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Ultrafiltration in Heart Failure

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Abstract and Introduction

Abstract

Fluid overload is a key pathophysiologic mechanism underlying both the acute decompensation episodes of heart failure and the progression of the syndrome. Moreover, it represents the most important factor responsible for the high readmission rates observed in these patients and is often associated with renal function worsening, which by itself increases mortality risk. In this clinical context, ultrafiltration (UF) has been proposed as an alternative to diuretics to obtain a quicker relief of pulmonary/systemic congestion.
This review illustrates technical issues, mechanisms, efficacy, safety, costs, and indications of UF in heart failure. The available evidence does not support the widespread use of UF as a substitute for diuretic therapy. Owing to its operative characteristics, UF cannot be expected to directly influence serum electrolyte levels, azotemia, and acid-base balance, or to remove high-molecular-weight substances (eg, cytokines) in clinically relevant amounts. Ultrafiltration should be used neither as a quicker way to achieve a sort of *mechanical diuresis* nor as a remedy for an inadequately prescribed and administered diuretic therapy. Instead, it should be reserved to selected patients with advanced heart failure and true diuretic resistance, as part of a more complex strategy aiming at an adequate control of fluid retention.

Introduction

Heart failure (HF) is a major health concern accounting for 1 million hospitalizations in the United States, with estimated total costs of about $37 billion in 2009.[1]

Fluid retention, clinically expressed by systemic and pulmonary congestion, still represents the main reason for hospitalization of patients with HF.[2,3] Congestion plays a central role in the progression of the syndrome[4] and is a relevant negative prognostic factor in both renal function worsening[5] and increased mortality risk.[6] Unfortunately, as many patients admitted to the hospital for HF—especially those with acutely decompensated HF (ADHF)—are discharged without any documented body weight loss and/or with persistent signs of congestion, readmission rate is high (24%-31% within 3 months). Therefore, in this clinical context, the relief of congestion is now considered a major target of treatment, which should be aimed at removing excess intravascular and extravascular fluid without causing further neurohormonal activation and/or renal function worsening. On these theoretical grounds, diuretics are still considered a keystone in the therapeutic approach to HF,[11–13] although diuretic resistance can be a relevant issue, especially in patients presenting with ADHF.[14] Diuretic refractoriness seems to be mostly influenced by renal function and by either inappropriate way of administration or inadequate dose.[14,15] Both diuretic resistance and the associated worsening of renal function occur more commonly in patients with HF having preexistent renal dysfunction; the triad cardiorenal failure, diuretic resistance, and worsening renal function, often occurring in the presence of marked persistent volume overload, represent the most extreme clinical feature of the so-called cardiorenal syndrome.[16]

Renal replacement therapies (RRT) have recently been adopted in cardiology units with indications far beyond those classically accepted in the nephrology units, such as end-stage renal disease or acute kidney injury. Actually, isolated ultrafiltration (IU) has been proposed as an alternative/complementary modality to diuretics in patients with HF showing coexistent systemic and pulmonary congestion, to relieve more quickly fluid overload.[17,18]

However, as clear-cut evidence concerning IU in HF is pending, the rationale, indications, and cost-effectiveness ratio of this approach to an otherwise highly relevant cardiological problem remain to be clearly defined. Moreover, IU cannot be considered entirely complication free, and its widespread use within the cardiology wards might also imply relevant logistic and economic problems.[19]

The aim of this review was to provide a brief account about (1) the general aspects and the basic mechanisms of fluid/solute transport underlying IU practice, (2) the rationale and therapeutic goals for its application, (3) clinical effectiveness and safety issues, and (4) economical and logistic aspects of the procedure.

Search Strategy

Studies were identified searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials up to May 31, 2010, combining the terms "heart failure" and "ultrafiltration OR hemofiltration". The search strategy was limited to English-language articles on adults. We did not include terms for study designs. We retrieved all full-text nonduplicated articles documenting clinical studies on IU in HF and describing patient characteristics, IU procedures, renal outcome, and adverse effects.

General Principles

All RRT modalities use an extracorporeal circuit through which blood is pump driven from a venous access into the filter, to be then returned into the patient, a procedure nearly always requiring blood anticoagulation. The extracorporeal treatment can bring about changes in blood composition by either removing plasma water or clearing plasma solutes. The RRT machine allows programming the desired fluid removal, both as to the amount (total weight loss per single session) and as to the rate (ie, hourly removal of fluids).

During IU, water crosses the semipermeable membrane in the filter by UF, that is, a process driven by the hydrostatic pressure difference across the filter membrane (Figure 1, *A*). Solutes with smaller size with respect to membrane pores, such as electrolytes and urea contained in that amount of plasma water, are removed concurrently (Figure 1, *B*) at the same concentration of the plasma water. Thus, UF, by affording an isotonic removal only, leaves unchanged the plasma concentration of low-molecular-weight solutes such as sodium and other small solutes.

