AQUAPHERESIS for Acute Decompensated Heart Failure in Adults – rationale and initial clinical experience in a single center

Akwafereza w leczeniu zaostrzenia przewlekłej niewydolności serca – uzasadnienie i początkowe doświadczenia kliniczne jednego ośrodka

Summary

20 consecutive patients presenting with acute decompensated diuretic-resistant heart failure were subjected to 1-11 sessions of isolated ultrafiltration, followed by hemodialysis when biochemically indicated. There were no major technical nor clinical problems to remove 2500-3500 ml/session and reduce the body weight by even 12 or 30 kg. The crude mortality rate was 45% for the whole group, but only 27.3% in patients aged less than 80 years. One patient below the age of 80, out of 9 discharged, needed concomitant hemodialysis, but only one of those over 80 out of 5 in need for concomitant hemodialysis survived. We conclude ultrafiltration is a safe procedure that could be offered to diuretic resistant patients with severe congestive heart failure, but the ensuing need for concomitant hemodialysis is a bad prognostic factor, especially in patients over 80 years of age.

Key words: ultrafiltration, hemofiltration, congestive heart failure, acute decompensated heart failure, renal failure

Streszczenie

Kolejnych 20 pacjentów z opornym na diuretyki zaostrzeniem przewlekłej niewydolności serca poddano 1-11 sesji izolowanej ultrafiltracji. W przypadku, gdy pojawiały się biochemiczne wskazania do leczniu nerkowego, po zakończeniu sesji ultrafiltracji wykonywano hemodializę. Nie stwierdzono istotnych klinicznych ani technicznych problemów w usuwaniu tą metodą 2500-3500 ml wody osocza w czasie pojedynczej sesji i redukowania w ten sposób ciężaru ciała o 12-30 kg. Śmierćność w całej grupie wyniosła 45%, ale była niższa u osób poniżej 80. roku życia (27,3%). Hemodializ wymagał jeden z 9 pacjentów mających mniej niż 80 lat i wypisanych ze szpitala, a tylko 1 z 5 powyżej 80. roku życia, którzy wymagali hemodializ został wypisany ze szpitala. Wnioskujemy, że izolowana ultrafiltracja jest bezpieczną procedurą leczniczą, która może być oferowana pacjentom z oporną na diuretyki ciężką niewydolnością krążenia, a dołączającą się konieczność leczenia hemodializami jest złym czynnikiem rokowniczym, zwłaszcza u osób po 80. roku życia.

Słowa kluczowe: ultrafiltracja, hemofiltracja, zastoinowa niewydolność serca, ostra niewydolność serca, niewydolność nerek
The reduction, or even total removal, of extra body fluid is crucial to the successful therapy of the acute decompensated heart failure (ADHF) in patients with advanced heart failure. This is usually achieved with the use of sau-

lurics, usually furosemide, indapamide, or torasemide, given orally in outpatient settings. If the in-patient treat-

ment for ADHF is needed, furosemide as intravenous bolus or infusion is the therapeutic gold standard.

ADHF is defined as rapid appearance or worsening of clinical symptoms resulting from systolic or diastolic heart dysfunction, cardiac rhythm disturbance, or inadequately low or elevated blood pressure. It is often considered when a patient with prior heart disease presents with symptoms of heart failure. This condition is different from chronic heart failure, as patients with ADHF often have a more rapid clinical course and may require urgent medical attention.

The most common factors that precipitate hospitalization for decompensated heart failure are (2):

• Noncompliance with medical regimen, sodium and/or fluid restriction.
• Acute myocardial ischemia.
• Uncorrected high blood pressure.
• Atrial fibrillation and other arrhythmias.
• Recent addition of negative inotropic drugs (e.g., verapamil, nifedipine, diltiazem, beta blockers).
• Pulmonary embolus.
• Nonsteroidal anti-inflammatory drugs.
• Excessive alcohol or illicit drug use.
• Endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism).
• Concurrent infections (e.g., pneumonia, viral illnesses).

