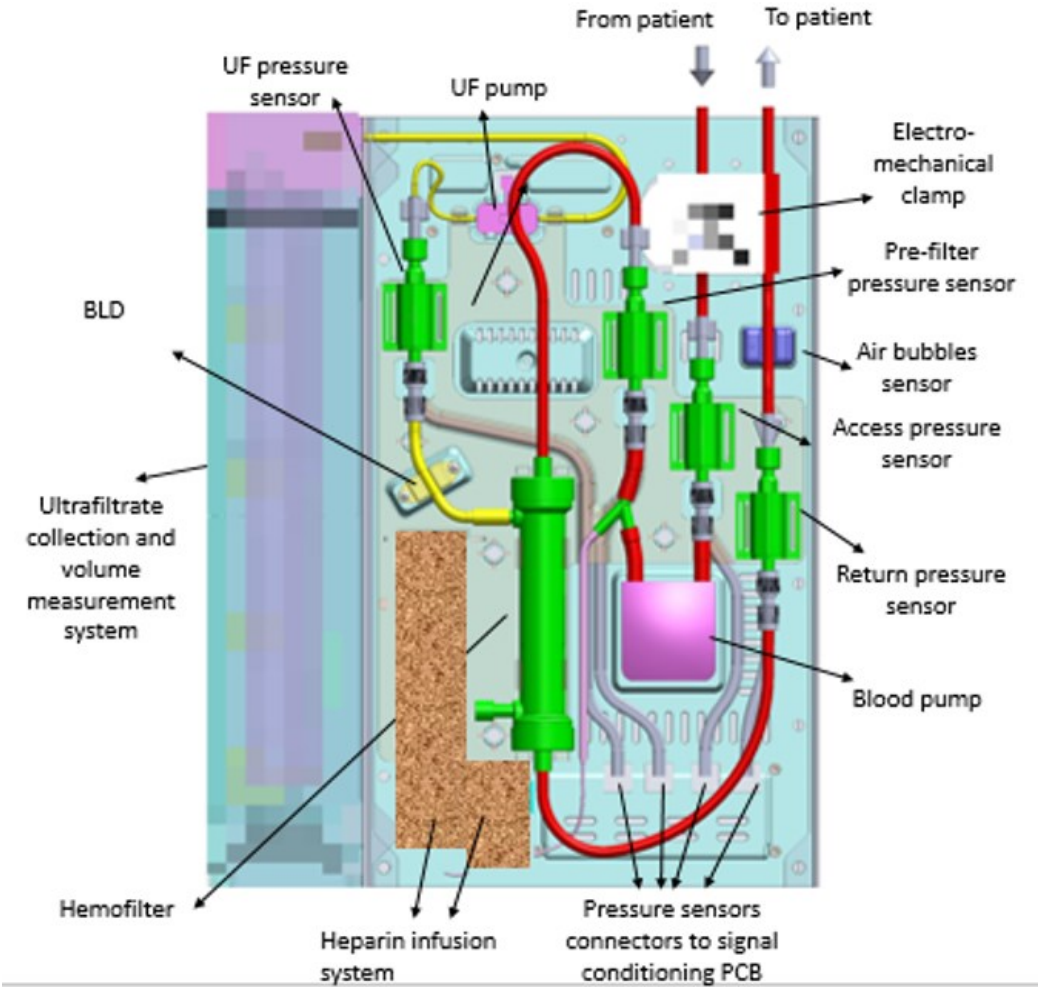


Figure 67. Reverse side of the "non-disposable panel" and components

In Figure 68, the CAD sketch and the prototype of the assembling of disposable panel on the non-disposable one are represented.


