

# Advanced Treatment of Refractory Congestive Heart Failure by Peritoneal Ultrafiltration with Icodextrin in Patients without End-Stage Renal Disease

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## Chapter

# Advanced Treatment of Refractory Congestive Heart Failure by Peritoneal Ultrafiltration with Icodextrin in Patients without End-Stage Renal Disease

*Božidar Vujičić, Koraljka Benko, Ana Petretić, Nenad Nemarnik, Matko Spicijarić, Dean Markić, Matej Bura, Fabio Kadum, Sanjin Rački and Alen Ružić*

## Abstract

In patients with Congestive Heart Failure (CHF), neurohormonal activation leads to fluid overload that can be treated with high doses of furosemide unless diuretic resistance and hyponatremia develop. End-stage CHF, including patients with normal or slightly deteriorated kidney function, can resist medical treatment. In some cases of refractory CHF, ultrafiltration (UF) is required. To manage a refractory CHF population, extracorporeal UF is commonly used as an emergency treatment, but peritoneal UF should be considered a follow-up therapy option. This method offers potential advantages over extracorporeal therapies, including better preservation of residual renal function, tighter control of sodium balance, less neurohumoral activation, and the possibility of daily treatment in the home environment. Using glucose as an osmotic agent leads to the deterioration of the peritoneal membrane. The UF properties of icodextrin depend on the dwell time, whereby the maximum effect of icodextrin concerning glucose is achieved at a prolonged dwell time. Icodextrin may offer improved peritoneal membrane biocompatibility compared with conventional glucose-based dialysates by decreasing glucose exposure, iso-osmolality, and reduced carbonyl stress. The proper anesthesia technique and surgical approach for peritoneal dialysis (PD) catheter placement in CHF patients must be based on the patient's characteristics, available equipment, and surgeon's experience. An open procedure using a transversus abdominis plane block for PD catheter placement in patients with CHF is strongly recommended.

**Keywords:** chronic heart failure, heart failure treatment, peritoneal catheter placement, peritoneal ultrafiltration, refractory chronic heart failure

## **1. Introduction**

Congestive Heart Failure (CHF) is a severe and common disease affecting up to 10% of adults. In patients with CHF, neurohormonal activation leads to fluid overload that can be treated with high doses of furosemide unless diuretic resistance and hyponatremia develop. End-stage CHF, including patients with normal or slightly deteriorated kidney function, can resist medical treatment. This patient group requires frequent hospitalizations for electrolyte imbalance, dyspnea, orthopnea, and oliguria. In some cases of refractory CHF (RCHF), ultrafiltration (UF) is required. To manage an RCHF population, extracorporeal UF is commonly used as an emergency treatment, but peritoneal UF (PUF) should be considered a follow-up therapy option.

Schneierman first reported using PUF successfully in heart failure (HF) [1]. Mailloux et al. concluded that PUF may be helpful in cardiac patients with concomitant renal impairment, electrolyte imbalance, preparation for cardiac surgery, and rapid deterioration of a previously stable cardiac state [2]. It has been known that PUF does not alter the course of HF but improves the congestive condition by correcting electrolyte imbalance, re-responsiveness to diuretics, weight loss, and overall clinical improvement [2]. A prospective non-randomized study including 20 patients with New York Heart Association (NYHA) class IV showed regression to NYHA class I, left ventricular systolic function recovery, a significant reduction in hospitalization days, and first-year mortality lower than expected [3]. Another prospective non-randomized study from 2010 enrolled 17 patients with RCHF initially treated with extracorporeal UF and PUF. All patients improved their NYHA functional status within the first 3 months, and hospitalization days significantly decreased after 1 year [4]. Using an intraperitoneal solution such as icodextrin promotes a slow and efficient PUF that cardiac patients tolerate better, is less invasive, improves residual renal function, and improves quality of life and clinical symptoms.

Therefore, proposing PUF for long-term outpatient treatment of RCHF seems reasonable.

## **2. Congestive heart failure**

HF or CHF is an inadequate ability of the heart to meet patients' metabolic demands. According to the current guidelines (European Society of Cardiology, 2021), it is defined as a complex clinical syndrome presenting with typical symptoms (fatigue, breathlessness, and ankle swelling) that can go together with signs (elevated venous pressure, pulmonary crackles, or peripheral edema). HF is caused by structural and/or functional heart abnormalities, which lead to high intracardiac pressures and/or reduced cardiac output [5].

The definition should involve elevated natriuretic peptide levels (brain natriuretic peptide—BNP, or N-terminal pro-brain natriuretic peptide—NTproBNP), which are a group of hormones produced by the myocardium cells and are released in the bloodstream in response to the wall stress [6].

The incidence of HF increases because of population aging and has become a leading cause of hospitalizations among patients over 65 [5].

Many conditions can cause HF. This includes high blood pressure, coronary artery disease (CAD), valvular heart disease (VHD), cardiomyopathies, arrhythmias, myocarditis, congenital heart disease, thyroid disease, chronic kidney disease (CKD), anemia, or toxic myocardium damage (alcohol, heavy metals, and chemotherapeutics).

## 2.1 Classification

The most used HF classification is based on left ventricular ejection fraction (EF). There are traditionally three phenotypes: HF with reduced ejection fraction (EF  $\leq$  40, heart failure with reduced ejection fraction (HFrEF)), HF with a mildly reduced ejection fraction (EF 41–49%, heart failure with mildly reduced and preserved ejection fraction (HFmrEF)), and HF with preserved EF (EF  $\geq$  50%, HFpEF) (**Figure 1**). EF is usually obtained by echocardiography. The explanation for this classification lies in many clinical treatment trials that showed different outcomes and heterogeneity between phenotypes.

Classification based on symptom severity and physical activity is the NYHA classification. NYHA has four functional classes (I–IV). Patients in class I have no limitation of physical activities, and there are no HF symptoms in ordinary physical activity. In contrast, patients in NYHA class IV have severe symptoms at rest and during minimal activity (**Figure 2**).

There are two main presentations of HF: acute and chronic. Acute heart failure (AHF) is a rapid or gradual onset of symptoms that require medical attention and/or hospitalization. AHF can be the new onset of HF (first manifestation, newly diagnosed) or, more often, decompensation of known chronic HF [5]. Besides left ventricular failure, there can be right ventricular failure (RVF). It is primarily due to left heart disease with secondary pulmonary hypertension, but there are some conditions in which RVF is isolated (arrhythmogenic right ventricular cardiomyopathy, RV myocardial infarction, etc.) [5].

Many HF patients worsen over time and progress into advanced HF. It is defined as persistent symptoms despite optimal therapy. Those patients often have systemic or peripheral congestion that requires high doses of diuretics or procedures like renal replacement therapy (RRT).

The incidence of advanced HF is increasing due to the aging of the population, a growing number, and better survival of HF patients. The criteria needed to define advanced HF include severe HF symptoms (NYHA III-IV) despite optimal medical therapy (OMT), severe cardiac dysfunction (defined by at least one of the following:

Type of HF	HFrEF	HFmrEF	HFpEF
	Symptoms with/without signs	Symptoms with/without signs	Symptoms with/without signs
	LVEF $\leq$ 40%	LVEF 41 – 49%	LVEF $\geq$ 50%
			Evidence of cardiac structural and/or functional abnormalities Raised natriuretic peptides

HF – heart failure, HFrEF – heart failure with reduced ejection fraction, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, LVEF – left ventricular ejection fraction

**Figure 1.**  
 Chronic heart failure definition and classification based on ejection fraction.

## Heart failure classification based on symptoms severity and physical activity

NYHA class	
I	No limitation of physical activities and no heart failure symptoms in ordinary physical activity
II	Mild symptoms and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest
IV	Severe limitations, symptoms even while at rest. Mostly bedbound patients

NYHA – New York Heart Classification

**Figure 2.**

*Chronic heart failure classification based on symptoms severity and physical activity.*

EF  $\leq$  30%, isolated RVF, severe and non-operable valve abnormalities, severe and non-operable congenital abnormalities, persistently high natriuretic peptides levels, and severe left ventricular diastolic dysfunction), episodes of congestion (systemic or pulmonary, requiring the use of high dose intravenous diuretics), attacks of low output states (requiring inotropes or vasoactive agents) or malignant arrhythmias causing more than one hospitalization in the last year, and severe impairment of exercise capacity (**Figure 3**). Further classification of advanced HF patients and assessment

All of the following despite optimal medical treatment
1. NYHA III or NYHA IV functional class
2. Severe cardiac disfunction; at least one of the following: <ul style="list-style-type: none"> <li>- LVEF <math>\leq</math> 30%</li> <li>- isolated RV failure (e.g., ARVC)</li> <li>- non-operable severe valve abnormalities or non-operable severe congenital abnormalities</li> <li>- high (or increasing) BNP or NT-proBNP values and severe LV diastolic dysfunction or structural abnormalities (according to the definitions of HFpEF)</li> </ul>
3. Pulmonary or systemic congestion that requires high-dose i.v. diuretics (or diuretic combinations) or episodes of low output requiring inotropes/vasoactive drugs <ul style="list-style-type: none"> <li>- malignant arrhythmias causing <math>&gt;1</math> unplanned visit or hospitalization in the last 12 months</li> </ul>
4. Severe impairment of exercise capacity with inability to exercise

NYHA – New York Heart Association, LVEF – left ventricular ejection fraction, RV – right ventricular, ARVC-arrhythmogenic right ventricular cardiomyopathy, BNP = B-type natriuretic peptide, NT-proBNP = N-terminal pro-B-type natriuretic peptide, HFpEF – heart failure with preserved ejection fraction

**Figure 3.**

*Advanced heart failure definition criteria (ESC2021).*

of advanced therapy can be done using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles [5].