The venous blood volume expansion, pulmonary and systemic (both, splanchnic and peripheral), typical of CHF, results from decreased cardiac output, vascular resistance or pathological flow between the cardiac cavities. Even if the effective blood volume (i.e. inside the big arterial vessels) in chronic heart failure has been well preserved, the venous compartment is enlarged, second to sodium and water retention resulting from renal hypoperfusion. The chronic renal hypoperfusion second to heart dysfunction (cardiorenal syndrome type II) triggers many adaptive mechanisms – activation of renin-angiotensin-aldosterone axis, vasopressin release, increased blood natriuretic hormone levels and many others. Fluid retention leads to the increased pre- or afterload, increased cardiac filling pressures, myocardiac distention and remodeling, which close the vicious circle of progressive heart injury (3), and further deteriorate renal filtration (GFR) (4). The last might also result directly from the increased splanchnic venous pressure (5). This remains true for the opposite situation, when the fluid retention is triggered by renal insufficiency.

It is well known the hemoconcentration resulting from intensive diuretic treatment correlates positively with reduction of GFR in CHF and the decreased post-hospital survival (6). The higher the dose of diuretics is needed for reducing hypervolemia the worse is the prognosis (7, 8). The reduction in GFR and the CHF are the well known independent risk factors for death in general population. The coexistence of the two is even more fatal (9), which clearly suggest, aggressive diuretic therapy resulting in worsening renal function should be avoided. Renal failure worsens prognosis in both, the systolic and the diastolic CHF, and the impact of renal failure is more visible in patients with preserved ejection fraction (10), and even more in those with coexhisting anemia (11). The episode of ADHF further worsens post-hospital CHF patients’ survival, irrespective of renal failure (12). In-hospital mortality is increased and the length of stay prolonged in ADHF patients with renal failure (13). Interestingly, heart failure in patients on chronic hemodialysis is not a frequent cause of death, for it accounts for 7% of death only (14).

Worsening of renal insufficiency leads to less secretion of diuretics into the tubular fluid, so it requires an increase in the total dose of diuretic for an effective amount reaches its site of action (15). However, the diuretic-induced activation of the renin-angiotensin-aldosterone system, results in an increased sodium and water reabsorption through a variety of mechanisms. Hypertrophy of distal tubule epithelial cells results in greater sodium absorption distal to the loop of Henle, the site of action of loop diuretics (16). In patients with decompensated heart failure, venous pressure is also elevated, leading to decreased absorption of oral agents and decreased renal blood flow and consequently, renal sodium excretion (17).

In case the diuretic resistance ensues, due to renal injury or any other cause, the retained fluid can be rapidly removed from the body by inducing massive diarhoea, the use of vasopressin receptor antagonists (vaptans), which is still not well established, or by a well know mechanical, extracorporeal support which enables to control the volume and rate of water removal.

The first action on blood taken by the kidney is to separate plasma water in the renal glomerulus. Exactly the same process is mimicked by dialysers and hemofililers in a process driven by exerting the hydraulic pressure difference between blood and the contralateral side of the semipermeable filtration membrane. This convective technique became available to dialysis patients in mid-seventies of the past century. And from the very first moment it was clear the procedure could be usefull in treating decompensated heart failure (18). This convective process has to be individually tailored regarding the volume and rate of fluid removal. If it takes several hours (usually more than 6), and the rate of ultrafiltration is of maximum 0.16 ml/min/kg lean body mass (usually 500 ml/h in adults), the procedure is called slow continuous ultrafiltration (SCCUF). The higher ultrafiltration volumes and higher ultrafiltration...
rates cause hemoconcentration and call for intravenous infusion of crystalloids to prevent it. In such case the process is called hemofiltration (HF). The infusion of a substitution fluid is the only factor to differentiate SCUF and HF. The last one can last longer than 24 hours, which is known as continuous hemofiltration. It is usually performed on venous blood (continuous veno-veno hemofiltration, CVVH). Quick removal of relatively small amount of plasma water is called isolated ultrafiltration (IUF), to differentiate it from the ultrafiltration (UF) occurring during hemodialysis.