From patient
To patient
UF pressure sensor
UF pump
Electro-mechanical clamp
Pre-filter pressure sensor
BLD
Air bubbles sensor
Access pressure sensor
Ultrafiltrate collection and volume measurement system
Return pressure sensor
Blood pump
Hemofilter
Heparin infusion system
Pressure sensors connectors to signal conditioning PCB

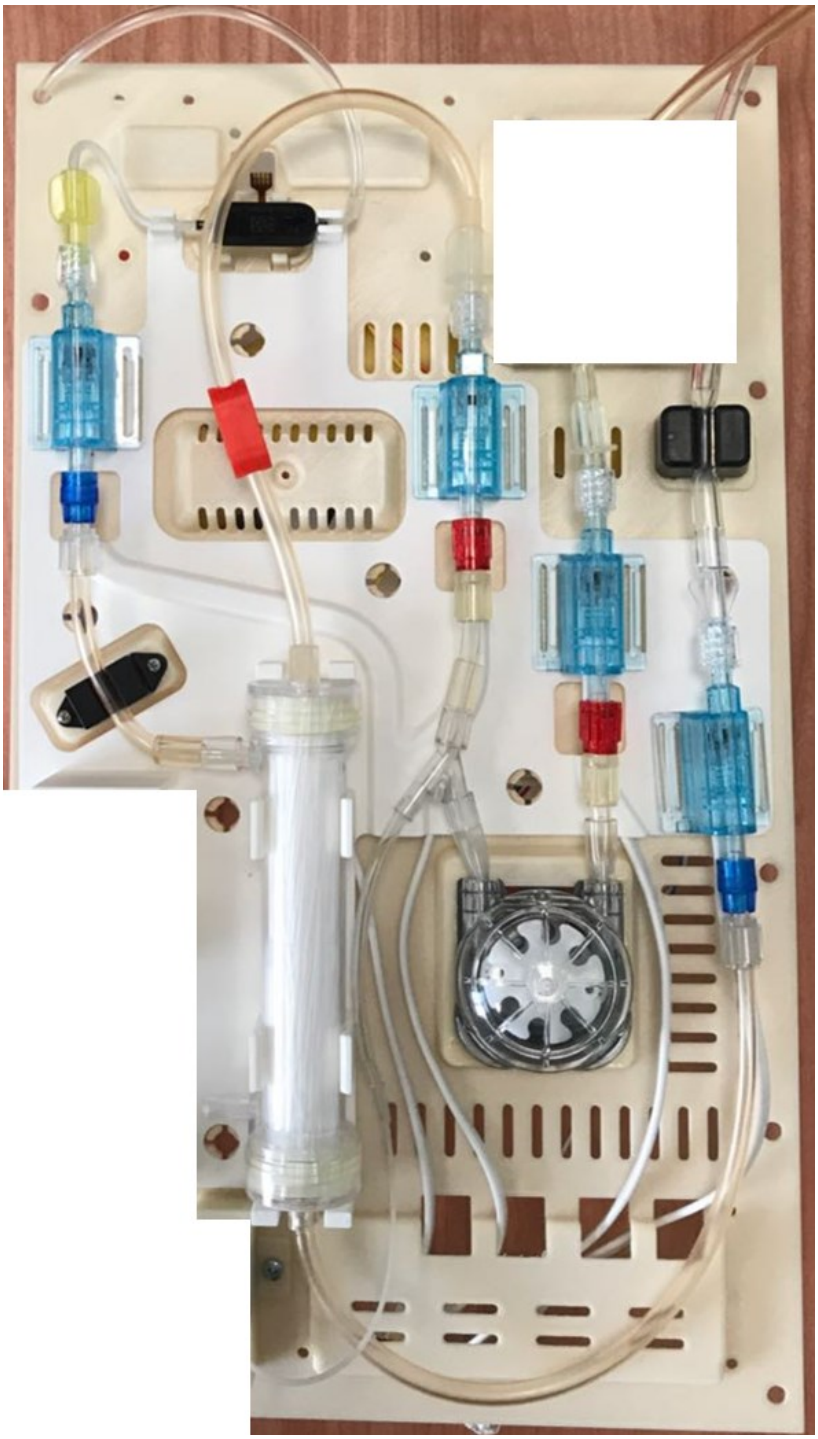


Figure 68. Mounting of the disposable panel on the non-disposable one

The inner part of the box contains the “electronics and controllers” layer. As shown in Figure 69, the main PCB, where the two microcontrollers have also been integrated, is approximately located in the center of the panel in order to minimize the electrical cabling. The microcomputer is positioned just below the main PCB, simplifying the USB cabling connection with the microcontrollers. On the right side of the panel, the driver of the clamp is visible. Furthermore, a cooling micro fan (not shown in the sketch) is mounted on the right wall of the box (opposite the UF tank) to generate forced ventilation in case the box internal temperature overcomes a set value.