## 2.2 Pathophysiology

Pathophysiologically, HF is defined as the inability of the heart as a pump to maintain the metabolic needs of the human body (failure to maintain adequate cardiac output). In this context, HF can be divided into systolic and diastolic dysfunction and left-sided and right-sided HF.

The most common cause of systolic dysfunction is ischemic heart disease. Other causes include dilated cardiomyopathy, chronic volume and pressure overload, chronic pulmonary diseases, and heart rhythm disorders. Diastolic dysfunction is most commonly due to pressure overload conditions causing pathological hypertrophy, not allowing the ventricle to relax. Common causes include hypertension, aortic stenosis, hypertrophic, and restrictive cardiomyopathy [7]. Cardiac output results from stroke volume and heart rate. Stroke volume is dependent on cardiac contractility (the inotropic state of the heart), preload (stretching of the cardiac myocytes before contraction), and afterload (the pressure that the heart needs to overcome to eject blood) [8].

In systolic dysfunction, the cardiac contractility is impaired, causing a decrease in stroke volume and, subsequently, a reduction in cardiac output, resulting in global hypoperfusion. At the same time, left ventricular end-diastolic pressure is elevated, resulting in increased left atrial pressure and causing a rise in pulmonary capillary pressure. These changes lead to pulmonary venous congestion.

Diastolic dysfunction is characterized by the inability of the left ventricle to adequately relax in diastole due to abnormal stiffness of the left ventricular wall. The result is an increased ventricular filling pressure with a subsequent increase in the pulmonary circulation pressure. Systolic function is usually maintained; however, in the setting of chronic pressure overload, it can also be impaired.

Right-sided HF is most commonly a result of left-sided HF; however, it can also develop as an isolated entity, secondary to pulmonary diseases (“cor pulmonale”) and due to increased right ventricular afterload. The main clinical presentation, in this case, is systemic venous congestion with minimal to no pulmonary congestion [9].

## 2.3 Prognostic factors

Despite the new therapeutic options (mainly for HFrEF), HF remains a progressive disease with a poor prognosis and a five-year survival rate of nearly 50% [10].

Prognostic factors related to higher mortality rates are advanced age (especially >75 y/o), male sex, and comorbidities such as diabetes, CKD, peripheral artery disease, atrial fibrillation, higher body mass index (BMI), lower systolic blood pressure, and chronic obstructive pulmonary disease [11].

Studies have shown that the mortality rate also increases with the number and duration of hospitalizations for HF. Regarding EF, HFpEF patients generally have a better survival rate than HFrEF patients. Transition in EF can also occur, and patients who progress to a lower EF have worse outcomes than those who remain stable or progress to a higher EF [5].

Laboratory tests such as natriuretic peptides, C-reactive protein (CRP), and serum sodium levels are also helpful in assessing patient prognosis. Serial natriuretic peptide measurements are used not only as a diagnostic tool but also to determine the efficacy of HF treatment and to evaluate prognosis. Patients with elevated levels of NT-proBNP and CRP correlate with worse clinical outcomes than those without elevation of both markers. Hyponatremia (serum sodium level of less than 135 mmol/L) is linked with increased mortality rates in HF patients. Diabetes is associated with worse clinical outcomes and greater hospitalization rates [12].

### **3. Chronic kidney disease**

CKD is classified into five stages according to the degree of kidney damage or glomerular filtration rate (GFR). Thus, patients with stage five CKD have a GFR of less than 15 ml/min/1.73 m<sup>2</sup> and are in the terminal stage of the disease: end-stage renal disease (ESRD). A better understanding of CKD, accompanied by the technological and scientific assumptions of dialysis techniques and kidney transplantation, has significantly improved the prognosis and survival of patients with ESRD. Despite the improvement of technology and clinical and scientific progress in treatment with RRT methods, the frequency of non-renal complications that significantly affect the morbidity and mortality of patients is increasing. The most important are cardiovascular complications, which impact treatment outcomes the most. Cardiovascular diseases are frequent in CKD, especially in ESRD, and are responsible for 40–60% of mortality in that population, according to data from national registries. The importance of cardiovascular diseases has been increasing in recent years with the appearance of an increasing number of elderly patients in whom diabetes and vascular diseases have led to CKD. In recent years, we have witnessed significant progress in understanding the causes and pathophysiology of cardiovascular diseases (CVD) and the possibilities of diagnosis, treatment, and prevention. Knowledge of the pathogenesis of cardiovascular complications, modern diagnostic options, methods of recognition, and treatment of these complications is of great importance to nephrologists and other doctors who care for ESRD patients.

Cardiovascular risk factors appear in the earlier stages of CKD and become more frequent in patients who begin treatment with renal replacement therapy. Risk factors for cardiovascular disease in patients with CKD include those that favor the development of ischemic heart disease, CHF, and left ventricular hypertrophy. Numerous risk factors, of which only general ones present in the general population, cannot explain the high incidence of cardiovascular diseases in patients with CKD. Timely diagnosis of CKD and effective treatment can delay the progression of CKD and the onset of ESRD. In the first and second stages of CKD, patients are usually checked by their family doctor. In the third stage of CKD, it is necessary to pay attention to the early metabolic complications of the disease. The fourth stage of CKD is the introduction to ESRD, and at that stage, the patient needs to be thoroughly familiarized with the RRT methods. Kidney and heart disease interaction manifests in the cardiorenal syndrome, which could significantly cause the worsening of both diseases. The clinical course of CKD is accompanied by numerous complications: renal anemia, mineral-bone disorders, progression of atherosclerosis, deterioration of CHF, development of protein-energy wasting, dyslipidemia, CVD, infections, diseases of the immune system, gastrointestinal disorders, neurological disorders, and others.



## **4. Cardiorenal syndrome and chronic heart failure treatment**

### **4.1 Cardiorenal syndrome: classification and pathophysiology**

Cardiorenal syndrome (CRS) results from inadequate heart and kidney function. It is caused by acute or chronic dysfunction of one of the mentioned organs, which then leads to acute or chronic dysfunction of another organ. The heart and kidneys jointly aim to regulate numerous processes in the human body, such as blood pressure, electrolyte and fluid homeostasis, and endocrine functions through natriuretic peptide, renin, erythropoietin, and vitamin D3. Because of the above, it is unsurprising that one organ's dysfunction leads to another's disorder. The term CRS itself was mentioned in 1951, and since then, numerous papers have been written to explain the pathophysiological mechanisms of the syndrome [13]. One of the most significant works on the mentioned topic was published in 2009. It resulted from the consensus conference of the Acute Dialysis Quality Initiative [14]. The paper above describes five subtypes of the syndrome, depending on whether it is caused by a primary disorder of the heart or the kidneys, and whether the onset is acute or chronic or is a result of a secondary process. Types 1 and 2 imply an acute or chronic heart disorder that leads to kidney dysfunction. Types 3 and 4 represent the opposite situation when acutely or chronically impaired kidney function leads to cardiac dysfunction. Type 5 represents a systemic process that leads to dysfunction of both organs.

Many authors have used observational and retrospective studies as precious sources to determine the epidemiological data of the syndrome. Uduman concluded that CRS type 1 is the most common. Given the lack of data sources, it is tough to distinguish the frequency of chronic types 2 and 4 [15]. A group of authors in India concluded with a cross-sectional study that around half of the observed patients with CRS had type 1, type 2, and type 4 prevalences of around 20% each. Representation of types 3 and 5 was only a few percent [16].

Recent papers by American scientists show how CKD affects 15–20% of adults globally. The leading cause of death in that population is CVD [17]. Also, a group of authors from Japan in the prospective cohort study called CKD-ROUTE have shown that the prevalence of CVD among CKD patients is around 26.8% [18]. The British authors did a similar study called CRISIS, presenting a slightly higher prevalence of 47.2% [19]. Vice versa, studies have shown that the prevalence rate of CKD in HF patients is 11 times higher than in the general population [20].