There are three types of engines enabling filtration – hemodialysis monitor to perform isolated ultrafiltration, continuous renal replacement therapy monitors to perform SCUF or CVVHF, and specialized ultrafiltration monitors to perform solely the SCUF. The last technology is currently commercially unavailable in Europe. All three techniques operate on venous blood, which means blood is taken from the splanchnic overloaded compartment and returned to it after the volume has been reduced by ultrafiltration. The access to venous blood to ensure sufficient extracorporeal blood flow is possible by insertion of a central catheter. Typically the 250-500 ml/h of water is removed, the blood flow varies 20-200 ml/min, and systemic coagulation is obtained with heparin infusion (1000 IU/h, adjusted accordingly to ACT). The volume of the In-circuit extracorporeal blood is small – 30-50 ml.

Removig only 2-3 l of plasma water in 4-6 hours promotes relief of dyspnea, reduces the right (-70%) and left (-45%) ventricular filling pressures, the pulmonary arterial pressure and arteriolar resistance, without significant variations in heart rate, aortic pressure, cardiac index, and systemic vascular resistance. The urinary output is substantially enhanced by the procedure (19). Even removing as little as 1.6 l of plasma water by aquapheresis resulted within the first 48 hours in significant, and sustained for at least three month, decrease in plasma renin, norepinephrine, and aldosterone. This was not observed after furosemide (20). Also the removal of more than 4 l of plasma water was safe and resulted in clinical improvement (21).

However, the intention to remove 4 liters of plasma water in 8 hours results, in 45% of patients, in plasma creatinine increase of at least 0.3 mg/dl (22). This means the ultrafiltration rate of 500 ml/min for longer than 6 hours, and decreasing body fluids by 3 liters, results in severe renal hypoperfusion (and even acute renal injury) in 45% of patients, and is similar to that caused by intravenous saluretics (23).

For the aforementioned reasons congestion, the most frequent reason for hospital admission due to heart failure, which is traditionally treated with loop diuretics, should be removed with UF, if resistance to diuretics ensues. Diuretics, particularly in high doses, can be deleterious. In addition, patients with renal hypoperfusion second to advanced heart failure present diminished response to loop diuretics. In such cases, ultrafiltration removes more body fluids as compared to diuretics, while demonstrating no major safety concerns, and decreasing re-hospitalizations within 90 days in selected groups of patients. Generally, ultrafiltration for removing water excess in diuretic resistant patients presenting with ADHF, or severe CHF is considered a safe, well tolerated procedure, which in some cases restores sensitivity to diuretics.

MATERIAL AND METHODS

The consecutive 20 adults (10 female, 10 male), aged 44-92 (mean 69, median 74 years of age) with clinical and radiological signs of acutely de-compensated congestive heart failure, started ultrafiltration for resistance to diuretics despite optimal pharmacotherapy. Six of them were older than 80 years of age (3 women, 3 men). All patients had plasma creatinine above normal values. If the urea plasma concentration had exceeded 200 mg/dl or anuria had been lasting for more than 12 hours, the ultrafiltration would have been followed by hemodialysis. In the first 6 patients, until the necessary experience has been gained, renal failure excluded from commencing the UF therapy. Each ultrafiltration session aimed to remove 3000-5000 ml within 3-5 hours (ultrafiltration rate 500-1000 ml/min), and was ceased prior to the intended volume has been removed only for clinical reasons (hypotension, arrhythmia, death). The standard dialysis equipment was used, and the vascular access was assured by the temporary dual lumen catheter placed into superior vena cava. The endpoint of observation was discharge from the hospital (primary endpoint) or death during hospitalisation, irrespective of previous cessation of ultrafiltration therapy.

The OpenEpi v 2.3.1 software (freeware) was used to calculate relevant statistics.

RESULTS

The outcomes of the treatment are presented in table 1.