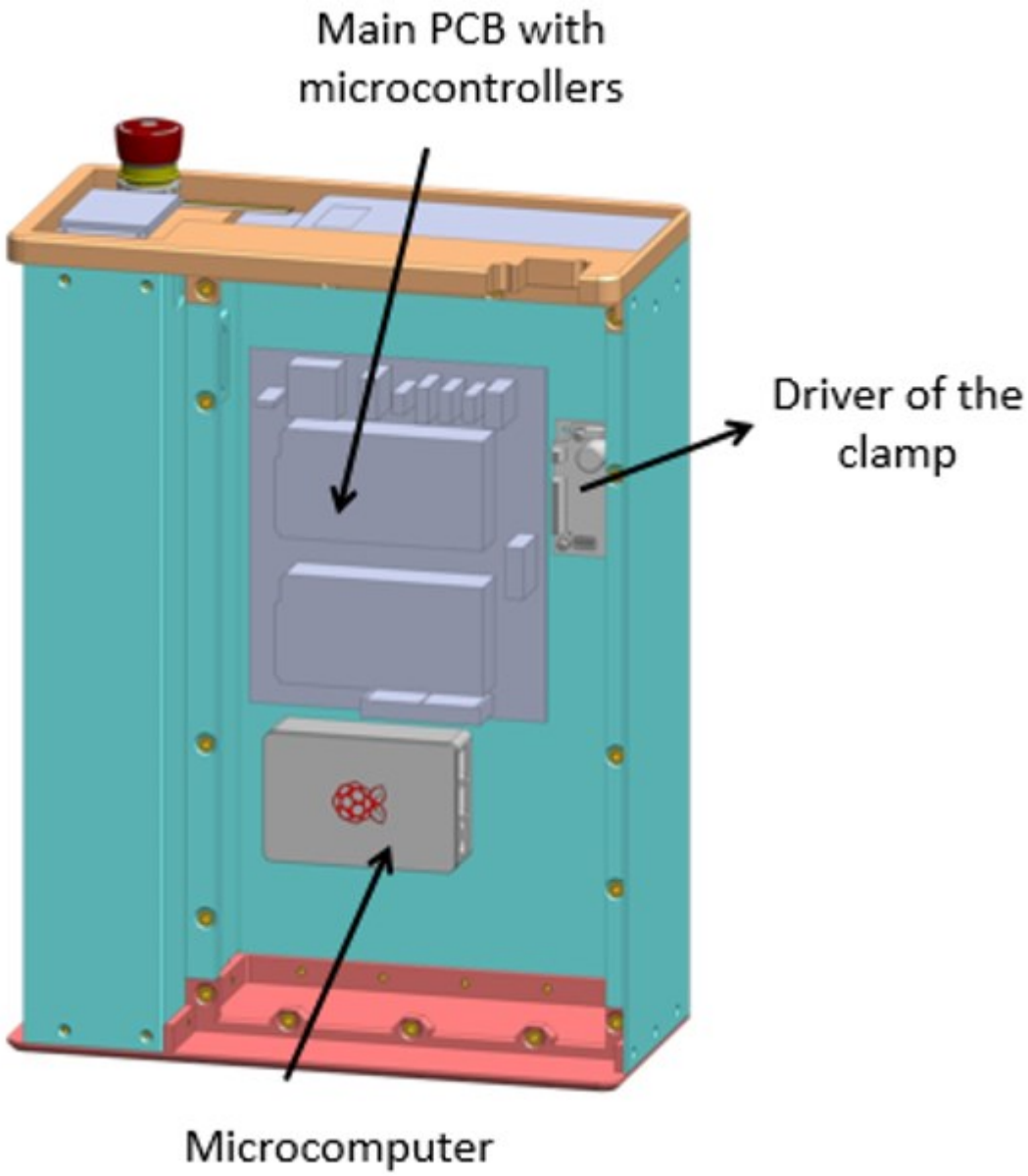


Figure 69. Inner part of the device containing the electronic layer

9. Conclusions

The research activity presented and discussed in this thesis has led to the development of an innovative, safe, and easy-to-manufacture wearable and portable system for extracorporeal blood ultrafiltration named WUF. Such a device can potentially bring important social benefits by improving the quality of life in patients suffering from fluid overload condition while possibly reducing costs related to long hospitalizations. Additionally, it should ensure significant clinical advantages compared to standard current technology, thanks to a slow but continuous fluid removal allowing improved overall patient's hemodynamic tolerance.

The solutions adopted in the WUF have exploited the newest technological advances in fields such as sensors, micro pumps, actuators, membranes and related devices, microcontrollers, microcomputers and additive manufacturing technologies. The proposed mechatronic design has proved that several off-the-shelf components can be successfully employed, nonetheless novel approaches can still be developed to design some critical components as the electro-mechanical clamp.

A considerable effort has been devoted to the design of an effective, efficient, safe and reliable control architecture. It has been proved that a couple of cheap and standard microcontrollers and a microcomputer allow meeting all these requirements. Then, an accurate definition of the control logic, based on clinical requirements and risk analysis, has been developed and structured in three main operational phases. These have been further divided into relevant clinical procedures, reflecting requirements arisen from the risk analysis and technical steps to be executed. In parallel, a user-friendly graphical interface has been developed, in order to allow hospital staff to manage the status and progress of the therapy from the beginning to the end.

An innovative layout paradigm has been introduced for the WUF, which involves:

- a box-like design that can easily fit a backpack or a trolley: it guarantees the best tradeoff between miniaturization and ergonomics;
- an original positioning of the vast majority of components on three independent planar panels: one for disposable devices, one for non-disposable components and one for electronic boards and controllers. Such an arrangement of components drastically simplifies and speeds up the in-hospital operations needed before and after a therapy with the WUF.

