Editorial

Ultrafiltration does not affect certain predictors of outcome in heart failure

Amir Kazory *

Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida, 1600 SW Archer Road Box 10224 Gainesville, FL 32610-0224, USA

ARTICLE INFO

Article history:
Received 22 January 2010
Accepted 14 February 2010
Available online 6 March 2010

Keywords:
Heart Failure
Hyponatremia
BUN
Mortality
Neurohormonal activation

ABSTRACT

Ultrafiltration as a therapeutic option for heart failure has been of more recent interest due to a proposed physiologic basis for its mechanism of action and the development of newer technology. Several studies have so far demonstrated its efficacy in rapid removal of fluid and improvement in congestive symptoms. However, there is currently no data on its impact on long-term outcomes of patients with heart failure. Moreover, evidence extracted from available studies does not support any beneficial impact on established predictors of mortality in this setting (i.e., blood urea nitrogen and serum sodium levels). This observation coupled with previous data indicating lack of expected beneficial effect on renal function highlights the emergent need for robust long-term outcome studies prior to expansion of the implementation of this complicated and costly therapy.

1. Introduction

Risk stratification of patient populations can potentially help physicians identify individual patients at higher risk in order to provide them with a customized treatment strategy and to more precisely predict their prognosis. Moreover, identification of the predictors of mortality can be helpful in assessing the potential impact of a therapeutic modality on patients’ outcomes through its effects on these variables. This is especially beneficial in cases of emerging treatment strategies where long-term morbidity and mortality data are not available. Although ultrafiltration therapy has been used in the treatment of heart failure (HF) since decades ago, it was not until very recently that a greater interest was generated with the development of newer devices and a number of robust studies. Currently, despite promising results regarding the efficacy and safety of the ultrafiltration in HF, there is no data on long-term outcomes of this modality [1]. Therefore, awaiting studies specifically designed for this purpose, the potential effect of ultrafiltration can be assessed through its impact on the established predictors of mortality.

2. Prediction of mortality

In 2003, Lee et al. developed a practical risk assessment model to predict mortality among hospitalized patients with HF [2]. This model used patient characteristics as well as clinical and laboratory information readily available at the time of admission. Serum sodium and blood urea nitrogen (BUN) were the only laboratory markers that were found in multivariate analysis to reliably predict mortality both at 30 days and 1 year. One year later, Felker et al. found similar results: BUN and serum sodium along with other factors such as systolic blood pressure were independent predictors of 60-day mortality in patients admitted for HF [3]. Beside the intermediate- and long-term outcomes, attempts have been made to identify the predictors of short-term outcomes. Using classification and regression tree analysis on data from Acute Decompensated National Heart Failure Registry (ADHERE), Fonarow et al. could identify BUN, systolic blood pressure, and serum creatinine to reliably risk stratify patients with HF for in-hospital mortality; a model that was later validated in a different patient population [4,5]. Similar results are found when specific subsets of patients with HF are evaluated. Kinugasa et al. specifically explored the markers of in-patient mortality in patients 65 years or older; BUN and serum sodium along with other factors such as low albumin level were again identified as predictors of in-hospital mortality [6]. Therefore, BUN and serum sodium are the two laboratory parameters that, along with various demographic and clinical factors, are consistently found to be the predictors of short-, intermediate-, and long-term outcomes across a large spectrum of patients with HF. Evaluation of the impact of ultrafiltration on these “modifiable” markers could be helpful in assessing its potential effect on outcomes.

3. Blood urea nitrogen

Recent studies suggest that in HF, BUN plays a distinct role beyond and above the assessment of renal function; it represents a surrogate marker for the degree of neurohormonal activation, the maladaptive response which represents the central pathophysiologic mechanism in HF [7,8]. Elevated levels of BUN have indeed been shown to indicate the “renal response” to a systemic pathologic process rather than
“renal dysfunction”. Therefore, it is not surprising that several studies have found a direct and strong relationship between elevated BUN and mortality across a large spectrum of patients with HF unrelated to renal function [2-5].

Mechanical removal of sodium and water from the intravascular sector via extracorporeal ultrafiltration, is an appealing therapeutic option as it can theoretically spare the macula densa, tubuloglomerular feedback mechanism, and neurohormonal activation [9]. Indeed, the lack of deleterious effects on renal hemodynamics and neurohormonal axis has been considered a major advantage of this therapy over standard treatment (i.e. diuretics). It would then be expected that this beneficial role be reflected in its effect on BUN. However, Among 9 available studies that have evaluated the efficacy and safety of ultrafiltration for HF, 6 have reported either no change or non-significant increase in BUN levels (Table 1). Interestingly, 2 studies demonstrated even an significant increase in BUN levels following ultrafiltration therapy. In one study, ultrafiltration therapy was compared with usual care; while both therapies resulted in significant weight loss compared to baseline (greater for ultrafiltration), only the ultrafiltration group demonstrated a significant increase in BUN after therapy (52 vs. 61 mg/dl respectively, p<0.01) [10]. Overall, the results of these trials do not support any beneficial role for ultrafiltration on BUN levels and neurohormonal activation in HF. It might be hypothesized that the beneficial impact of ultrafiltration can be masked by the efficient extraction of fluid resulting in intravascular volume depletion, decrease in GFR, and secondary elevation in BUN levels unrelated to neurohormonal activation. However, in the study by Filippatos et al., where baseline BUN was identified as a predictor of post-discharge mortality, no correlation could be found between the change in BUN during hospitalization and change in body weight [11]. Moreover, the reduction in GFR per se is also known to be associated with adverse outcomes in HF [12]. While it was hoped that ultrafiltration do not portend the deleterious effects of diuretics on renal function, a study by Rogers showed that it indeed is associated with a reduction in measured GFR to a degree similar to that of diuretics [13]. We have previously reported that current available studies on ultrafiltration in HF do not support any beneficial impact for this therapy on renal function assessed by serum creatinine or estimated GFR [14].