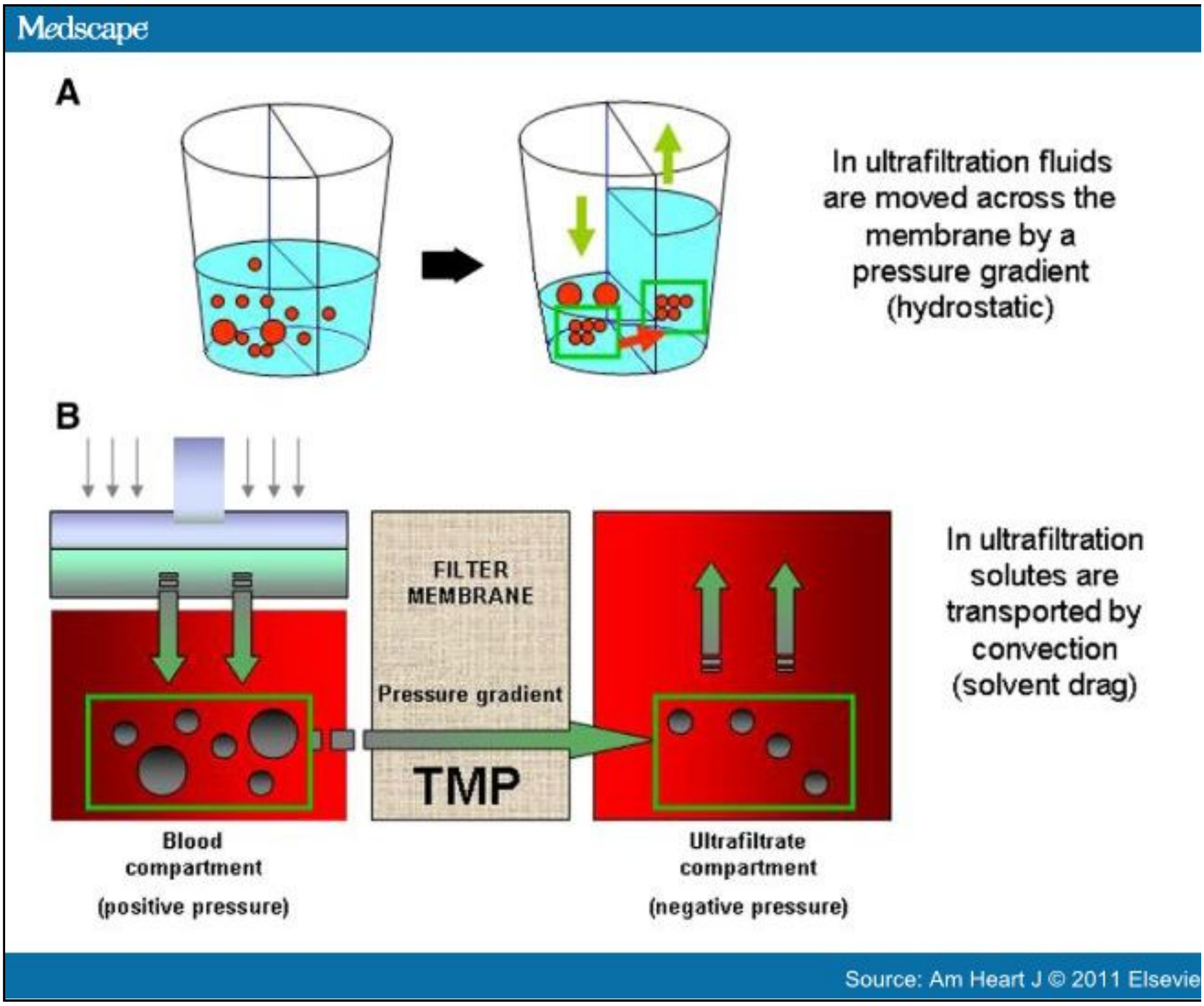

Figure 1. Water and solute transport in IU. Water molecules cross semipermeable membranes by UF, that is, a fluid shift driven by a hydrostatic pressure difference (TMP), according to the formula:
Hourly fluid removal in IU = TMP K_{UF}
where K_{UF} is the UF coefficient of the filter, that is, the intrinsic permeability of the membrane. It represents the theoretical amount of plasma water transported in the unit of time per unit of TMP applied across the membrane (mL/mm Hg per hour). For example, given a filter K_{UF} of 10 mL/mm Hg per hour, if TMP is 150 mm Hg, the maximum ultrafiltrate volume in 1 hour (hourly UF rate) will be 150 × 10 = 1.5 L. Hourly UF rate is directly set on the machine that modulates TMP according to the programmed weight loss. Solutes are *dragged* along with plasma water across the membrane (solvent drag: solutes with molecular size lower than membrane pores are transported with the solvent) (B). Urea (60 D) or electrolytes (sodium 23 D and potassium 35 D) will be moved easily; on the contrary, high-molecular-weight solutes (eg, albumin 69 000 D) will not undergo the solvent drag effect. *TMP*, Transmembrane pressure; *D*, Daltons.