A backpack design should be more suitable for younger patients who can easily wear the device during daily activities, while a trolley design should be more indicated for elderly patients who can perform the ultrafiltration therapy comfortably at home. Clearly, these reasonable hypotheses should be confirmed by extensive ergonomic investigations on (target) patients.

Both the commercial and the customized components of the WUF have been extensively tested and validated. The final commissioning of the prototype, manufactured with an extensive use of additive technology, allows confirming that the project for a wearable solution for ambulatory ultrafiltration in patients with fluid overload has been successfully completed from an engineering view point.
In order to make the WUF compliant with the specific European Regulations, Directive and technical standards (mentioned in Chapter 4) regarding medical devices, the prototype needs first of all to be tested *in vitro* under medical supervision, in order to assess its safety, effectiveness and reliability.

In particular, during the *in vitro* test, some possible open issues, that can be evaluated only by having the final complete prototype, can be addressed, including:

- eventual electro-magnetic disturbances generated by the electric PCBs;
- bugs in software integration and system testing;
- device-related usability problems.

This process, which requires a deep analysis and a long testing period (estimated in 6 months), is necessary to prepare an exhaustive documentation for the procedure of obtaining the CE mark by European Union. The in vitro testing phase will be performed in the Department of Nephrology of the San Bortolo Hospital.

Since the WUF device does not introduce any new therapy for the treatment of fluid overload patients (ultrafiltration is a well-known clinical modality in this population and has been deeply studied in literature), no animal in vivo studies need to be performed before starting the clinical trial on humans.

Consequently, after having obtained the CE mark, the subsequent step will be a phase-1 trial in humans after adequate regulatory license and Ethical Committee approval.

Finally, a comparison between the main features of the available prototypes for renal replacement therapies and the WUF is proposed in the following Table 19.