4. Serum sodium

Hyponatremia, a common finding in the setting of HF, is of hypervolemic type; there is a disproportionate retention of both sodium and water, with the increase in body fluid volume exceeding that of the total sodium content. Activation of the renin-angiotensin-aldosterone system (RAAS) and impaired response to natriuretic peptides are among the factors leading to the retention of sodium while the impaired water excretion is due to the enhanced reabsorption of the water in the proximal tubules as well as disturbance in the diluting ability of the distal nephron due to increased arginine vasopressin (AVP) release. Hyponatremia is an established marker of adverse outcomes in HF and it has indeed been shown that the degree of hyponatremia correlates with the severity of the disease in this setting [15]. Current therapies for HF such as thiazide diuretics and aldosterone receptor blockers can also contribute to this complication [16].

Isolated ultrafiltration represents a convective-based extracorporeal modality that extracts isotonc fluid from blood across a semi-permeable membrane. Since the concentration of solutes (e.g. sodium) is similar in the plasma and ultrafiltrate, this therapy does not have the ability to alter plasma levels of electrolytes [17,18]. This has been offered to be another advantage of ultrafiltration over standard therapy in HF [19]. However, based on the pathophysiological mechanisms of hyponatremia in HF (e.g., inappropriately elevated levels of AVP), it is conceivable that an improvement in hemodynamic

### Table 1
Summary of studies on ultrafiltration for heart failure; impact on BUN and serum sodium levels.

<table>
<thead>
<tr>
<th>Study design and protocol</th>
<th>Number of patients</th>
<th>Baseline BUN (mg/dl)</th>
<th>Post-UF BUN (mg/dl)</th>
<th>Baseline sodium (mEq/l)</th>
<th>Post-UF sodium (mEq/l)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaski (2003) [21]</td>
<td>No control group, a total of 25 treatment sessions</td>
<td>21</td>
<td>46.2</td>
<td>48.4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bart (2005) [22]</td>
<td>RCT, early single 8- hour UF plus usual care vs. usual care alone</td>
<td>40</td>
<td>36</td>
<td>44</td>
<td>137</td>
<td>136</td>
</tr>
<tr>
<td>Costanzo (2005) [20]</td>
<td>No control group, one session of UF for each patient</td>
<td>20</td>
<td>53</td>
<td>54</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td>Liang (2006) [23]</td>
<td>No control group, number of UF sessions at the discretion of physician (1 to 5 sessions)</td>
<td>11</td>
<td>69</td>
<td>NR</td>
<td>138</td>
<td>NR</td>
</tr>
<tr>
<td>Dahle (2006) [24]</td>
<td>No control group, UF sessions stopped at discretion of physician</td>
<td>9</td>
<td>36.3</td>
<td>37.8</td>
<td>130.4</td>
<td>128.6</td>
</tr>
<tr>
<td>Costanzo (2007) [19]</td>
<td>RCT, Single session early UF therapy, duration and rate of removal at discretion of physician</td>
<td>200</td>
<td>32</td>
<td>NR</td>
<td>139</td>
<td>NR</td>
</tr>
<tr>
<td>Jaski (2008) [25]</td>
<td>No control group, retrospective cohort, each patient with one or more sessions of UF therapy</td>
<td>100</td>
<td>47</td>
<td>NR</td>
<td>137</td>
<td>136</td>
</tr>
</tbody>
</table>

BUN: blood urea nitrogen, UF: ultrafiltration, RCT: randomized controlled trial, NR: not reported.
and neurohormonal status be reflected in the amelioration of the level of serum sodium. Therefore, while from a mechanistic standpoint, the ultrafiltration technique is not expected to directly alter serum sodium levels, it could indirectly affect it. The results of the recent ultrafiltration studies concerning the impact on serum sodium is summarized in Table 1. Seven studies could not find any significant change in serum sodium. Surprisingly, in two studies ultrafiltration therapy was followed by a decrease in serum sodium; one compared it with diuretic agents and found that, similar to diuretics, ultrafiltration significantly decreased serum sodium levels [20].

5. Conclusion

With the advent of newer portable devices, there has been an increasing interest in the use of ultrafiltration for the treatment of HF. The current trials have shown its efficacy and safety with promising results in terms of the rapid relief of congestive symptoms. However, the assessment of its impact on the known predictors of mortality does not support a potential beneficial effect on long-term outcomes. Whether this translates into lack of such an impact for ultrafiltration needs to be evaluated by studies specifically designed to address this question.

Acknowledgement

The author of this manuscript has certified that he complies with the Principles of Ethical Publishing in the International Journal of Cardiology [26].

References