#### *4.1.1 Type 1: acute CRS*

CRS type 1 represents an acute worsening of heart function caused by AHF, acute coronary syndrome (ACS), or cardiogenic shock, leading to kidney injury and/or dysfunction [14]. All treatment strategies are explained in ESC guidelines, depending on the event's cause. Avoiding all potential nephrotoxins, such as contrast solution, and carefully monitoring cardiac and renal biomarkers is very important. The studies have shown that almost 30% of the patients hospitalized due to AHF had worsening renal function, which led to a higher number of deaths, complications, and longer length of stay [21]. One of the most important mechanisms leading to acute kidney injury (AKI) is lower kidney perfusion due to lower cardiac output and activation of the renin-angiotensin-aldosterone system (RAAS) [22]. Also, the critical mechanism is diuretic resistance of the kidneys, probably caused by sodium retention and the already-mentioned contrast-induced nephropathy.

#### *4.1.2 Type 2: chronic CRS*

Chronic CRS is caused by CHF, which leads to kidney injury or dysfunction. This mechanism has several causes, including chronic hypoperfusion of the kidneys, venous congestion, endothelial dysfunction, subclinical inflammation, and rapid atherosclerosis. Management strategy of this type is the same as the previous one: treat the primary cause of HF according to ESC guidelines and avoid nephrotoxins and prerenal factors that can lead to AKI. Due to CHF as a cause, kidney injury or dysfunction often progresses to CKD. As mentioned before, sometimes it is tough to distinguish the primary cause of CRS, whether CHF or CKD arose and caused CRS type 2 or 4. In some cases, cardiac re-synchronization or RRT can be used. A critical study was published in 2007 in the prestigious American Journal of Cardiology. In this clinical trial, almost 8000 patients with CKD were divided into two groups, depending on their EF. The patients were divided into systolic and diastolic HF subgroups; the cut-off value was EF 45%. The study has shown that CKD-associated mortality was higher in those with diastolic than systolic HF. Precisely, in the diastolic HF group, extra deaths per 10,000 person-years were 71% higher [23].

#### *4.1.3 Type 3: acute renocardiac syndrome*

In types 3 and 4 CRS, as the word order tells, the worsening of the kidney function leads to heart injury and/or dysfunction. Type 3 represents an acute worsening of kidney function or AKI. According to Kidney Disease: Improving Global Outcomes (KDIGO) foundation guidelines, the criteria for AKI are an absolute 0.3 mg/dL rise within 48 hours or a 50% relative rise in serum creatinine over 7 days. It is essential to mention that KDIGO was established by the National Kidney Foundation of the United States, and the mentioned guidelines are from 2012 [24]. The causes of AKI are numerous, and some of them are acute pyelonephritis, glomerular or tubular diseases, hypoperfusion of the kidneys, and obstruction of the urinary tract. Consequences of AKI can be fluid and sodium retention, a disorder of electrolytes or humoral mediators and toxemia. All mentioned could cause ACS, cardiac arrhythmias, or AHF. Sometimes, it is hard to determine whether the heart or kidney acute dysfunction appeared first. An excellent example of the connection between types 1 and 3 is called cardiac surgery-associated AKI. The probable etiology of AKI is renal hypoperfusion during the procedure, as well as hemodilution, hypothermia, and inflammatory responses, which cause constriction of afferent arterioles. After the procedure, a low cardiac output state with persistent hypotension worsens the patient's condition. It leads to CRS type 1 [25]. Consequently, AKI leads to fluid overload, which causes further deterioration of cardiac dysfunction or CRS type 3.

#### *4.1.4 Type 4: chronic renocardiac syndrome*

In some patients, CKD leads to heart disease, injury, and dysfunction. It is described as type 4 CRS. As mentioned before, the leading cause of death in patients with CKD is CVD, and the prevalence of CVD correlates with the stage of CKD. It is essential to define the criteria for CKD as abnormalities of kidney structure or function for more than 3 months. Cause, GFR, and albuminuria categories must be classified [26]. Very often, CKD has a place in cardiology guidelines together with arterial hypertension and diabetes. Those three chronic conditions coexist in most patients, leading to vascular stiffness, cardiac and renal fibrosis, left ventricular

hypertrophy, sodium, and volume overload. Another important mechanism is anemia in CKD, which can cause peripheral ischemia and activation of RAAS and, consequently, sodium and volume retention. Vascular stiffness is one of the leading causes of CVD. It results from numerous events such as chronic inflammation and oxidative stress of the vessel, mineral and bone disorder, chronic uremia, and hyperphosphatemia, which causes soft tissue calcification.

#### 4.1.5 Type 5: secondary CRS

The last type of CRS is caused by a systemic condition that leads to heart and kidney injury and/or dysfunction. That condition can be acute or chronic. Some causes are sepsis, amyloidosis, diabetes, and systemic lupus erythematosus. Recently, published papers have shown that sepsis-associated AKI (S-AKI) is a frequent complication with 12% up to 33% incidence [27, 28]. As expected, patients with S-AKI had much worse outcomes. A group of Chinese authors published a systematic review and meta-analysis, which included 47 observational studies and more than 55 thousand patients [29]. The study has shown that 20 factors were statistically significant as predisposing for S-AKI. Some are septic shock, hypertension, diabetes mellitus, abdominal infection, vasopressor administration, etc. Type 5 is probably the most complex type to determine because chronic conditions, such as hypertension, diabetes, or amyloidosis, can be a part of some other CRS subtype. Similar to previous types, to prevent *circulus vitiosus*, the aim is to cure the primary cause.

## 4.2 Treatment of heart failure with reduced ejection fraction (HFrEF)

The main goals of treatment of HFrEF ( $EF \leq 40\%$ ) are reduction in overall mortality, prevention of recurrent hospitalizations, and improvement in quality of life. The cornerstone of treatment consists of pharmacological therapy that should be applied before other interventions, according to the 2021 European Society of Cardiology Guidelines for diagnosing and treating acute and chronic HF and the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.

Renin-angiotensin-aldosterone system (RAAS) blockers, beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA) are recommended as the baseline treatment for these patients. In addition to this therapy, the sodium-glucose cotransporter two inhibitors (SGLT2I) are recommended to reduce cardiovascular and all-cause mortality due to worsening HF regardless of diabetes status. A general recommendation is to titrate all these drugs to maximally tolerated doses to improve outcomes (**Figure 4**). Loop diuretics are recommended for the reduction of symptoms and improvement in clinical status. Diuretics reduce the number of hospitalization days but do not decrease the risk of death in these patients. Angiotensin-converting enzyme (ACE) inhibitors are the first group of drugs that reduced mortality in clinical trials, including patients with HFrEF. The primary mechanism of action is a reduction in afterload, preload, and shear stress on the myocardial wall, which results in increased cardiac output and renal blood flow and a reduction in myocardial remodeling. Angiotensin-receptor blockers (ARB) are recommended to reduce cardiovascular mortality and hospitalizations related to HF in patients intolerant to ACE inhibitors. However, according to clinical trials, ARBs did not show a decrease in all-cause mortality.

In addition to ACE inhibitors with diuretics, BB substantially decreases mortality and morbidity and improves quality of life. It should be initiated immediately in

BB	ACE – I/ARB/ARNI	MRA	SGLT2I
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BB - beta-blocker, ACE – I - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker, ARNI - angiotensin receptor-neprilysin inhibitor, MRA - mineralocorticoid receptor antagonist, SGLT2I - sodium- glucose co-transporter 2 inhibitor

**Figure 4.**  
Treatment of HFrEF for all patients - to reduce mortality.

hemodynamically stable, euvolemic patients. Bisoprolol, carvedilol, and metoprolol succinate are three BBs that reduce mortality and the number of hospitalization days. MRA, alongside ACE inhibitors and BB, also reduce the mortality risk of hospitalization days and improves symptoms; therefore, they should also be initiated as the first-line treatment in patients with reduced EF, but with caution in patients with impaired renal function and elevated serum potassium. Eplerenone is preferred because of its fewer side effects.

Newer clinical studies with angiotensin-receptor-neprilysin inhibitors, in comparison with ACE inhibitors, showed high superiority in reduction of cardiovascular and all-cause mortality, the number of hospitalizations due to worsening of HF, as well as improvement in clinical status and possible diuretic reduction [30].

Another significant approach to managing HFrEF is cardiac device treatment and rhythm control (**Figures 5 and 6**). Some antiarrhythmic drugs reduce sudden death rates but do not reduce all-cause mortality. Some may even increase mortality in primary prevention of sudden cardiac death (SCD); implantable cardioverter defibrillators (ICD) are used instead to reduce all-cause mortality and prevent SCD in patients with reduced EF, which are expected to survive for more than 1 year with good functional status [31].