Terms such as *ultrafiltration* and *hemofiltration* are often used interchangeably, especially in cardiology, but they are in fact quite different. Ultrafiltration (UF) designates either the water transport mechanism during RRT or an RRT modality of isolated fluid removal from blood. For the sake of clarity, a UF session should be properly designated as IU. One should use this term to avoid confusion with hemofiltration, a modality which is still based on the convective removal of plasma water but requires also the partial or total replacement of the latter by a *clean* solution having known electrolyte concentrations (usually 2–3 L/h in continuous forms of hemofiltration or up to 6–8 L/h in high-volume hemofiltration/hemodiafiltration) (Table I). Obviously, hemofiltration has a depurative efficiency much higher than IU.

Table I. Comparison of characteristics of hemodialysis, hemofiltration, and IU

	Hemodialysis	Hemofiltration	IU
Solute transport mechanism	Diffusion*	Convection†	Convection†
Water transport mechanism	Ultrafiltration‡	Ultrafiltration‡	Ultrafiltration‡
Fluid replacement need	No	Yes (2–8 L/h)	No
Depurative efficiency (small solutes)	High	High	Negligible§
Depurative efficiency (cytokines)	Negligible	Negligible‖	Negligible
Single session duration	4 h	4–24 h¶	4–8 h
Rhythm	Daily schedule or every other day in acute patients	Daily schedule or every other day in acute patients	Daily schedule or every other day according to fluid removal needs
	Three times per week in long-term patients	Three times per week in long-term patients	

* Driving force for solute transport is the concentration gradient between blood and dialysis fluid across the filter membrane.
† Solutes are transported by the *solvent drag effect* in the ultrafiltrate.
‡ Driving force for water transport is the hydrostatic pressure gradient across the filter membrane between blood compartment and ultrafiltrate compartment (transmembrane pressure [TMP]).
§ Excluding sodium.
|| Higher efficiency in the case of high-volume hemofiltration (6–8 L/h).
¶ Twenty-four hours in the case of continuous venovenous hemofiltration.

Today, there are filters in the market allowing the achievement of a wide range of UF rates during IU. The main limitation in achieving high UF rates, hence highly negative fluid balance, is not technical but clinical as it depends on the patient's hemodynamic status. Individual tolerance to fluid removal during IU depends in fact on the complex interplay of several factors influencing the vascular refilling rate (VRR): hourly UF rate, cumulative weight loss, hemodynamic status at baseline and cardiovascular responses to weight loss, acute/chronic comorbidities, and other factors.[20] Vascular refilling rate, which defines the rate of fluid transferral from the extravascular (interstitium) to the intravascular compartment, cannot be directly measured. In the most favorable condition, although IU removes plasma water from blood, the circulating plasma volume is progressively refilled by fluid drained from the interstitium (edema zones). This is caused by the parallel rise in oncotic pressure created by the increasing concentration of proteins in the vascular compartment. If UF and refilling rates are well balanced, no major changes in plasma volume will occur.[20] On the other hand, the greater the discrepancy between UF and VRR (UF rate > VRR), the higher the risk of hypovolemic hypotension, leading eventually to renal hypoperfusion with worsening of kidney function. Vascular refilling rate has been estimated in 7 to 10 mL/kg per hour;[21] hence, as a practical rule, hourly weight changes between 0.5 and 1 kg should be well tolerated by patients with HF.[20] When highly negative cumulative balance is needed without exceeding the above-indicated prudential hourly UF rate, unless otherwise dictated by emergency conditions (eg, pulmonary edema in an oliguric patient), there are 2 reasonable options: either to prolong IU duration or to distribute total weight loss on different IU performed on consecutive days.

Rationale and Therapeutic Goals

The complex rationale proposed for IU in patients with HF is illustrated in Table II, which also shows therapeutic goals suggested in the literature.[22,23]

Table II. Rationale and therapeutic goals of IU in HF

Rationale	Therapeutic target	Comments
Fluid balance regulation	More rapid relief of systemic and pulmonary congestion as compared to usual therapy with diuretics	The main component of the rationale for IU in HF
Solute regulation	Correction of hyponatremia, hyperkalemia, and metabolic acidosis	Because of its operational characteristics, IU is unable to correct serum electrolyte/acid-base derangements
	Reduced incidence of hypokalemia	IU leaves unchanged serum potassium levels
	Correction of azotemia	Because of its operational characteristics, IU does not significantly improve BUN levels
	Removal of cytokines and myocardial depressant factors	No evidence. Unrealistic based on the operational characteristics of the treatment and filter performances
	Higher mass clearance of sodium, with more effective reduction of sodium pool as compared to diuretics	The ultrafiltrate has a higher sodium concentration if compared to urine after loop diuretics
Homeostasis control	Restoring sensitivity to diuretics	Scarce evidence
	Osmoceptor resetting	Not demonstrated
	Reduced neurohormonal activation (reduced activation of the macula densa mechanisms and TGF, sympathetic nervous system, and RAAS axis)	Limited data available
Reduced costs	Shortened hospital LOS	Partially supported by the cost-effectiveness analyses available so far
	Decreased rate of readmission	
Other	Facilitation to parenteral/enteral nutrition	A purely theoretical rationale
	Facilitation to blood component transfusion	Iron and erythropoietin therapies are able to reduce transfusional needs in patients with HF

BUN, Blood urea nitrogen; *RAAS*, renin-angiotensin-aldosterone axis; *TGF*, tubuloglomerular feedback.

