EXTRACORPOREAL ULTRAFILTRATION IN REFRACTORY HEART FAILURE

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ABSTRACT

Heart failure (HF) is a major health and social problem and despite the advances in medicine it still remains the main cause for hospitalizations in the developed world. The main sign of decompensation is hypervolemia, which in refractory HF is difficult to treat with the currently available medications. This review studies in detail ultrafiltration (UF) as a safe, effective and promising method for management of refractory congestive HF. The procedure, the prominent clinical studies in this field, as well as the main indications and contraindications are described.

Keywords: heart failure, hypervolemia, ultrafiltration

Water retention and the related to it edematous syndrome are the main signs of heart failure (HF) decompensation and the reason for more than 90% of hospitalizations (1). Hypervolemia contributes to HF progression, deteriorates the prognosis and increases the mortality rate. All current recommendations aim to achieve a normovolemic state (11,2,16), which during the end stages of HF, when there is diuretic resistance (DR), is practically impossible. Despite the fact that the intravenous application of loop diuretics leads to quick diuresis and clearance of the pulmonary congestion and dyspnea, their continuous use decreases their effect. Prolonged treatment with high doses of loop diuretics is linked to an increased mortality rate, which is a result of neurohumoral activation, electrolyte imbalance, and an impact on the cardiac and renal function (7,13). Ultrafiltration (UF) is an alternative method for water and salt extraction, which safely improves the hemodynamics in HF (4). Extracorporeal UF has been known since the inception of dialysis therapy, but it was first in 1974 when Marc Elliot Silverstein and associates demonstrated the possibility of using it as a method of fluid extraction (17). Later, in 1979, the American nephrologist Robert Gerhardt applied this method in patients with refractory HF and hypervolemia (8). There is
METHODS AND PRINCIPLES

UF consists of fluid extraction from the blood by means of semipermeable membrane (hemofilter) as a response to a transmembrane gradient, which is generated, on one hand, by the difference in the hydrostatic pressure between the blood and the filtrate, and by the oncotic pressure of plasma proteins, on the other. An artery or a vein is cannulated for this purpose after which the blood passes through the device and is returned, using a separate pathway, to the venous system. A central access via a jugular or femoral vein is used in general, but recently cannulation of a periphery vessel has started being used as well. There are two UF regimens depending on the goals, which is used for: intermittent (4-8 hours) and continuous (for 72 hours).

UF helps salts, the size of which is smaller than the pores of the membrane, to pass passively and thus, their concentration in the ultrafiltrate remains the same as that in the plasma. The product is an isotonic or an isonatremic ultrafiltrate as opposed to the hypotonic fluid, which is a result of the use of diuretics. Because the serum electrolyte concentration on both sides of the membrane does not change in UF, no hypokalemia or hypomagnesemia, often seen with the application of diuretics, is observed. In addition, diuretics lead to a more prolonged intravascular hypovolemia and inhibition of the reverse reabsorption of chlorides in macula densa, which increases renin secretion and subsequently leads to increased water and salt retention. Since in UF the speed of extraction and return of fluid to the blood, respectively, is constant, no prolonged intravascular hypovolemia and neurohumoral activation is observed. The speed of water and salt filtration depends mainly on the transmembrane gradient and can be managed via changes in this gradient: increase of the blood flow or suction on the side of the ultrafiltrate. It is important to maintain a constant rate in UF so that the extracellular fluid gradually fills the intracellular space, thus ensuring a constant blood volume. If this speed is too high, it may lead to dysynchrony between extraction and return of blood and to blood volume decrease, and consequently to hypovolemia with hypotension. It is also necessary to maintain adequate anticoagula-
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• склонност към хиперкоагулация;
• систолно АН < 85 mmHg;
• контраиндикации за антикоагулация;
• системна инфекция.

Няма ограничения относно етиологията на СН, но множество проучвания отчитат по-добри резултати при исхемична или неисхемична дилатативна кардиомиопатия в сравнение с клапни пороции.

По време на провеждане на процедурите е необходимо преустановяване на диуретичното лечение и съответно калий-пестящи и заместващи медикаменти. Спорно е използването на инотропни средства, които са изключени в повечето проучвания, но няма конкретна контраиндикация за тяхното използване и при необходимост могат да бъдат прилагани за поддържание на сърдечен дебит. Останалите медикаменти, като АСЕ ингибитори, ангиотензин рецепторни блокери (АРБ), бета-блокери, нитрати и др., нямат отношение към УФ и не се налага да бъдат преустановявани.