In primary prevention, ICD is indicated in patients with symptomatic HF of ischemic etiology and EF of 35% and lower despite OMT in 3 months or more to

Diuretics
ICD, CRT – P, CRT – D

ICD - implantable cardioverter-defibrillator; CRT – P - cardiac resynchronization therapy pacemaker, CRT – D - cardiac resynchronization therapy with defibrillator

**Figure 5.**  
Treatment of HFrEF for selected patients -to reduce hospitalisation/mortality.

Atrial fibrillation	Anticoagulation, PVI, digoxin
Coronary artery disease	Revascularization – PCI, CABG
Valvular heart disease (AS, MR)	TAVI, MV repair

PVI – pulmonary vein isolation, PCI – percutaneous coronary intervention, coronary artery bypass graft, AS – aortic stenosis, MR – mitral regurgitation, TAVI – transcatheter aortic valve implantation

**Figure 6.**  
Management of comorbidities.

reduce all-cause mortality. The same criteria should be considered in other etiologies of HF as clinical trials in those patients also showed a reduction of all-cause mortality with significant evidence but with lower absolute benefit because patients with non-ischemic cardiomyopathy have a lower risk of SCD.

In secondary prevention, it is recommended to use ICD in patients who suffer from a ventricular arrhythmia causing hemodynamic instability unless there is a reversible cause or a recent myocardial infarction occurred in the last 48 hours before arrhythmia. Cardiac resynchronization therapy (CRT) implies the implantation of a three-electrode pacemaker or implantable defibrillator (one electrode for the right atrium and two for each ventricle) that improves cardiac function and quality of life. This type of therapy showed a reduction of morbidity and mortality in selected patients with vast QRS complexes who are symptomatic and have low EF (<35%) despite optimal medical therapy. In case of high-degree atrioventricular (AV) block and indication for ventricular pacing, CRT is preferred rather than right ventricular pacing, and in patients with worsening HF with EF of 35% and lower who already have implanted pacemaker or ICD, an upgrade to CRT device should be considered [5].

#### **4.3 Treatment of heart failure with mildly reduced and preserved ejection fraction (HFmrEF and HFpEF)**

Although there are no specific clinical trials in patients with mildly reduced EF, considering that these patients have some similar clinical characteristics to patients with reduced EF, equal medical treatment can be deemed to act on further myocardial remodeling, prevent worsening HF, and reduce hospitalizations related to HF. There are some retrospective trials in which HFmrEF treatment in these patients was potentially beneficial, but more tests are required to draw evidence-based conclusions.

In the DELIVER trial, dapagliflozin (SGLT2I) reduced the combined risk of worsening HF or cardiovascular death in patients with an EF of 40% and more [32].

In the case of HFpEF (EF  $\geq$  50%), no specific treatment showed a reduction in all-cause mortality. Besides dapagliflozin, empagliflozin reduced the combined risk of the primary outcome (first hospitalization and cardiovascular mortality) in HFpEF patients, mainly due to reduced risk of hospitalization related to HF despite diabetes status [33].

Loop diuretics are used to reduce symptoms of congestion and improve quality of life, but they do not reduce overall mortality. Moreover, in HFpEF patients, there is a general emphasis on screening for comorbidities and reducing and managing underlying risk factors.

#### **4.4 Advanced heart failure management**

Management of advanced HF includes pharmacological therapy, RRT, short- and long-term mechanical circulatory support (MSC), and heart transplantation (HTx) (**Figure 7**). Regarding pharmacological treatment, inotropes (milrinone, dobutamine) and inodilators (like levosimendan) may improve symptoms, hemodynamics, and cardiac output. It can help improve heart, lung, and kidney perfusion [34]. They can also be used in chronic settings as palliative therapy in patients with no other therapeutic options.

Advanced HF is often characterized by worsening kidney function and diuretic resistance. Sometimes, high doses of intravenous potent diuretics (even in combination, like furosemide with acetazolamide, hydrochlorothiazide, indapamide,

Short-term MCS (BTR, BTD)
Long-term MCS as DT
HTx

MCS – mechanical circulatory support, BTR – bridge to recovery, BTD – bridge to destination, DT – destination therapy, HTx – heart transplantation

**Figure 7.**  
*Treatment for selected advanced heart failure patients.*

or mineralocorticoid antagonists) are needed to commence diuresis with relief of symptoms and signs of congestion. When failure of pharmacological therapy occurs, RRT should be considered. It can be used in patients with or without kidney disease. The most used modality of RRT is UF, either by central venous catheter (extracorporeal therapy) or by peritoneal catheter. Extracorporeal treatment is used more in acute settings, and central venous catheters can be placed in the internal jugular, subclavian, or femoral, usually with ultrasound guidance using the Seldinger technique. PUF is a chronic treatment modality in selected patients with resistant congestion, either as destination therapy (in patients not candidates for MCS or HTx) or in patients waiting for MCS or HTx.

In terms of insertions, MCS can be percutaneous, intracorporeal, or extracorporeal, and considering the time of their use, they can be short- and long-term support. Percutaneous MCS are intra-aortic balloon pumps, the Impella family of devices, Tandemheart, and extracorporeal membrane oxygenation (ECMO). ECMO is also considered extracorporeal MCS and can be placed peripherally or centrally. Intracorporeal MCSs are left ventricular assist devices (LVAD), right ventricular assist devices (RVAD), or biventricular assist devices (BiVAD). They are surgically placed.

Short-term MCS is used in a few clinical scenarios in patients that require urgent circulatory support (cardiogenic shock, primarily refractory to medical therapy). It can be used as a bridge to recovery, bridge to bridge, or bridge to decision. Long-term MCS, such as LVAD, can be used as a bridge to HTx, a bridge to candidacy for HTx, or as destination therapy [5].

HTx is the gold standard for treating advanced HF [5]. There must be no contraindication for HTx. Post-transplantation survival is around 90%, with improved quality of life and physical status.

Management of advanced HF is complex, challenging, and expensive. It requires dedicated expertise in highly specialized centers. There must always be a plan for stopping procedures when they become futile due to disease trajectory and disease progression with conversion to symptom control in dignified end-of-life care (palliative care).

## 5. Extracorporeal ultrafiltration

Extracorporeal UF is a mechanical pump-driven therapy that emerged as an option to overcome diuretic resistance. With this procedure, the volume and fluid removal rate is customized by clinicians to the needs and clinical characteristics of the patients.

Asymptomatic CHF patients have reduced sodium excretion in response to volume expansion compared to normal subjects. This abnormal fluid state leads to physiological abnormalities in multiple organ systems. Increased water in the myocardium can lead to ischemia and reduced contractility [35]. Hypervolemia may be related to a reduced excretion capacity or increased salt and water retention in the presence of decreased adequate circulating blood volume. The most common causes are endothelial damage, protein retention capacity, loss of plasma oncotic pressure, and reduced renal perfusion due to impaired cardiac function. Disturbed neurohormonal activation, excessive tubular sodium reabsorption, change in hemodynamics, oxidative stress, inflammation, and use of nephrotoxic drugs are essential factors of adverse cardiorenal interactions in CHF patients [36]. Diuretic agents remain the primary treatment for fluid overload. Although effective early in HF, diuretics become ineffective in the progression of the disease due to the development of unresponsiveness [37].

UF could safely improve hemodynamics in HF patients as an alternative sodium and water removal method. Some isolated schedules of UF may be too aggressive and result in severe hemodynamic instability. That is why continuous extracorporeal techniques have been applied to patients with excellent clinical outcomes. A stable hemodynamic state, good cardiovascular response, and adequate diuresis are the most common effects of continuous extracorporeal fluid removal methods. Hemodynamic instability is the driving factor behind the physician's decision to initiate extracorporeal UF, and the treatment was postponed until it became indispensable. This has been overcome with the development and availability of better-tolerated treatment modalities such as continuous RRT. Earlier intervention should always be considered because it is not justified to wait until the appearance of severe symptoms [38].

The UF process produces water from plasma in response to a transmembrane pressure gradient across a semipermeable membrane. The sieving capacity of UF membranes is responsible for the UF of crystalloids but not of cells or colloids. When hydrostatic pressure exceeds oncotic pressure, iso-osmotic ultrafiltrate is generated.

UF is performed from the patient's blood and then returned to the patient through separate access to the venous circulation. Adequate UF rates are needed for extracellular fluid to refill the intravascular space and gradually maintain sufficient blood volume. If the UF rate is too high, there is a decrease in intravascular volume, reflecting the reduction in total blood volume. Maintaining circulating blood volume, accurately determining the amount of fluid to be removed, and optimizing the fluid removal speed are essential for the success of the therapy [39]. Different techniques can be used for the hypervolemic patient to achieve an adequate fluid balance: UF, hemofiltration, and dialysis together with UF. Pure UF is only a fluid removal technique; others can simultaneously purify the blood. According to their frequency and duration, the treatments are classified as acute (single session up to 4 h), intermittent (single sessions up to 4 h repeated daily or three times a week), or continuous (24 h/day or as required).

### **5.1 Isolated intermittent ultrafiltration**

Intermittent isolated UF is carried out several hours daily to remove a desired amount of excess volume (1–2 L) [40]. The procedure can be repeated daily and uses standard hemodialysis (HD) equipment without dialysis fluid. Considering the short duration of the therapy, the effectiveness of this technique is in a higher UF rate. Sometimes, the UF rate may be too high, leading to significant hemodynamic instability. Many patients respond to diuretics again after one or more treatments with this method.