The most relevant issue is fluid removal and improvement of pulmonary/systemic congestion; instead, no significant correction of hyponatremia (at least directly), azotemia, hypo/hyperkalemia, or metabolic acidosis/alkalosis nor a significant removal of high-molecular-weight substances (eg, *myocardial-depressant factors* and cytokines) can be expected from IU[19,24] because of its operational characteristics.

Most of the positive hemodynamic/respiratory effects attributed to IU (Table III) can be related to a general improvement in the heart/lung interaction, with ensuing reduced respiratory workload and oxygen consumption.[25–29]

Table III. Proposed mechanisms of the positive effects of IU on cardiopulmonary function in HF

Heart and peripheral circulation	Lung
Relief of cardiac edema	Reduced extravascular lung water
Improved diastolic function	Reduced shunt effect with improved gas exchange and oxygenation
Improved afterload (reduced peripheral vasoconstriction for increased cathecolamine clearance)	Reduced dead space
	Increased vital capacity
Removal of cytokines and myocardial depressant factors	Reduction of respiratory workload

Clinical Effectiveness and Safety Issues

Effectiveness in Clinical Trials

Nephrologists have been using IU for at least 60 years to reduce congestion in patients with end-stage renal disease. Indeed, UF is routinely performed as a part of standard hemodialysis sessions when fluid removal is needed (Table I).[30,31]

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§ Excluding sodium.
|| Higher efficiency in the case of high-volume hemofiltration (6–8 L/h).
¶ Twenty-four hours in the case of continuous venovenous hemofiltration.

Starting from the 1990s, along with the publication of studies on the cardiopulmonary effects of IU in HF,[25–29,32,33] this technique has also been increasingly used in cardiology. Table IV summarizes the most recent data.[17,33–39]

Table IV. Recent clinical studies on the effects of IU in HF

Reference	Patients and treatment	End points	Results	Total ultrafiltration and weight change	
Bart et al, 2005[35]	RCT, early, single 8-h IU + diuretic therapy (20 patients) vs diuretic therapy alone (20 patients)	• Weight change at 24 h • Fluid removal at 24–48 h • Global CHF and dyspnea assessment • Electrolytes and creatinine • LOS	• Greater fluid removal with IU, improved global dyspnea, and CHF symptom assessments • No differences in weight change, serum electrolytes and creatinine, and LOS	• 4650 mL with IU vs 2838 mL with diuretics • Weight change 2.5 kg vs 1.86 (*P* NS)	
Costanzo et al, 2005[34]	• Case series • 19 patients with diuretic-resistant ADHF • *Early IU*, started within 4.7 ± 3.5 h of admission	• MLWHFQ • NYHA class • BNP	• 60% of patients discharged in 3 d • MLWHFQ improved • BNP reduced • NYHA class improved • Reduced readmissions	Total ultrafiltration 8654 ± 4205 mL Weight change 6 kg Diuretic dose not reported	

	and continued up to ADHF symptoms resolution		• Clinical improvement persisting at 30 and 90 d		
Liang et al, 2006[37]	• Case series • 11 patients with *diuretic-resistant* ADHF • 32 IU sessions	• Removal of 4 L of fluid per 8 hour IU	• Negative fluid balance in all patients • No data on weight change	Of 32 treatments, fluid removal N3500 mL in 13, 2500–3500 mL in 11, and ≤2500 mL in 8	
Dahle et al, 2006[38]	• Case series • 19 patients with ADHF • Treatment duration 33 ± 20 h	• Weight change • Total fluid removal	• Weight loss with IU	• Ultrafiltration rate 400 mL/h for 4 h, then 200 mL/h • Total UF 7.0 ± 4.9 L • Weight loss 6.9 ± 0.5 kg	Pe rep

Costanzo et al, 2007[42]	• RCT, multicenter
	• 200 patients with ADHF (100 on IU and 100 on diuretic therapy)
	• IU within the first 24 h of admission
	• IU duration and rate at the discretion of the attending physicians
		• Primary end Points
		  ◦ Weight loss
		  ◦ Dyspnea score at 48 h
		• Secondary end points
		  ◦ Weight change at 48 h
		  ◦ Rehospitalization rate
		
		Safety: changes in renal function, serum electrolytes, and arterial pressure
			• Greater weight loss with IU vs diuretic group
			• Similar dyspnea score
			• Lower readmission rates with IU
			• No differences in serum creatinine levels
			• No difference in hypotension rate
				• Ultrafiltration rate 400 mL/h for 4 h, then 200 mL/h
				• Total UF 7.0 ± 4.9 L
				• Weight loss 6.9 ± 0.5 kg
				• Mean UF rate 241 mL/h for 12.3 ± 12 h (max 500 mL/h)
				• Weight loss 5.0 ± 3.1 kg with IU vs 3.1 ± 3.5 vs diuretics	