		FEATURES						
		Therapy efficiency	Layout	Weight	Remote control	Power consumption	Software and control architecture	Development and miniaturization of safety components
DEVICE	WUF	✓	✓✓	✓	-	-	✓	✓✓
	WAK	✓✓	✗	-	✓✓	✗	✓	✗
	ViWAK	✗	-	✓✓	*	*	-	-
	AWAK	✗	-	✓✓	*	*	-	-
	WHF	✓	✗	✓	✓✓	✗	✓	✗
	RAD	✓	✗✗	✗	✓	*	✗	-
	iNephron	✓	✓	✓	-	*	✓	✓
	WAKMAN	✓	-	-	✓	*	✗✗	*

Table 19. Evaluation table referring to the main features of WUF and other prototype devices. Legend: ✓✓ = very good, ✓ = good, - = normal, ✗ = bad, ✗✗ = very bad, * = not enough available data.

"Therapy efficiency" needs to be intended as the clinical effectiveness of the device of treating patients with fluid overload; "layout" is the spatial arrangements of all components (disposable and not disposable) which can facilitate the ordinary operativity of the device; "remote control" is the level of development of the software for the telemedicine; "software and control architecture" needs to be intended as effectiveness, efficiency, safety and reliability of software and microcontrollers; "Development and miniaturization of safety components" degree of innovation in developing mechatronic components of the device.

Based on these results, the WUF has the best average mark with respect to other prototypes and is particularly innovative for what concerns layout and the development and miniaturization of safety components.

Thus, the WUF can be considered as an extremely promising prototype in the field of wearable devices for extracorporeal blood ultrafiltration.

Appendix A

In collaboration with researchers and clinicians of IRRIV and Department of Nephrology of San Bortolo hospital of Vicenza, a theoretical study has been carried out to select the minimum size, and in particular the lumen, of the catheter for the WUF. The lumen of a catheter is usually expressed in French, and it is most often abbreviated as Fr. The French size is three times the diameter in millimeters.

From the hemodynamic point of view, it is necessary to take into account the Hagen-Poiseuille law:

$$\Delta P = \frac{(128 \cdot \eta \cdot Q \cdot L)}{\pi \cdot d^4}$$

where ΔP is the pressure drop along the catheter, η is the blood viscosity, Q is the blood flow, L is the catheter length and d is the inner diameter of the catheter.

Considering that blood viscosity does not vary so much (it depends on blood characteristics like hematocrit and protein concentration), the main parameters affecting pressure drop are the geometrical characteristics of the catheter (diameter and length). In particular, pressure drop is proportional to the fourth power of the diameter. Consequently, it would be desirable to increase the size of the diameter in order to reduce as much as possible the pressure drop and to avoid the catheter's collapse as well.

On the other hand, the catheter diameter cannot be excessively large, because it may fill the vein too tightly, possibly leading to a damage of vein wall, together with an increased risk of stenosis or thrombosis. A good compromise between these two aspects needs to be reached.

In Figure 70 a Hagen Poiseuille law-based selection of the minimum diameter of a single lumen catheter for a wearable device is represented.

In particular, the following assumptions were considered:

- desirable blood flow of 50 ml/min, as defined by project requirements;
- constant and standard length of the catheter for adults, L = 19cm;
- patient venous pressure = 10 mmHg.

The whole pressure drop between patient vessel and access pressure detecting point in the extracorporeal circuit is due almost entirely to the catheter.