## **5.2 Slow continuous ultrafiltration**

Its primary aim is to safely and effectively manage fluid overload in refractory edema without overt acute renal failure (ARF). This technique is mainly applied in patients with CHF NYHA IV. Slow continuous ultrafiltration (SCUF) can be performed with low blood flow rates (50–200 mL/min) in the veno-venous modality. The UF rate is usually 100–300 mL/h, according to fluid balance needs. The frequent complications from arterial cannulation are the primary reason the arterio-venous modality is rarely used. It is required to control the UF rate to maintain the desired volume status. Otherwise, higher UF rates would require fluid resuscitation. No fluids are administered as dialysate or replacement fluids, as the primary purpose of treatment is to achieve volume control. However, isolated UF is not a blood purification modality and solute clearance is irrelevant. UF in SCUF is iso-osmotic and isonatric, and water and sodium removal cannot be dissociated. That is possible because sodium elimination is linked to the sodium plasma water concentration. A small surface area filter can be used with reduced heparin doses to maintain the effectiveness of the therapy because low UF and blood flow rates are required. Removing myocardial depressant factors in the ultrafiltrate, reduction in preload, and modulation of the RAAS axis seem to be possible pathophysiological mechanisms underlying clinical improvement [41].

## **5.3 Continuous veno-venous hemofiltration**

Continuous veno-venous hemofiltration (CVVH) produces a large ultrafiltrate volume across a high-permeability membrane. The advantages of CVVH include liberal fluid management, optimal clearance of uremic toxins, including middle molecules, and hemodynamic stability. The ultrafiltrate produced during CVVH is wholly or partly replaced with appropriate replacement solutions to achieve desired therapeutic goals. Replacement fluid can be infused before (predilution) and/or after (postdilution) the hemofilter. The decision on when to start CVVH should be based on the severity of organ failure and ARF. Early initiation should be considered at oliguric ARF and/or a steep rise in serum creatinine despite adequate fluid resuscitation. This method removes fluid with considerable solute clearance and blood purification [42]. The hemodynamic response is inimitable due to the possibility of dissociating water from sodium removal. In CVVH, the composition of ultrafiltrate is similar to plasma water, but sodium concentration in the replacement solution significantly affects the sodium balance.

## **5.4 Continuous hemodialysis/hemodiafiltration**

The principal advantage of continuous hemodialysis/hemodiafiltration (CVVHD/HDF) is the ability to remove large volumes of fluid, avoiding the hypotensive episodes caused by intermittent HD. It is indicated for managing patients with ARF who are hemodynamically unstable and/or must receive large volumes of fluid or both. UF volumes are optimized to exceed the desired volume of excess water. Solute removal is both diffusive and convective. To perform a successful CVVHD/HDF, optimal clinical tolerance to fluid removal is critical. In a setting of too aggressive UF, blood volume may decrease due to a too-slow intravascular refilling, leading to severe hemodynamic instability [43].



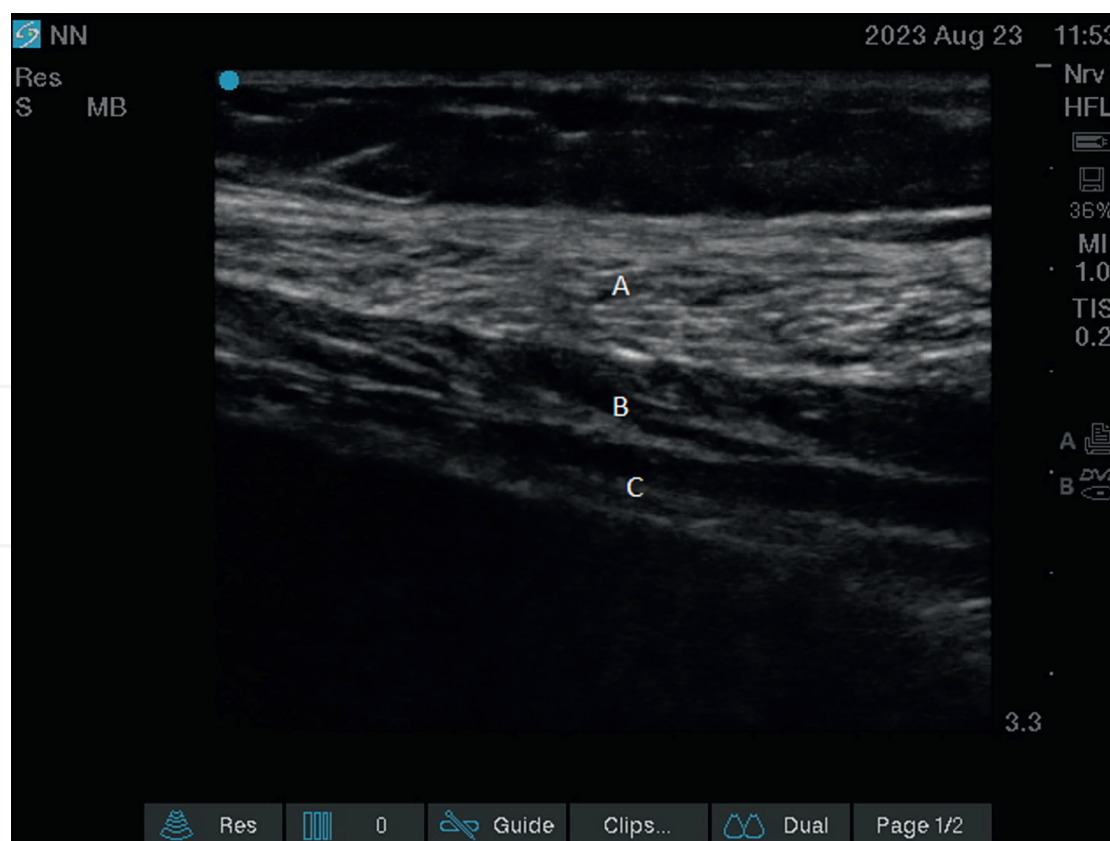
## 6. The peritoneal dialysis catheter placement in patients with chronic heart failure: anesthesiology and surgical perspective

Adequately positioned peritoneal dialysis (PD) catheter is necessary for successful long-term PUF [44]. PD catheter insertion can be performed using different surgical methods, such as open approach, laparoscopy, and peritoneoscopy, or percutaneously [45, 46]. For all of these procedures, some anesthesia is required. The anesthesia techniques used for PD catheter placement are general (most utilized), spinal, regional, and local anesthesia [47].

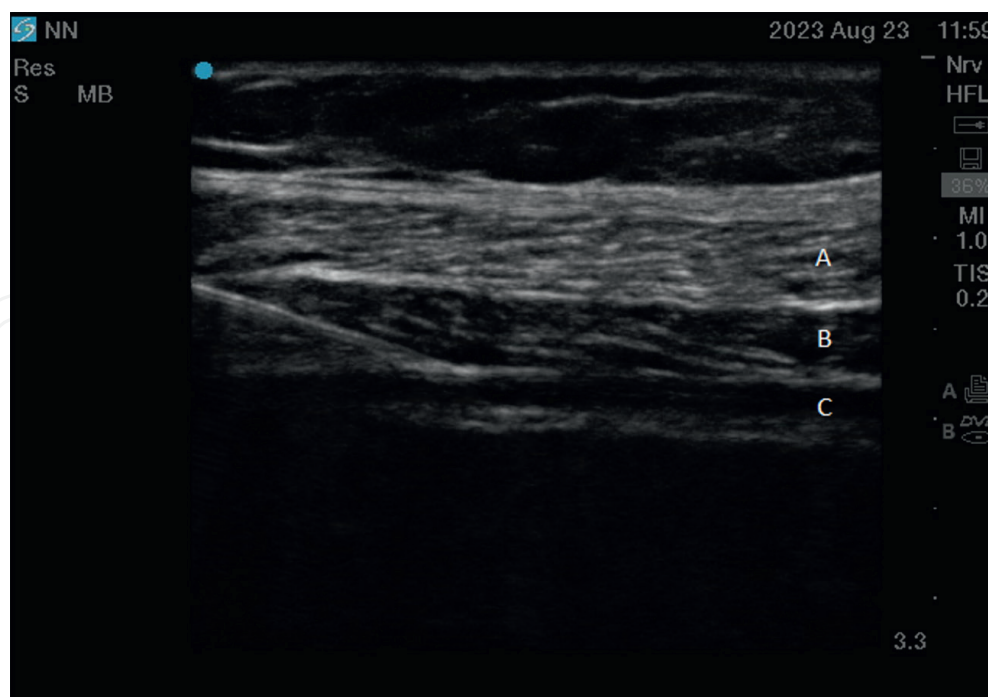
### 6.1 Anesthetic considerations, including transversus abdominis plane block

PD catheter placement using an open approach usually requires general, neuraxial, and rarely local anesthesia. Local anesthesia is preferable for patients with significant comorbidities. However, the local infiltration of an anesthetic can produce edema and bleed at the incision site, which disturbs the surgical field. In most patients, especially obese ones, local anesthetic infiltration must be repeated, which can be connected with the patient's fear and anxiety. General anesthesia is usually required for laparoscopic PD catheter placement [46].