Jaski et al, 2008[39]	• Case series • 100 *overloaded* patients with CHF • One or more IU per patient (mean 2.1 ± 1.2)	Removal of 2–6 L of fluid over each 8–12 h IU	Fluid removal and weight loss in all patients at discharge	• Total UF 7.0 ± 3.9 L (median 6.3 L) in 2 ± 1.2 sessions (2–6 L in 8–12 h) • Weight loss 6.3 ± 6.4 kg (median 6 kg)	Pe No

NS, Not significant; *ACEI*, angiotensin-converting enzyme inhibitors; *ARB*, angiotensin receptor antagonists; *BNP*, brain natriuretic peptide; *CVC*, central venous catheters; *MLWHFQ*, Minnesota Living With Heart Failure Questionnaire; *NYHA*, New York Heart Association; *AP*, arterial pressure.

Most of the studies are retrospective cohort studies on small patient groups, without controls and with short follow-up. Exceptions are represented by 2 randomized controlled trials (RCTs) on patients with ADHF.[17,35] In the RAPID-CHF study,[35] a single 8-hour IU was carried out within the first 24 hours of admission and compared to usual care. Subsequent IU sessions were allowed after an assessment at 24 hours. The amount of fluid removed in the IU group at 24 and 48 hours was statistically different from controls, without any difference in weight loss and hospital length of stay (LOS). The UNLOAD study[17] is an RCT aimed at comparing IU with diuretic therapy in 200 patients with ADHF. Primary end points were weight loss, dyspnea score at 48 hours, and readmission rate. The last one was reduced in the IU arm, but LOS was not different from the control group; weight loss was higher with IU. Because IU allowed a greater weight loss and a more negative fluid balance, as well as a lower 90-day resource use, it was suggested as an alternative to diuretics. Unfortunately, the study has many limitations, most of them acknowledged by the authors themselves:[22]

- Patients with hypotension/hemodynamic instability and/or vasoactive inotropes excluded
- Fluid overload assessment lacking
- Mean loop diuretic equivalent dose at 20% to 25% of maximum suggested dose by guidelines
- Suboptimal administration of loop diuretics (intravenous [IV] bolus in 2/3 of patients)
- Diuretic dose in the standard therapy arm at the discretion of attending physicians
- Isolated ultrafiltration duration, rate, and weight loss at the discretion of attending physicians
- No demonstration of physiological superiority of IU (neurohormonal activation), for equivalent fluid removal and weight change obtained
- Study groups not controlled for total amount of fluid removed and weight change
- No data on compliance with low-salt diet
- Fluid restriction 2 L/d

As diuretic treatment was suboptimal according to current suggestions from recent guidelines[11,12] or expert recommendations,[14,15,40] readmission rates may not have differed had both treatments resulted in a similar degree of weight loss.[41] However, a recent post hoc analysis of the same data compared the readmission rates of the subgroup of patients treated by IU with those of patients who had received diuretics by IV continuous infusion; the amount of fluid removed by IU and by IV diuretics was similar, but fewer readmissions and unscheduled emergency department or office visits were observed with IU.[42]

Renal Function Impairment and Other Adverse Effects

Table V illustrates the effects of IU on hemodynamic and neurohormonal status. No major adverse effects have been documented with this procedure,[25–29,32,34] provided that hourly weight loss and VRR are matched.[21] Instead, an aggressive approach to weight change by IU might negatively impact on both systemic hemodynamics and, consequently, renal function.[29] Accordingly, in patients with HF with hemodynamic instability, IU (usually lasting 4–8 hours) should be preferably planned over a more prolonged session, up to 24 hours if needed (slow continuous ultrafiltration).[43]

Table V. Hemodynamic and neurohormonal effects of IU in HF

	IU effects
Hemodynamic variables	
Cardiac index	Unchanged or increased
Heart rate	Unchanged
Mean arterial pressure	Unchanged
Peripheral vascular resistances	Unchanged or reduced
Right atrial pressure	Reduced
Pulmonary artery pressure	Reduced
Pulmonary wedge pressure	Reduced
Pulmonary vascular resistances	Unchanged or reduced
Peak exercise capacity	Improved
Neurohormonal variables	
Norepinephrine	Reduced
Plasma renin activity	Reduced
Aldosterone	Reduced
Brain natriuretic peptide	Reduced

In general, in patients with HF, worsening of renal function at hospital admission and/or during the hospitalization is frequently observed, although often underestimated, and represents an independent predictor of increased morbidity and mortality.[44]

High-dose loop diuretics have been blamed for adverse effects in patients with HF, in terms of both renal function worsening and increased mortality risk,[44] thus supporting the rationale for alternative methods of fluid removal such as IU. However, the negative prognostic effect of diuretics has not been demonstrated so far in RCTs,[41] and other studies have documented a strong association between improvement in systemic congestion obtained with diuretics and survival after hospital discharge.[6,10] For this reason, both the need for high doses of diuretics and the same condition of *refractoriness* to diuretics could simply represent markers of severity of illness and renal failure, rather than causative factors.[41]