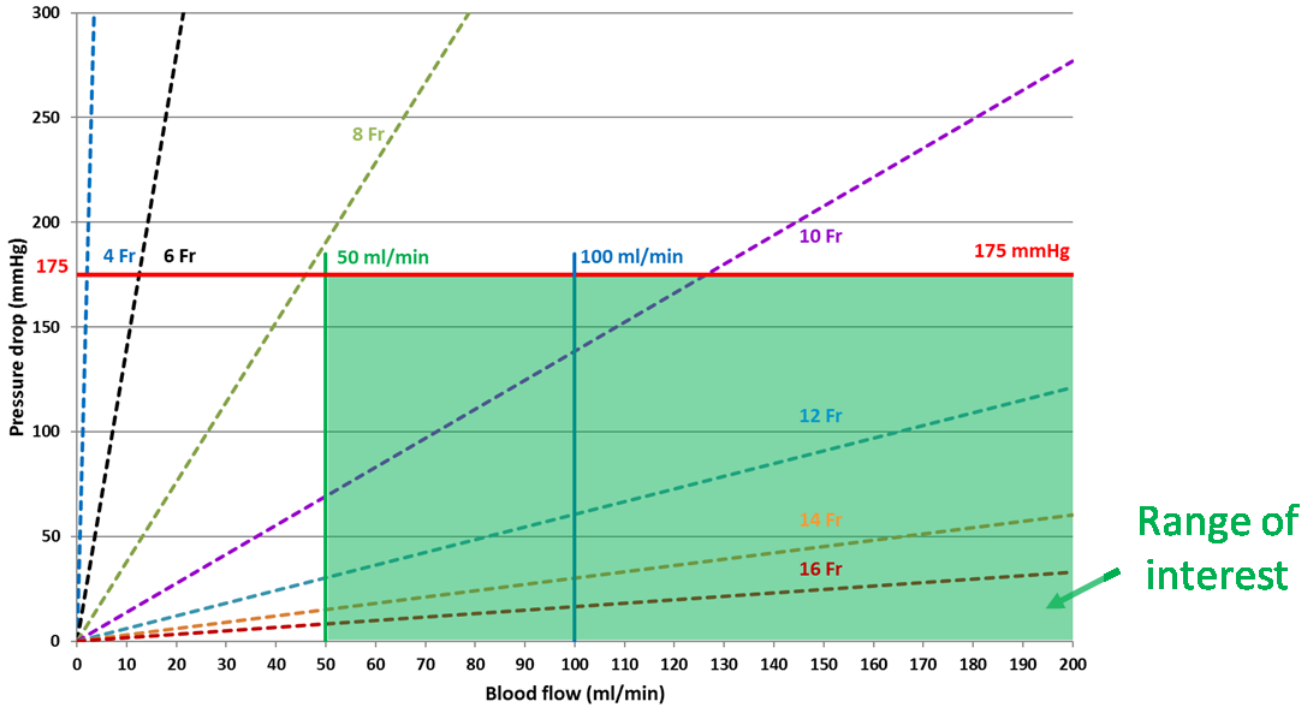


Figure 70. Graph comparing the reachable blood flow and pressure drop inside the catheter. Color lines represent catheters with different sizes of the lumen. Green area represents the acceptable range between ΔP and catheter size for the desired blood flow. For 50 ml/min of blood flow, a 10 Fr is the minimum acceptable size of the lumen.

In the access side of the catheter, which is more critical for the selection than the return one, the minimum pressure difference (ΔP) along the length of the device should not exceed 350 mmHg [54] to avoid hemolysis and catheter collapse. However, this value does not take into account that blood flow is not uniformly laminar, the curvilinear deformation of the catheter after implantation and tubing roughness. For these reasons, a strict safety factor equal to 2 was taken into account to determine an acceptable value of pressure drop ΔP':

$$\Delta P' = \frac{\Delta P}{2} = 175\ mmHg$$

Considering a dual D lumen catheter, in such conditions, a minimum size of 10 Fr (corresponding to an external diameter of 3.34 mm) catheter is required (Figure 71), matching technical requirements and clinical/ergonomics needs.

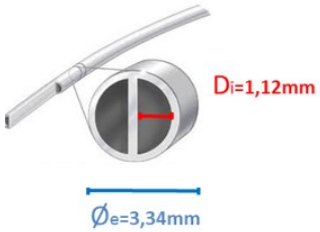


Figure 71. Geometrical characteristics of the selected catheter

Appendix B

The management of pressure signals coming from the sensors deserved an important and specific investigation. In order to do this, dedicated in vitro tests (Figure 72) have been carried out in hospital using blood. The aims of the test were:

- to collect pressure values similar to in vivo ones;
- to understand if a sample rate of 20 Hz (easily achievable by the Arduino microcontrollers) was adequate to detect immediately any obstruction;
- to understand which was the best value to be retained in a moving average (easily implementable in the Arduino microcontrollers) to properly filter the signals.