The CHF patients represent a group with an increased risk for anesthetic procedures, especially general anesthesia. For this reason, less invasive methods and



**Figure 8.** Ultrasound image (linear ultrasound probe) visualised all three muscles of the abdominal wall: external oblique (A), internal oblique (B), and transversus abdominis muscle (C). The space between the internal oblique and transversus abdominis muscles (transversus abdominis plane) is a target area for applying a local anaesthetic. (Author's archive).



**Figure 9.** *Ultrasound image (linear ultrasound probe) showing a plane needle and needle tip positioned in the transversus abdominis plane just before injecting the local anaesthetic. All three muscles of the abdominal wall are visualised: external oblique (A), internal oblique (B) and transversus abdominis muscle (C). (Author's archive).*

techniques are being used. One of these is the transversus abdominis plane (TAP) block. It is a newer regional anesthesia technique, more precisely, a type of peripheral nerve block. The target area is a fascial layer between the transversus abdominis and internal oblique muscles. In this plane are situated thoracolumbar nerves (T7-L1), which supply the anterolateral abdominal wall (**Figures 8 and 9**). Using a TAP block, analgesia from the skin to the parietal peritoneum is achieved, and recently, a TAP block was used for PD catheter surgery [48, 49].

We recommended a combined ultrasound-guided subcostal and posterior approach using a linear, high-frequency probe (6–15 MHz) as we described previously [48, 49]. Briefly, when the TAP is identified, the needle is advanced in the targeted area, and local anesthetic is injected. In most patients, 30 mL of 0.25% levobupivacaine hydrochloride or 30 mL of 0.75% ropivacaine is used. Standard equipment used for patient monitoring includes an oxygen saturation probe, a non-invasive blood pressure monitor, and an electrocardiogram. Cold and pain sensation tests (pinprick) are used before the operation. About 30 minutes after the TAP block, a skin incision is possible. Just before the skin incision, all patients received additional drugs, such as sufentanil (10 mcg) and/or propofol (0.1–0.2 mg/kg), for a better analgesic/sedation effect [48, 49].

## 6.2 Preoperative management

As for any surgical procedure, patients must sign informed consent before the operation. Preoperatively, thromboprophylaxis (low molecular weight heparin) and antibiotics (cefazolin) were administered in all patients. The patient's position depends on the surgical approach, but a supine position is mainly used. The skin is disinfected with an antiseptic solution.

### **6.3 Open approach**

The patient is in the supine position. In our institution, in concordance with the patient's will, we put the PD catheter on the side of the patient's dominant hand (most often the right side). We use a vertical paramedian, infraumbilical skin incision 3–4 cm long for all patients. The incision includes skin, subcutaneous tissue, anterior and posterior rectus sheath, preperitoneal tissue, and parietal peritoneum. The PD catheter (Tenckhoff type, two cuffs) is inserted in the peritoneal cavity. Both cuffs must be outside the peritoneum. The deep cuff is usually tied with the suture, which closes the peritoneum. After completing all the layers, the PD catheter is tunneled (inverse U shape), with an exit site different from the incision site. The proximal cuff is situated in the subcutaneous tissue, and the distal cuff is preperitoneally. The skin suture for the PD catheter's fixation is unnecessary because the catheter is fixed with sutures, including a deep cuff and peritoneum [48].

### **6.4 Laparoscopic approach**

The patient is supine, with the surgeon on the right side (if the right-sided implantation is planned) and the assistant on the left side. The scrub nurse is on the side of the surgeon. The monitor is usually opposite the surgeon or near the legs. A periumbilical incision is used to create a pneumoperitoneum. In most cases, three trocars are used. One is in the camera's periumbilical position (10 mm), and two are in both lower abdominal quadrants. Through the left lower abdominal quadrant, a 5-mm trocar is placed usually for grasper, and on the right lower quadrant, the specially designed trocar (the so-called "Čala's trocar" according to his inventor). Čala's trocar is a metal trocar, with the possibility to be dismantled and through its internity, the PD catheter could be inserted (**Figure 10**) [45]. After trocar placement, the patient is placed in the Trendelenburg position, and the whole abdomen is explored. Via the Čala's trocar, a PD catheter is inserted in the peritoneal cavity using grasper for directed catheter deep in the pelvis. During catheter insertion, the deep cuff must be placed in a preperitoneal position, not in the peritoneal cavity. The Čala's trocar is dismantled and removed, and the catheter must be clamped to prevent exufflation of the peritoneal cavity. A subcutaneous tunnel is made with the finger, and a skin exit site is created. PD catheter is fixed to the skin in its exit site. After PD catheter fixation, the exufflation of CO<sub>2</sub> is performed, the trocars are removed, and their exit sites are closed.

Another trocar is placed when the deep cuff goes inside outside the peritoneal cavity. A suture is put laparoscopically to decrease the hole in the peritoneum and prevent migration of the deep cuff, which stays in an extraperitoneal position. If the patient has intrabdominal adhesions, adhesiolysis must first be performed using ultrasound or bipolar scissors.

### **6.5 Peritoneoscopic approach**

This approach is partly similar to laparoscopic and is made under local anesthesia and in the supine position. First, the pneumoperitoneum is created. The guide is then inserted through the small skin incision through the abdominal wall in the peritoneal cavity with the optical control using a small diameter endoscope (peritoneoscope). After verification of proper position, the channel is dilated, and the catheter is inserted into the abdominal cavity.



A



B



C

**Figure 10.** *Cala's trocar is a metal trocar (A), with the possibility to be dismantled (B) and through its internity, the PD catheter could be inserted (C). (Author's archive).*

## 6.6 Selecting the best method for PD catheter insertion

CHF patients have substantially more comorbid conditions than the general population, leading to higher mortality in this group of patients. General anesthesia impacts the pulmonary and cardiovascular systems contrary to peripheral nerve block and local anesthesia, whose influence is negligible. For this reason, peripheral nerve block and local anesthesia can be recommended for placing PD catheters in patients with CHF, especially those with significant comorbidities. The guideline for choosing a PD catheter insertion approach is shown in **Table 1** [50].

Compared to general anesthesia, a TAP block has increased anesthetic induction time and requires additional equipment (ultrasound), performance time, and technical skill. A TAP block provides a longer duration and better quality of analgesia

Patient's characteristics	Previous major intraabdominal surgery and peritonitis	No last major intraabdominal surgery and peritonitis
Patient suitable for general anesthesia	1. Laparoscopic approach 2. Open approach	1. Laparoscopic approach 2. Percutaneous approach (x-ray) 3. Open approach or peritoneoscopic approach 4. Percutaneous approach (without x-ray)
Patient non-suitable for general anesthesia (reconsider TAP block or local anesthesia)	1. Open approach	1. Percutaneous approach (x-ray) 2. Open approach or peritoneoscopic approach 3. Percutaneous approach (without x-ray)

*The table is modified according to the International Society of Peritoneal Dialysis (ISPD) guidelines [50].*

**Table 1.**  
 Guideline for selecting a PD catheter insertion approach.

compared to local anesthesia [51]. In our institution, the TAP block is used as a primary anesthetic technique for PD catheter surgery for all patients, but especially for elderly patients and patients with significant comorbidities. Complications from a TAP block are rare and include nerve injury, injection site bruising, infection, allergic reaction, and liver laceration [52]. Contraindications for TAP block include infection at the injection site, patient refusal or inability to cooperate, allergy to local anesthetics, and coagulopathy [53]. An elevated BMI index was not a barrier to a successful TAP block [48, 49].

## 6.7 Outcomes of different PD catheter placement approaches

The two most common methods for PD catheter placement are open and laparoscopic approach [54]. Catheter malfunction is lower in the laparoscopic approach (13%) than in open surgery (35%). The one-year catheter survival rate was higher in the laparoscopic group compared to the open surgery group, but in the other study, this difference was not found [51, 55]. Dialysate leakage, exit-site infection, and peritonitis incidence between the laparoscopic and open surgery groups were similar [56].

The successful implantation of a PD catheter using a TAP block as a primary anesthetic method is from 82.2 to 94.2% in ESRD patients [48, 49, 57–60].

Such data is not available yet for CHF patients. Still, the use of TAP block as the primary anesthetic technique for PD catheter insertion should be considered in this patient group (authors' opinion).

## 7. Peritoneal ultrafiltration

### 7.1 Peritoneal membrane

The peritoneum is the most extensive serous membrane in the body, with a total surface of about 1.8 m<sup>2</sup>. Human skin has a similar overall surface area. It helps to protect and separate the internal structures of the abdomen and pelvis.