<table>
<thead>
<tr>
<th>Age group</th>
<th>UF only</th>
<th>UF + HD</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80</td>
<td>8</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>≥ 80</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DISCHARGED</td>
<td>9</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>DEATH IN HOSPITAL</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>13</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>SUBTOTAL</td>
<td>13</td>
<td>7</td>
<td>20</td>
</tr>
</tbody>
</table>
The discharge from hospital was possible in 11 cases (55%) which equals to crude mortality rate of 45% (35.7% and 66.7% in aged less than and more than 80 years of age, respectively – Yates corrected chi² = 0.616, p = 0.433 > 0.05, OR = 3.6; 95% CI < 0.534-23.445 >; p = 0.336 > 0.05). Out of 20 patients 7 required hemodialysis (35%). The need for hemodi-
alysis increased slightly, but insignificantly, the risk of death and odds ratio for death (RR = 2.321, 95% CI < 0.896-4.424 >; p = 0 > 0.05 and OR = 5.625; 95% CI < 0.822-37.253 >; Fisher’s exact p = 0.160 > 0.05), which resulted in decreased, insignificantly, chances for hospital discharge (RR = 0.413, 95% CI < 0.119-1.091 and OR = 0.178; 95% CI < 0.027-1.217 >, Fisher’s exact p = 0.160 > 0.05).

Out of patients aged more than 80 years died 75%, who needed both, ultrafiltration and hemodialysis. The in those under 80 years of age was 33.3%. There was no significant difference in mortality, relative risk of death and odds ratio for death between the younger and older group (the Yates corrected chi² = 0.024, p = 0.876 > 0.05, RR = 1.125; 95% CI < 0.594-2.332 >, p > 0.05, OR = 1.500; 95% CI < 0.993-25.856 >, Fisher’s exact p = 1.000 > 0.05). Only one patient needed hemodialysis in the group of 9 patients aged less than 80 years who were discharged from the hospital. Out of 11 discharged patients 2 needed transient hemodi-
alysis and only four patients out of 9 who died, did not.

Up to 11 sessions in one patients were performed, and the usual volume of ultrafiltration at single session was 2500-3500 ml. The reduction of body weight was not always possible, but in one case the loss of 12 kg in 5 sessions and 30 kg in 2 sessions only in another, were achieved.

The hypotension episode during ultrafiltration ses-
sion have been rare and it has never been possible to differentiate between cardiac and hypovolemic etiolo-
ogy of the ensuing complication.

**DISCUSSION**

Aquapheresis is a relatively new, and expensive, tool to fight ADHF. As such, its use off clinical trials is usually reserved for the most difficult, resistant cases. The results of aquapheresis performed by us in a low in number and extremely unselected group of patients can be suggestive only, since no control group, nor any randomization were intended. This was a purely obser-
vational, retrospective study on intervention outcomes in an off-clinical-trial setting. As such the study shares all the drawbacks and all the shortfalls of non-rando-
mised trials. However, this is also the unique value of the study, for it consists in everyday clinical reality and refers to common patients.

The very encouraging results of using UF in the very first 6 ADHF patients at our hospital were already publi-
shed elsewhere (24). The need for hemodialysis excl-
luded ADHF patients from this initial subgroup of pa-
tients. The following unselected 14 patients were older as compared to the first 6 cases reported (42.8% over 80 years of age, and only 7.1% below 50 years of age) and, contrary to the first 6 cases, they frequently deve-
doped renal failure as part of the multorgan dysfunc-
tion second to terminal heart failure. As a result, the crude mortality rose from 16.6% in the first 6 patients to 57.1% in the 14 to follow. The change in our appro-
ach to resistant ADHF, i.e. the inclusion of all consecu-
tive patients can partly reflect the different outcomes of standard care as compared to clinical trials seen in everyday clinical practice. Due to the low number of patients and the lack of standardized inclusion criteria, the variety of clinical conditions made any patients’ clustering meaningless. Looking at the demography and co-morbidity variables we could see the extreme dispersion of data and many subgroups would remain zero. The inclusion of such variables would be redundant, and we decided to drop their use. This is why we focused on the two most obvious variables – more advanced age and developing need for hemodialysis, which seemed to worsen the prognosis.