Доказателства от основните клинични проучвания:

На Табл. 2 е направен преглед на основните клинични проучвания в тази област. Интерес представлява най-голямото проучване в тази област UNLOAD (5), резултатите от което са публикувани през 2007 г. То е проспективно, рандомизирано, мултицентрово проучване за ранна УФ спрямо венозен диуретик при пациенти, хоспитализирани по повод сърдечна недостатъчност и хиперволемия. Установено е, че макар УФ да няма предимства пред стандартната диуретична терапия за намаляване на субективната симптоматика, пациентите с УФ имат значително по-голяма редукция на тегло в първите 48 ч. след УФ и по-малко рехоспитализации в следващите 90 дни. При групата с УФ оралната доза фуроземид намалява, което в известна степен означава, че УФ blockers (ARBs), beta blockers, nitrates, etc. are not related to UF and do not have to be discontinued.

Proof from the Major Clinical Studies:
Table 2 presents an overview of the major clinical studies in this field. The study of the largest scale UNLOAD (5), the results of which were published in 2007, is of special interest. It is a prospective, randomized, multicenter study on early UF compared to intravenous diuretic in patients hospitalized for heart failure and hypervolemia. It has been established that, even though UF had no advantages over the standard diuretic therapy for subjective symptom management, in patients with UF there was significantly higher weight loss in the first 48 hours after UF and fewer rehospitalizations in the subsequent 90 days. In the group with UF, the dosage of oral furosemide decreased, which, to an extent, meant that UF had an impact on DR. Up to this moment, this is the study that describes best the advantages of UF. It was followed by a substudy with the same design, but looking for the impact of UF on renal function and hemodynamics (18) (Rogers, 2008), which, however, did not prove any significant benefits of UF in regard to renal function. In 2009 and 2010, Cristina Giglioli and associates conducted 2 studies on the effects of UF on cardiac hemodynamics (9,10). The last study, ULTRADISCO (10), compared two patient groups – with UF and with intravenous diuretic. Significant effects of UF on the hemodynamic indicators were determined, without influencing considerably indicators, such as systolic BP, diastolic BP, heart rate, etc. as opposed to the impact after the use of diuretics alone. At the same time, a significant decrease of NT-proBNP, aldosterone, creatinine, and subjective symptoms was registered. These two studies present UF in a new way and will probably initiate more studies in this field.

UF from a Nephrologist’s Point of View:
For the most part, studies and UF are conducted in...
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A close collaboration with a nephrologist. Theoretically, there are significant benefits for the kidneys in comparison to diuretics. UF helps avoid the activation of the renin-angiotensin-aldosterone system (RAAS), the sympathoadrenal system (SAS), and the inclusion of tubuloglomerular feedback. The extracted ultrafiltrate is isotonic compared to the plasma and contains a higher amount of salts than urine extracted with diuretics. In addition, direct fluid extraction from the intravascular space leads to a decrease in the central pressure and an increase of re-

<table>
<thead>
<tr>
<th>Researcher/Year</th>
<th>Title</th>
<th>Patients</th>
<th>Method</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Jaski et al./2003 (12)</td>
<td>Peripherally inserted venovenous UF for rapid treatment of volume overload</td>
<td>25 patients</td>
<td>Simplified system for UF with peripheral access</td>
<td>Every 8 hrs there is &gt; 1L extracted fluid and significant weight loss registered; no side effects</td>
<td>The peripheral access is reliable for quick fluid extraction via UF</td>
</tr>
<tr>
<td>M. R. Costanzo et al./2005 (6)</td>
<td>Early UF in patients with decompensated HF and diuretic resistance</td>
<td>20 patients</td>
<td>Early UF started at the 4.7±3.5th hour before intravenous diuretic</td>
<td>Early dehospitalization &lt;3 days; &lt;1 rehospitalization for a 30-day period; BNP decrease at discharge and on day 30</td>
<td>UF before i.v. diuretic decreases the stay and rehospitalizations</td>
</tr>
<tr>
<td>B. Bart et al./2005 (3)</td>
<td>UF vs usual care for hospitalized patients with HF (RAPID-HF)</td>
<td>40 patients</td>
<td>Comparison of 8-hour UF in combination with standard care and standard measures alone</td>
<td>Almost twice the amount of extracted fluid and weight loss in the UF group</td>
<td>Early UF is reliable, well tolerated and leads to significant weight loss and fluid extraction</td>
</tr>
<tr>
<td>M. R. Costanzo/2007 (5)</td>
<td>UF vs i.v. diuretics for patients hospitalized for acute decompensated HF (UNLOAD trial)</td>
<td>200 patients</td>
<td>Comparison of UF with intravenous diuretic</td>
<td>Every 48 hrs more extracted fluid and weight loss; similar change in the dyspnea; on day 90 – less rehospitalizations with shorter hospital stay and less unplanned doctor visits in the UF group</td>
<td>UF leads to better weight loss, decreases rehospitalizations in a 90-day period and is an effective alternative therapy to diuretics</td>
</tr>
<tr>
<td>H. Rogers/2008 (18)</td>
<td>A randomized, controlled trial of the renal effects of UF as compared to furosemide in patients with acute decompensated HF</td>
<td>19 patients</td>
<td>Urine output, GFR, renal plasma flow in UF compared to a diuretic</td>
<td>No difference in GFR and renal plasma flow in both groups</td>
<td>UF does not lead to significant differences in renal hemodynamics in comparison to i.v. diuretic therapy</td>
</tr>
<tr>
<td>C. Giglioli, 2010/ (10)</td>
<td>Effects of UF vs. diuretics on clinical, biohumoral and haemodynamic variables in patients with decompensated HF (ULTRADISCO study).</td>
<td>30 patients</td>
<td>Monitoring the biohumoral and hemodynamic effects of UF compared to intravenous diuretics</td>
<td>UF patients have significantly fewer HF signs and symptoms, a decrease of aldosterone and pro-BNP, and an improvement of multiple hemodynamic parameters</td>
<td>UF improves cardiac hemodynamics, when compared to i.v. diuretics</td>
</tr>
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</table>