The functions of the peritoneum:

- a. Regulation of fluid for nutrient and mechanical purposes
- b. Maintaining the position of organs by suspending them with ligaments
- c. Prevention of friction while organs move
- d. Conduction of vessels and nerves to the viscera

Peritonitis is inflammation of the peritoneum. Inflammation most often occurs as a result of a fungal or bacterial infection. Microorganisms can enter the abdomen due to an abdominal injury, some other condition such as perforation of a gastric ulcer, or during therapeutic procedures such as dialysis, esophagogastroduodenoscopy, gastrostomy. Inflammation of the peritoneum is a severe condition that requires urgent treatment. There are several types of peritonitis: acute and chronic by course, serous, fibrous, purulent, hemorrhagic by sort, diffuse, and circumscribed by localization. It can be divided into primary, secondary, and tertiary.

#### *7.1.1 Structure of the peritoneal membrane*

It consists of two layers: the parietal peritoneum (the outermost parietal layer), which surrounds the abdomen and pelvis, and the visceral peritoneum (inner visceral layer), which wraps around the abdominal organs. A potential space between the two layers contains small amounts of serous fluid (water, electrolytes, and immune cells). This fluid is a form of protection and acts as a lubricant between the layers. The parietal peritoneum covers the abdominal and pelvic walls and the diaphragm. The visceral peritoneum covers the intraperitoneal organs and forms various folds throughout the abdominal cavity. The greater omentum is a large fold of the visceral peritoneum and extends from the stomach downwards. Another fold of visceral peritoneum is the lesser omentum, which extends from the lesser curvature of the stomach to the liver. In addition to pain, the parietal peritoneum is sensitive to temperature, pressure, and laceration. The pain from the visceral peritoneum is poorly localized. It is only susceptible to extension and chemical irritation.

The visceral and parietal peritoneum has a similar histological structure: mesothelium, basal lamina, and submesothelial stroma. While mesothelium and basal lamina appear similarly throughout the abdomen, the submesothelial stroma may vary in thickness. Mesothelial cells are of mesodermal origin and, under specific conditions, can become even more similar to mesenchyme [61]. The mesothelial cells were considered inactive and contributed only to lubrication. It is known today that they play a crucial role in peritoneal homeostasis and produce a whole range of enzymes, cytokines, growth factors, and proteoglycans. They also provide the first line of defense against microorganisms and harmful chemical substances, which is why it is essential that the mesothelium can regenerate quickly and smoothly after injury.

At the basal surface, mesothelial cells are supported by the basal lamina. It consists of a layer of extracellular matrix less than 100 nm thick, composed of type IV collagen and laminin.

Connective tissue or stroma supports the mesothelial cells and the basal lamina. This supportive layer comprises collagen, mainly type I fibers, proteoglycans, fibronectin, (myo)fibroblasts, adipocytes, and blood and lymphatic vessels [62].

According to its structure, the peritoneum is a semipermeable membrane. Through its intercellular junctions and stomata, passive transport of liquids and dissolved substances takes place, as well as active transport through the formation of pinocytotic vesicles. The transport of dissolved substances and small molecules through the peritoneum occurs quickly because the stroma, basal lamina, and mesothelium do not create resistance [63]. Transportation of large molecules is possible due to the network of collagen, fibronectin, elastin, and transcellular carriers in mesothelial cells [64]. The capacity of the peritoneum to transport fluids enables peritoneal UF/dialysis. Due to dialysate in the peritoneal cavity, UF and diffusion of water, salt, and uremic toxins through the membrane occur. Chronic exposure of the peritoneum to the dialysate evokes functional and morphological adaptations of the peritoneum. Chronic inflammation, progressive fibrosis, and angiogenesis thickening of the submesothelial stroma eventually lead to its loss of UF and blood purification capacity [65].

### 7.1.2 Aquaporins

The capillary endothelium, the interstitial space of the peritoneum, and the mesothelium represent a barrier to the exchange of soluble substances and water in the capillaries of the peritoneal cavity [66]. It should be emphasized that with this transport through the “pore” of the capillary walls, solutes larger than glucose are excessively lost, and the interstitium also modifies the transport of solutes *via* the barrier mentioned above [67]. The fluid exchange across the peritoneal membrane during PD is best explained with a “three-pore” model. The spaces between individual endothelial cells (inter endothelial clefts) represent the primary route for small-solute and fluid exchange. The radius of these clefts (“small pores”) is cca. 40–50 Å. The small pores markedly impede the transit of albumin (36 Å) and ultimately prevent the passage of larger molecules, such as  $\alpha_2$ -macroglobulin and immunoglobulins. The transendothelial pathways of the “large pores” (radius approx. 250 Å) are responsible for the penetration of large proteins into the interstitium and the peritoneal cavity [68]. Osmotic water transport occurs through ultra-small, water-only pores (radius approx. 2.5 Å), to which the capillary wall is highly susceptible.

Aquaporins (AQPs) are a family of integral plasma membrane proteins. Their discovery gave us insight into the molecular mechanisms for water transport through biological membranes. AQPs are usually specific for water permeability and exclude the passage of other solutes. All AQPs are impermeable to charged solutes, and water molecules traverse the AQP channel in a single file. It was assumed that water leaked through biological membranes, but the rapid movement of water across some cells remained unexplained. Although it had been predicted that water pores must exist in very leaky cells, it was not until 1992 that Peter Agre at Johns Hopkins University identified a specific transmembrane water pore later called aquaporin-1 (AQP1). AQP1 comprises a single peptide chain consisting of approximately 270 amino acids. It is distributed in the endothelium of capillaries, venules, and small veins of the peritoneum and is functionally identical to ultra-small pores [69].

An experimental mouse model showed that AQP1 is the most represented member of the AQP family in the peritoneum and is the only one found in the capillary endothelium. It was also experimentally shown that deletion of AQP1 does not affect the expression of other AQPs and the diameter or density of peritoneum capillaries. These data prove that AQP1 is important in peritoneal transport mechanisms [70].

Under non-PD conditions, approximately 60% of the net capillary UF occurs through small and 40% through large pores. Only 1–2% of total peritoneal transport occurs through ultra-small, water-only pores.

Under PD conditions, fluid removal is mainly reinforced by an osmotic agent in the peritoneal cavity. The osmosis mechanism is markedly affected by the type of osmotic agent used. For example, glycerol (radius approx. 3 Å) is a small osmotic agent with a weak effect on small pores and primarily on ultra-small, water-only pores. Unlike glycerol, glucose (radius approx. 3.7 Å) performs its ultrafiltration effect equally through ultra-small and small pores. Polyglucose (radius approx. 15–20 Å), a high-molecular-weight osmotic agent, ultrafilters liquid mainly through small pores. Polyglucose (radius approx. 15–20 Å), a high-molecular-weight osmotic agent, ultrafilters liquid mainly through small pores [71]. It is believed that AQP1 mediates 40–50% of osmotic-induced UF. A drop in dialysate sodium concentration is expected after 60 to 90 minutes of the dwell, as free water is transported through these pores, and this phenomenon is known as sodium sieving.

The relationship between AQPs, UF capacity, and sodium filtration is still debated in PD. On the other hand, understanding the molecular structure and role of ultra-small pores is vital for clinical practice regarding patient volume optimization.

### *7.1.3 Physiologic considerations*

The final net UF in the peritoneal technique results from multiple transport mechanisms within the tissue surrounding the peritoneal cavity. Free water is transported through ultra-small pores, and an adequate volume of dialysate forces water and dissolved matter into the surrounding tissue. To achieve adequate UF from the capillaries of the peritoneum, it is necessary to maintain a high osmotic pressure in the peritoneal cavity. The osmotic pressure in the interstitium is lower than that in the peritoneal cavity. It is equal to the osmotic pressure in the plasma already in the first millimeter of tissue next to the peritoneum. Pure ultrafiltrate without dissolved substances results from the difference in osmotic pressure in the blood capillary and is produced by AQP1. If intraperitoneal pressure is too high, insufficient UF occurs. The most common reason for this is peritoneum inflammation when, due to capillary hyperpermeability, the osmotic agent quickly dissipates. Fibrosis of the peritoneum is the second possible reason because there is a reduced osmotic pressure near the blood supply, and there is no force to transport the fluid through the scar to the cavity. To solve problems in net UF, the key is to lower the volume and, secondary, the intraperitoneal pressure. Preventive measures are necessary to reduce chronic inflammation and peritonitis and preserve the peritoneal membrane and its transport characteristics.

The osmosis process is vital for transperitoneal water transport. Water moves from a low to high solute concentration area across a semipermeable membrane across all three pores. The effective surface area of the peritoneal membrane, the hydraulic conductance of the peritoneal membrane, the concentration and type of the osmotic agent used, and the influence of hydrostatic and oncotic pressure gradients across the peritoneal capillary are the factors that are responsible for the transcapillary water movement.