Data on the effects of IU on renal function in HF are scarce.[45] Small observational studies showed no changes in renal function (serum creatinine) when IU was compared to diuretics in stable patients with HF[25–27,33–38] (Table VI). In one article, only glomerular filtration rate (GFR) and renal plasma flow were directly measured, without any difference documented between IU and diuretics.[46] In a small case series of 11 patients from the Mayo Clinic receiving a total of 32 IU sessions, 5 (45%) of 11 patients underwent hemodialysis during the same or a subsequent hospitalization after IU.[37]

Table VI. Renal effects of IU

	Study design and protocol	IU features	Creatinine	Creatinine	Comments

			before IU (mg/dL)	after IU (mg/dL)	
Bart et al, 2005[35]	• RCT, IU as an adjunct to diuretic therapy • Single, early 8-hour IU + usual care (diuretic therapy) vs usual *care* alone • Additional IU allowed only after 24 h from enrollment	• Maximum UF rate 500 mL/h • Cumulative fluid removal in the IU group 4650 mL at 24 h	1.6	1.9	• No changes in renal function either in patients on diuretic therapy
Costanzo et al,2005[34]	• Case series • 19 patients with diuretic-resistant ADHF • Single IU session per patient	• Maximum UF rate 500 mL/h	2.12	2.2	• No changes in renal function
Liang et al, 2006[37]	• Case series • 11 patients with ADHF • IU number at the discretion of the attending physicians (1–5 IU per patient)	• 32 IU, each 8 h	2.2	2.3	• In 5 patients (45%), serum creatinine levels increased by N0.3 mg/dL • In 4 patients, dialysis needed during the same hospitalization period
Dahle et al, 2006[38]	• Case series • 19 patients with ADHF • IU discontinued at the discretion of the attending physicians	• 400 mL/h for 4 h, then 200 mL/h • Mean IU length: 33.3 ± 20 h	1.4	1.4	• No changes in renal function • Serum sodium levels at discharge lower in the IU group
Costanzo et al,2007[42]	• RCT, multicenter • 200 patients with ADHF (100 on IU and 100 on diuretic	• Max UF rate 500 mL/h • Mean fluid	1.5	Trend to creatinine increase in the IU group	• No changes in serum creatinine in the 2 groups

	therapy) • IU within the first 24 h of admission • IU duration and rate at the discretion of the attending physicians	removal 241 mL/h for 12.3 ± 12 h			• More patients with serum creatinine level increase of N0.3 mg/dL in the IU group at 24–48 h and at discharge
Jaski et al, 2008[39]	• Case series • 100 overloaded patients with CHF • One or more IU per patient (mean 2.1 ± 1.2)	• Removal of 2–6 L of fluid over 8–12 h (7 L in 2.1 IU per patient) • UF rate 500 mL/h	1.8	1.9	• No changes in serum creatinine levels • Greater urine output with furosemide
Rogers et al, 2008[46]	• RCT • Single IU within 24 h from admission • 19 patients with ADHF (10 on IU and 9 on diuretic therapy) • Urine output, GFR (by iothalamate), and RBF (by *para*-aminohippurate)		GFR 37 mL/min	GFR decreased by 3.4 and 3.6 mL/min in IU and diuretic therapy, respectively	• No differences in GFR or RBF

RBF, Renal blood flow.

Apart from renal and hemodynamic complications, IU shares problems that are typical of any other RRT technique based on an extracorporeal circulation (Table VII), being the most commonly observed are those linked to CVC use and circuit clotting.[19]

Table VII. Complications of IU

Complications	Mechanisms	Consequences
Technical		
Air embolus	Air entry in the extracorporeal circuit is caused by disconnection in a segment between venous access and blood pump	Hypoxemia and acute respiratory failure
Hemolysis	Tubing defects or highly negative aspiration pressures from CVC line	Acute kidney injury and hyperkalemia

Filter reaction	Membrane or circuit bioincompatibility	Systemic inflammation
	Allergic mechanisms	With filters sterilized by ethylene oxide
Premature circuit clotting	Hemostasis activation in critical points of the circuit (air-blood interfaces, filter, segments with blood stagnation, etc)	Anemia if no blood restitution from circuit, increased transfusional needs, and more frequent replacement of filters and circuits
Hemorrhagic		
Blood losses from the circuit	Accidental disconnection of circuit lines	Higher risk with low-pressure circuits based on peripheral venous access and simplified machines for IU (reduced level of monitoring and few alarms)
	Faulty detection of reduced venous pressures in the circuit	
Filter rupture	Very high TMP values	Circuit clotting and blood loss in the ultrafiltrate
Hemorrhage	Systemic anticoagulation by antihemostatic agents used for the circuit	Anemia and increased transfusional needs
Thrombocytopenia	Heparin induced	HIT I-II, thrombosis, and hemorrhages
Hemodynamic		
Hypotension	Ultrafiltration rate exceeds vascular refilling rate	Hypovolemia, hypotension during IU, prerenal azotemia, syncope, and shock
Renal function worsening	Prolonged hypotension during IU	Postprocedural oliguria and chronic dialysis
CVC Related		
Arterial puncture	Accidental arterial puncture during CVC positioning	Local hemorrhages, hematoma, and hemothorax (subclavian artery puncture)
Pneumothorax	Accidental pleural puncture during CVC positioning	Acute respiratory failure
Infection	Infection of CVC insertion site, intraluminal shift of pathogens, usually Gram positive	Sepsis
CVC Occlusion	Thrombus	CVC malfunctioning, blood recirculation, and reduced efficiency of RRT
Venous stenosis	Central vein stenosis (usually subclavian vein)	Upper arm edema and CVC malfunctioning
CVC Malfunctioning	Arterial line collapse during blood aspiration or partial/total occlusion of venous line of CVC	Increased risk for premature circuit clotting and increased antihemostatic drug needs