The miniaturized peristaltic pump selected for the WUF has been used.

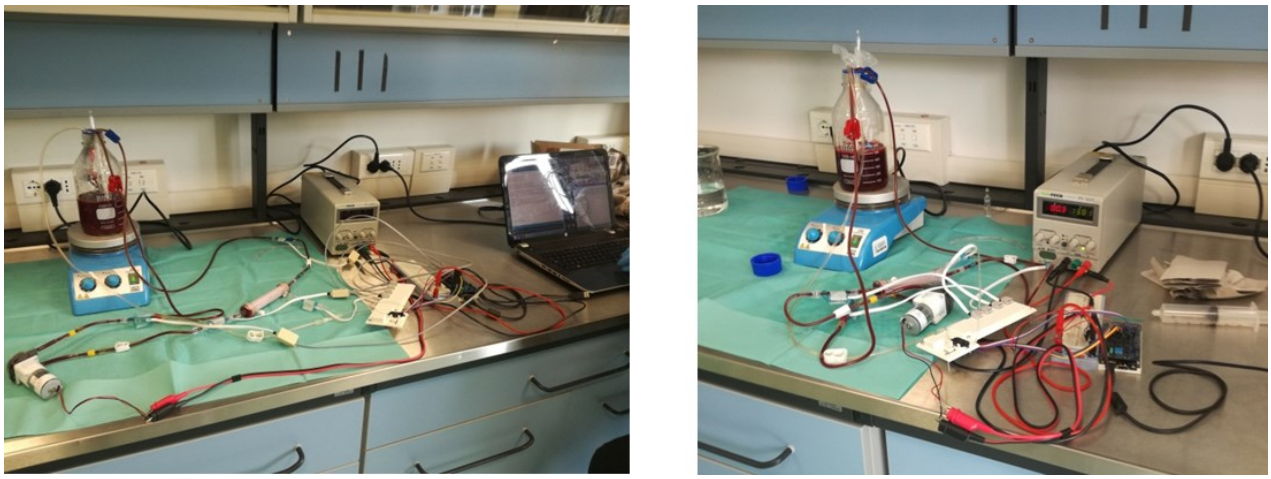


Figure 72. Setup of the in vitro experiment for testing the pressure sensors

The peristaltic pump generates a periodic pressure signal caused by the so-called peristalsis phenomenon (it can be easily recognized in Figure 73). The period of the phenomenon clearly depends on the desired blood flow, and in the end, on the velocity of the pump. Since the chosen peristaltic pump has two rolls, each complete revolution of the pump rotor produces two peristalsis phenomena. In terms of blood flow, the target is between 50 and 70 ml/min which, based on the diameter of the rotor and of the pipe, is achieved by running the pump at about 42-60 rpm, but since there are 2 rolls, it means that the period of the peristaltic phenomenon is between 0.5 and 0.7 seconds corresponding to a frequency between 1.4 and 2 Hz. Based on these evaluations, a 20 Hz sample rate seems far enough to catch the phenomenon.