Tab.2. Major clinical studies

появява ДР. До този момент това е проучването, което отчита в най-голяма степен предимствата на УФ. То бива последвано от подпроучване със същия дизайн, но търси влиянието на УФ върху бъбречната функция и хемодинамиката (18) (Rogers 2008 г.), което обаче не доказва особени ползи по отношение на бъбречната функция при провеждане на УФ. През 2009 и 2010 г. Cristina Giglioli и сътр. провеждат 2 проучвания за ефектите на УФ върху сърдечната хемодинамика (9,10). Последното проучване ULTRADISCO (10)
sparing two groups of patients with UF and venous diuretics. Established were the effects of UF in the setting of hemodynamic parameters, without the presence of intubation, diastolic AH, and other parameters. A decrease in the UF resistance after UF has been established and some authors suggest that it is a result of the removal of inflammatory cytokines and toxins during UF. However, nephrologists think that UF is a treatment method for heart and not for kidney failure. It does not impair the renal function like the use of diuretics but it also does not lead to an improvement in regard to the main indicators, such as creatinine clearance, glomerular filtration rate (GFR), renal plasma flow, which has been established by all conducted clinical trials up to this moment (13, 15). It is probably due to this fact that current studies are conducted in patients without kidney failure.

Possible Adverse Effects of UF:
Ultrafiltration is a safe and well tolerated by patients method, the adverse effects of which are similar to those of other extracorporeal methods. Rare side effects are (14):

- air embolism;
- bleeding from the venous access spot;
- hemolysis;
- bio-incompatibility: extremely rare due to the new polymers, which are used in this method; it presents with hypotension, fever, and broncho-spasm;
- allergic reactions;
- side effects related to the speed of UF: they are usually a result of non-compliance between extraction and return of fluids; they are characterized by hypotension and a possibility of acute circulatory reaction;
- infection of the central venous catheter;
- clotting in the catheter;
- deterioration of the present renal insufficiency and an eventual need for dialysis.

Financial Costs/Benefits Ratio:
Because HF is a leading cause for hospitalizations worldwide, the costs of which increase continuously, it is thought that each method, which can help decrease the number of hospitalizations and the length of hospital stay, is economically advisable. It is true that UF requires expensive equipment, supplies (central catheters, etc.) and still requires the participation of specialists from different fields (nephrology, dialysis, cardiology, intensive care), but with the improvement of the equipment, the introduction of portable devices, which do not necessitate a central venous access and well-trained staff, the financial
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- chest pain;
- chest pain of abrupt onset;
- heart failure; and
- pulmonary edema.

Costs could decrease significantly.

**Future Perspectives of UF:**
The main unresolved issues are related to understanding the inner mechanisms of the UF process and its benefit apart from fluid extraction. The reason for the decrease of the number of hospitalizations and the improvement in the diuretic response after UF is still being investigated. There are no studies on the long-term safety and the impact of UF on cardiac remodeling. There is no data on whether the positive effects of UF are due only to the mechanical fluid extraction or the removal of pro-inflammatory cytokines and other mediators also plays a significant role. A model of introducing UF as a treatment method for patients in outpatient setting is being developed. All these questions generate interest in this method and are a reason for the increased application of UF in routine practice.

**CONCLUSION**
The increasing number of rehospitalizations and the related costs require the introduction of new methods for efficient management of hypovolemia in decompensated HF. Ultrafiltration is a fast, safe and reliable method for the treatment of refractory HF. The use of UF in suitable patients leads to quick improvement of symptoms, leads to the possibility of a shorter hospital stay and to a decrease in the number of rehospitalizations, as well as to an improvement of the patients’ functional capacity without any significant adverse effects. Future clinical trials will give an answer to many unsolved problems about the inner mechanism of action of UF and its long-term effects.

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