HIT, Heparin-induced thrombocytopenia.

Costs

The economic burden of IU is difficult to quantify because costs are influenced not only by the type of machine and disposable material, but also (not only construction) by the number of treatments performed, as well as by the clinical context/logistic situation of the treatment (cardiology or nephrology wards or in the intensive care unit). Three different types of machines are available for IU, each corresponding to different logistic/clinical conditions and costs (Table VIII). The higher costs inherent in the IU therapy could be offset by the reduced use of medical resources during the follow-up; in fact, at least in the United States, more than one third of the costs of treatment of patients with HF is incurred because of readmissions for HF within 6 months from discharge.[47]

Table VIII. Electronic supplement

Available machines and cost issues for IU
Dedicated machines
– Aquadex Flexflow 100 (CHF Solutions Inc, Brooklyn Park, MN)
– Dedyca (Bellco, Mirandola, Italy)
Simplified machines (low-level monitoring and few or no alarms) recently made available on the market. These systems are based on filters with low surfaces (0.12–0.25 m2) and *K*UF values (about 5 mL/mm Hg per hour). The main pitfall is the high cost of disposables (€900 for the complete circuit). These machines are essentially intended for cardiology wards and can be used also with peripheral venous accesses.
Machines for continuous RRT
Prismaflex (Gambro-Hospal)
Multiflow (Fresenius)
Genius (Fresenius)
Lynda (Bellco)
Aquarius (Edwards)
Machines for RRT optimized for continuous RRT modalities (eg, continuous venovenous hemofiltration). Replacement fluid is needed, which is marketed as sterile bags (a sterile 5-L bag cost about €10); the cost of filter/circuit used is about €150–250. These systems are routinely used in the ICU.
Machines for standard hemodialysis/hemofiltration
AK 200 ULTRA S (Gambro)
Artis (Gambro)
4008 H (Fresenius)
5008 (Fresenius)
Formula (Bellco)
Integra (Bellco)
Machines for standard hemodialysis/hemofiltration, currently used in nephrology units and ICUs. They represent the cheapest option as the cost for one high surface filter (1.3–2 m2) and its circuit is only €20–50. Ultrapure dialysis/replacement fluid is directly produced online by the machine from salt concentrates, at the cost of a few euro cents per liter.

Recently, a cost-consequence analysis of the UNLOAD trial data underscored the importance of payer perspective in estimating the costs of IU compared with conventional therapy;[48] although IU is likely more expensive if evaluated from the societal and hospital perspective, it might be in fact cost-saving if considered from the Medicare perspective.

General Recommendations

All of the recent clinical practice guidelines on HF failed to recommend IU as a class I therapeutic option.[11,12,49] On the other end, the widely accepted safety and efficacy of diuretics are clearly reflected in the class I recommendation for IV loop diuretics in case of congestion and/or ADHF.[11,12,49] The main indication for IU in guidelines is the relief of fluid overload when true diuretic refractoriness exists (class IIa, level B recommendation).[11,12] Consulting a nephrologist experienced in RRT is deemed as appropriate before opting for IU.[12,49]

Coexisting acute respiratory failure (acute pulmonary edema), especially in oliguric patients, might be added as an emergency indication. A flowchart concerning the use of IU as a complementary adjunct option to diuretic therapy in ADHF/chronic heart failure (CHF) is illustrated in Figure 2. Isolated ultrafiltration could be a reasonable option for those patients with true diuretic resistance and in whom renal dysfunction is related more to potentially reversible hemodynamic/fluid overload status derangements (such as systemic and renal congestion) than to kidney structural changes.[50] Otherwise, advanced renal failure, along with metabolic alterations and symptoms typical of the uremic syndrome (azotemia, hyperkalemia, metabolic acidosis, etc), should dictate a different approach (hemodialysis, peritoneal dialysis, hemofiltration, etc).