Only one patient over 80 years of age with acute decompensated heart failure resistant to diuretics sur-
vived if the need for hemodialysis ensued. None of these two factors influenced, however the outcomes in statistically significant manner, most probably second to low number of the patients sample. Even so, we con-
sider the results of our treatment encouraging, especi-
ally, because, even in this unselected, and terminally ill patients, we could achieve good clinical outcome (discharge from hospital) in every second extremely severe case.

The procedure we used did not differ significantly from that in randomised trials, but we performed it in an unselected group of very old people. The relative simplicity of the procedure and lack of serious com-
plcations encourage us to implement it more frequent-
ly and earlier in the clinical setting, as suggested by others.

The only four randomized trials on ultrafiltration EUPHORIA, UNlOAD, ULTRADISCO and RAPID-CHF further confirmed the different hemodynamic impact of ultrafiltration as compared to diuretics. The ultrafiltration group showed significant improvement in stroke vol-
ume index, cardiac index, cardiac power output, dP/dtmax, and cardiac cycle efficiency, which remained stable or decreased during diuretic therapy. The systemic vascular resistance significantly decreased, and systolic and diastolic blood pressures remained constant. These UF-induced changes were accompa-
nied by significant decrease in N-terminal proBNP and aldosterone levels, which remained unchanged in diu-
retic group (25). Ultrafiltration of 5 l of plasma water in ADHF patients resulted in less rehospitalisations within the first 3 post-discharge month as compared to diu-
retics alone (26). Ultrafiltration is associated with fewer
rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure (27), but the effect becomes evident only 30 days after hospital discharge (28). It has been also proved, the 6 kg body weight reduction with UF normalizes plasma sodium, and this effect lasts at least 3 month (29). Starting UF within the first 12 h of diuretic therapy allows for additional 3 kg of body weight reduction within 48 h, when each of the 8 hours-long UF session removed 3.2 l of plasma water (30).

The ultrafiltration procedure results in blood volume reduction, increase in systemic (venous) hematocrit and protein concentration (31, 32) and cause the interstitial fluid inflow to prevent further blood volume reduction. This plasma refilling in oedematous patients is slightly increased above the normal plasma refilling rate of 5.6 ± 1.4 ml/(min*mm Hg*50 kg LBM) (33), seen in euvoelemic patients. The refilling rate is somehow independent from hemococoncentration, since even at stable hematocrit, it decreases along with ultrafiltration induced body fluid reduction (34). The ultrafiltration results also microcirculatory changes lead to volume shifts from the micro- to the macrocirculation with adjustment of the macrovascular Hctsys during UF. A compliant microcirculation acts as a blood reservoir allowing volume compensation during UF (30).

The diuretics and ultrafiltration reduce body fluids volume, but ultrafiltration makes it more physiological way. Importantly, the effect of ultrafiltration is long-lasting. Unfortunately, for technical and economical reasons it is less convenient in everyday use as compared to diuretics – needs central vein catheterization, trained staff etc. As we were able to show in our small, unselected group of patients, it can be safely, and with reasonably good results, used even in elderly. The need for concomitant dialysis ensuing in elderly is a bad prognostic factor. Our small in number therapeutic group does not allow to declare the same is truth in younger patients, but the slightly increased risk of death in such clinical conditions was noticed. The best results were observed under age of 80 if the renal failure did not call for hemodialysis. For the ultrafiltration was usually performed in patients with renal hypoperfusion we absolutely support the statement Section 4.5.2.1. of the ACCF/AHA guidelines: “If all diuretic strategies are unsuccessful, ultrafiltration or another renal replacement strategy may be reasonable. Ultrafiltration moves water and small to medium-weight solutes across a semipermeable membrane to reduce volume overload.” Because the electrolyte concentration is similar to plasma, relatively more sodium can be removed than by diuretics. Consultation with a kidney specialist may be appropriate before opting for any mechanical strategy to affect diuresis” (35).

CONCLUSIONS

In our experience ultrafiltration could be a second-line inpatient therapeutic modality offered to the diuretic-refractory patients presenting with severe congestive heart failure, irrespective of age. The concomitant need for hemodialysis seems to worsen the prognosis, especially in patients aged more than 80 years.

BIBLIOGRAPHY


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