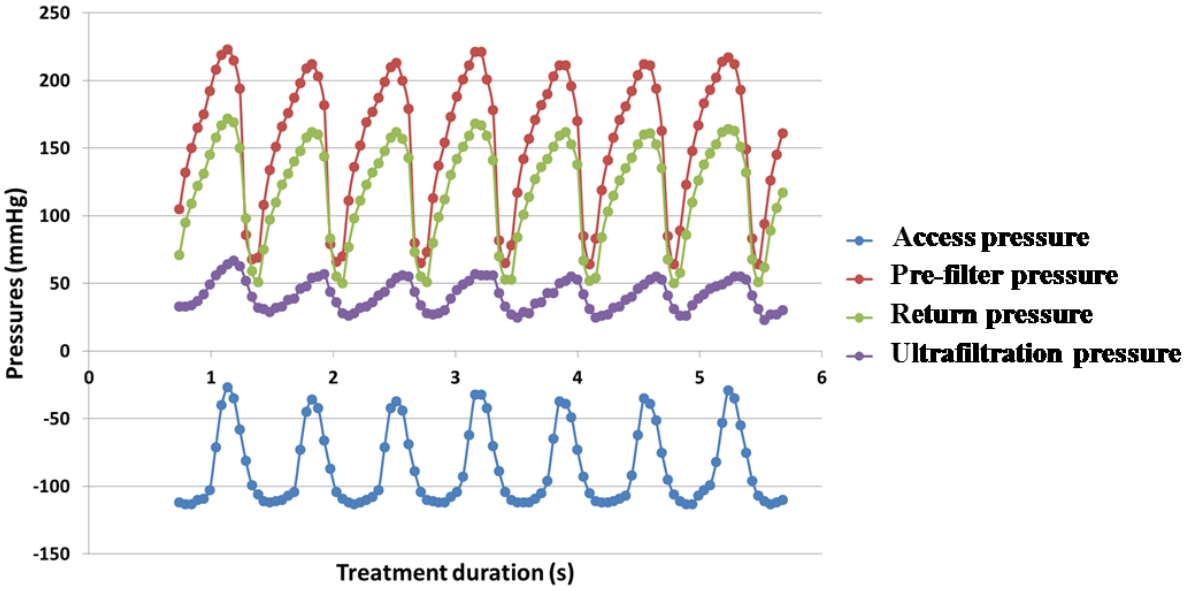


Figure 73. Typical signal patterns read by the sensors during the ultrafiltration therapy

One the one hand it is appropriate to reduce the peristalsis phenomenon in the signals in order to minimize the risk to generate wrong alarms (apparent pressure peaks above the maximum limits), on the other the detection of the peristalsis phenomenon can be usefully exploited to measure the pump rotor velocity and to check whether the device is running properly. In order to meet both these requirements the sensor signals have been low-pass filtered by a 16-tap moving average filter, which introduces a cut-off frequency at about 0.5 Hz. As shown in Figure 74 by analyzing the filtered signal, the effect of an occlusion in the circuit can be detected in just 0.7 s, a period considered clinically appropriate.

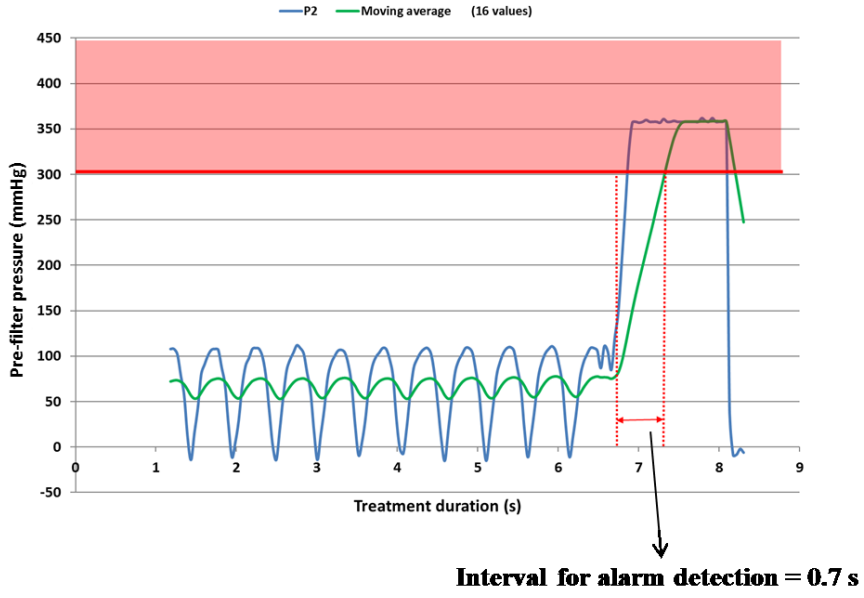


Figure 74. Original and filtered signals of pre-filter pressure sensor

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