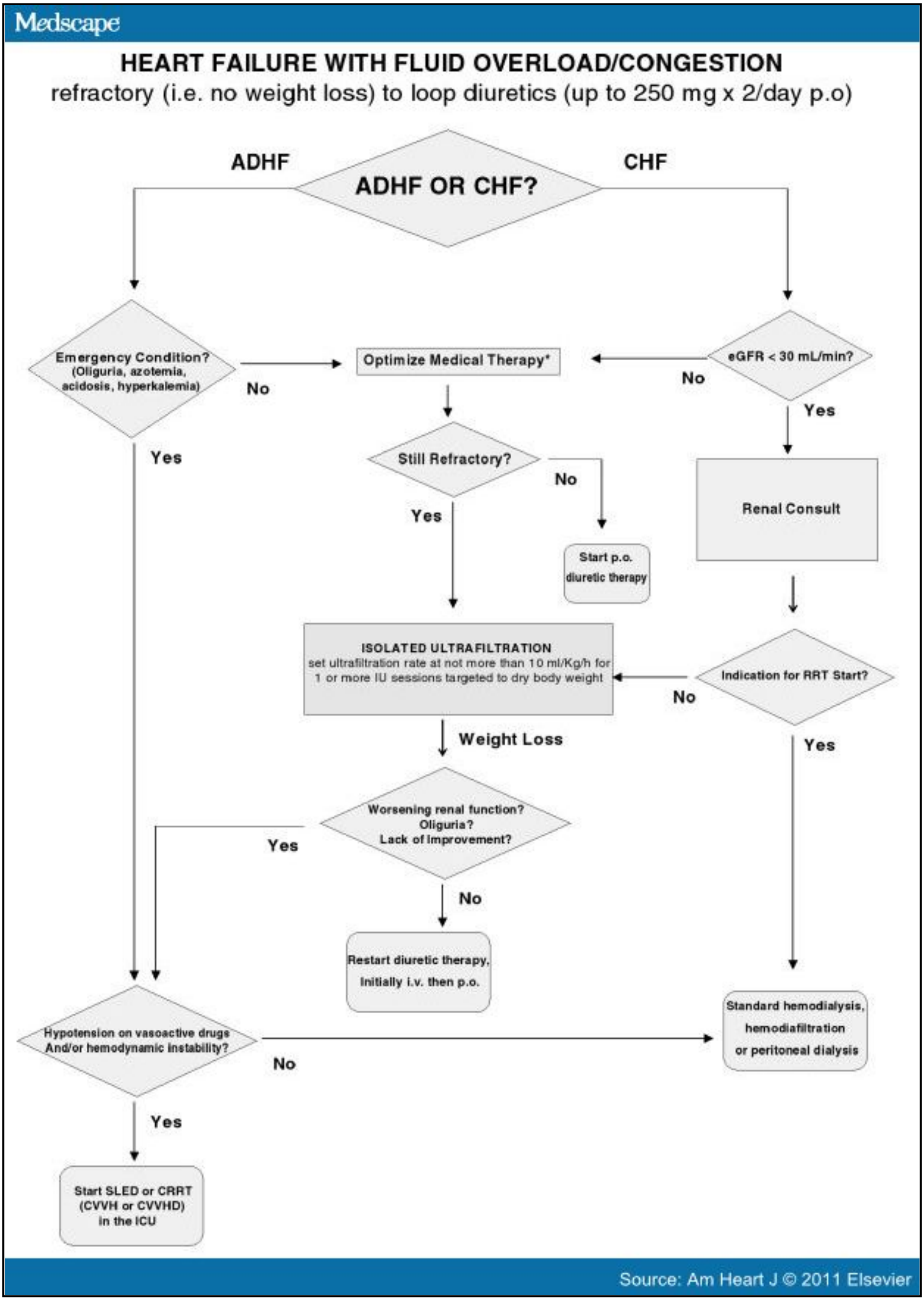

Figure 2. Flowchart for IU in HF. A practical approach to HF with fluid overload is presented. *Optimized medical therapy: checking causes of pseudorefractoriness to diuretic therapy such as high-sodium diet, water intake, drugs, anemia, and so on; prescribing fluid and sodium restriction (≤2 g NaCl and ≤500 mL/24 h of water per day); shifting to IV diuretics continuous infusion; and combining classes of diuretics affecting

different areas of the nephron (ie, acetazolamide, thiazides, and aldosterone antagonists). *BUN*, Blood urea nitrogen; *CRRT*, continuous renal replacement therapies; *CVVH*, continuous venovenous hemofiltration; *CVVHD*, continuous venovenous hemodialysis; *eGFR*, estimated glomerular filtration rate; *ICU*, intensive care unit; *SLED*, sustained low-efficiency dialysis.

Conclusive Remarks

Isolated ultrafiltration should be mainly regarded as a therapeutic option complementary, and by no means alternative, to diuretics for fluid removal in patients with HF. Relevant open questions are those concerning the indications of IU, as a unique decision-making tool for IU in HF is lacking.[50] Pending clear-cut evidence, this treatment should be reserved for conditions of true refractoriness to pharmacologic treatment, that is, when patients remain in positive fluid balance despite fluid/salt restriction and optimal diuretic treatment (maximal allowed doses, continuous IV infusion, sequential nephron blockade with different classes of diuretics, etc). When, in HF, diuretic resistance is associated with oliguria, azotemia, hyperkalemia, metabolic acidosis, and so on, different RRT techniques (hemodialysis, hemofiltration, etc) are requested.

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