In the initial phase, the intraperitoneal volume is dominated by transcapillary UF. It is influenced by the crystalloid osmotic gradient created by glucose. On the other hand, it also governs relatively constant hydrostatic and oncotic pressure gradients (so-called “Starling forces”) [72]. Intraperitoneal volume increases as the



transcapillary UF rate exceeds lymphatic and tissue absorption [73]. The transcapillary UF rate decreases because of the steep decline in glucose concentration. A positive net UF occurs due to fluid transport imbalance because transcapillary UF exceeds lymphatic absorption. A state of balance in fluid transport that does not increase intraperitoneal volume is reached when the transcapillary UF rate drops to a value equal to the lymph flow rate. At that point, the intraperitoneal volume peak is reached. The negative net UF due to fluid absorption results from a difference between the decreasing transcapillary UF rate and the constant lymphatic tissue absorption, representing a new state of fluid transport imbalance.

A linear and stable decline is the second and last phase of intraperitoneal volume change. The peritoneal cavity's drainage time is responsible for the net clinical effect of peritoneal fluid movement. The drained volume may approach or even be less than the instilled volume if drainage is delayed until the end of the final phase.

Using glucose as an osmotic agent leads to the deterioration of the peritoneal membrane. Its well-known harmful effects on the peritoneum may lead to failure of the PD treatment in the mid-to-long term. With this in mind, an extensive effort has been made to find more biocompatible dialysis solutions, including icodextrin.

#### *7.1.4 Advantages and safety considerations related to icodextrin solution*

The icodextrin was launched in the mid-1990s, and its use has increased over time as more than 30,000 patients globally were receiving icodextrin treatment [74].

Different glucose concentrations in the PD solution are primarily used to meet the different UF needs. However, glucose has short-lived effects as an osmotic agent and degrades quickly in the peritoneum. Longer dwells of glucose solutions can often result in net fluid reabsorption from the dialysate into the patient rather than the expected outcome. Furthermore, glucose degradation products are formed, which harm the peritoneum, resulting in its damage in terms of fibrosis. These changes result in the peritoneum's functional inefficiency and the treatment method's viability [75]. Finally, these solutions lead to metabolic disorders such as hyperinsulinemia, hyperlipidemia, and hyperglycemia. Using icodextrin provides improved UF for long dwells compared to glucose solutions. It is also more efficient in volume status control. Further, Goossen et al.'s systematic review and meta-analysis demonstrated decreased mortality with icodextrin use [76]. Additional benefits from icodextrin are glucose-sparing properties, lipid status improvements, and echocardiographic parameters with reduced left ventricular mass.

The UF properties of icodextrin depend on the dwell time, whereby the maximum effect of icodextrin concerning glucose is achieved at a prolonged dwell time of 10–14 hours. Sometimes, full results are achieved as early as 10 hours of dwell, with minimal UF effect after that time. Compared to conventional glucose-based dialysates, icodextrin may offer improved peritoneal membrane biocompatibility by reducing glucose exposure, iso-osmolarity, and lesser carbonyl stress [77, 78]. Furthermore, the study of Posthum et al. showed that the concentrations of various peritoneal membrane markers (interleukin-8, CA125, amino-terminal propeptide of type III procollagen, and carboxyterminal propeptide of type III) did not differ between patients treated with glucose and icodextrin over 2 years [79]. Other clinical studies have confirmed that icodextrin is a safe and well-tolerated osmotic alternative solution to glucose [80]. The most significant side effect reported from using icodextrin is a skin hypersensitivity reaction [81]. Most likely, the hypersensitivity reaction is mediated by the immune complex. The peritonitis rate does not differ

between patients treated with icodextrin and those treated with glucose solutions only, which has been confirmed in several randomized, controlled studies [82]. Long-term intraperitoneal use of icodextrin can permanently increase the plasma's maltose, maltotriose, and other oligosaccharides. This is significant because elevated maltose levels can interfere with specific glucose and amylase tests [83]. Therefore, one should be careful when interpreting the results of such tests when using icodextrin.

The most common antibiotics used to treat peritonitis (vancomycin, cephalosporins, and gentamicin) are compatible and stable with icodextrin [84]. Finally, the use of icodextrin has been associated with falls in serum sodium concentration and slight increases in serum osmolality, which are usually not clinically significant.

## **7.2 Rationale for peritoneal ultrafiltration in congestive heart failure**

PUF is a treatment modality aimed at patients with diuretic-resistant CHF to control fluid retention adequately. While extracorporeal UF is more commonly used to treat acute decompensated HF, PUF has been proposed for long-term treatment of RCHF, especially in elderly patients, as a soothing therapeutic modality or as a bridge to definitive surgery or HTx. The potential benefits of this treatment modality include a quality-of-life improvement since it is a home-based therapy, better control of congestion and no need for central venous access (no problems associated with anticoagulation), and a reduction in hospitalization rates [85].

However, still unanswered questions show a need for future studies, starting with the patient inclusion criteria. According to Bertoli et al., an ideal candidate for PUF would be a patient with both CHF and CKD, on optimal medical therapy and at least three hospitalizations in the previous year. Secondly, it is still being determined if PUF would be suitable for patients with all HF types since, in most studies, patients had left ventricular systolic dysfunction [86].

## **7.3 Peritoneal ultrafiltration prescription in congestive heart failure**

The global prevalence of HF is increasing due to aging populations, insufficiently controlled cardiovascular risk factors, and prolonged survival. Significant progress has been made in treating HF in recent decades due to new disease-modifying drugs and increasingly sophisticated devices [87]. However, the effectiveness of treatment is limited in some patients, and palliative care is the only option to improve the quality of life. Although progress has been made in the treatment of heart failure with improved survival, RCHF remains a growing health problem, already a significant cause of hospitalization, with associated costs [88]. CRS is dominated by a comprehensive pathophysiology in HF, regardless of EF. It is associated with poorer outcomes, more than 40% of all-cause mortality, and is a significant driver of repeat hospitalizations. Renal venous congestion and arterial insufficiency lead to “excretory renal failure” due to critical changes in intraglomerular filtration pressure. This results in inadequate volume control that causes recurrent cardiac decompensation [89]. Extracorporeal HD or UF is an alternative for treating congestion in case of diuretic resistance. HD is conventionally reserved for patients with concomitant ESRD, and UF is more commonly used in patients without ESRD [90]. There are conflicting results from clinical studies comparing UF with pharmacological therapy. In the UNLOAD study, patients treated with UF had better control of volume status and a lower frequency of hospitalization for HF than those treated with diuretics. However, in the CARESS-HF study, there was no difference in weight loss between

patients treated with UF and those treated with higher doses of diuretics [3, 91]. More elevated serum creatinine values were observed in the group of patients treated with UF, which the authors assumed was due to a transient decrease in intravascular volume during this procedure.

More recently, there has been increased interest in UF via the peritoneal membrane with the updated terminology of PUF, reflecting the goal of fluid extraction across the peritoneal membrane [92]. PUF in RCHF reduces the incidence of decompensation episodes, which is particularly significant as each episode incrementally adds to mortality. Compared to extracorporeal therapies, this method offers potential advantages such as better preservation of residual renal function, tighter control of sodium balance, less neurohumoral activation, and the possibility of daily treatment in the home environment [93].

On the other hand, PUF offers excellent flexibility in a prescription best suited for a given patient. Success has been reported using a single-night time exchange with icodextrin. It is recommended to start the therapy with a smaller volume of the single-night icodextrin exchange and gradually increase it to the maximum tolerable level, which gives us an appropriate UF rate. The icodextrin exchange can be done twice daily in cases of greater hypervolemia. Such a prescription should be used for up to 2 weeks and then turn into one single-day exchange. An incremental therapeutic approach of the single-night exchange can be continued after achieving volume optimization of the patient, including regular outpatient monitoring. This implies pausing the therapy one or more days a week, according to the instructions of the supervising medical staff.

## **8. Conclusions**

The presence of CKD is a poor prognostic factor in patients with CHF, and a number of these patients develop resistance to conventional medical therapy, primarily diuretics. PUF is a viable modality for both the short- and long-term managements of patients with RCHF. The role of PUF in short-term control is limited to situations where extracorporeal UF is not possible or available. However, for the long-term management of patients with RCHF, PUF should be the therapy of choice for ambulatory UF. It can be used as a bridge therapy for definitive interventions or palliative treatment for these patients. Using an intraperitoneal solution such as icodextrin promotes a slow and efficient PUF that better preserves residual renal function, is less invasive and is better tolerated by cardiac patients, improving clinical symptoms and quality of life.

Patients with CHF are usually fragile, with multiple comorbidities. The proper anesthesia technique and surgical approach for PD catheter placement in CHF patients must be based on the patient's characteristics (including comorbidities and previous operations), available equipment, and surgeon's experience. An open approach using a TAP block for PD catheter placement in patients with CHF is strongly recommended.

However, there is a need for controlled trials to define subgroups of patients with RCHF who are most likely to benefit from this treatment method. Non-randomized but more extensive observational studies should also be performed to provide more information and establish the best protocol for managing RCHF in patients without ESRD. Cost-benefit analyses and reimbursement policies should be implemented. All this may lead to a more widespread use of PUF with icodextrin in this group of patients.

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