REVIEWS

Therapeutic approach to cardiorenal syndrome

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Abstract: Cardiorenal syndrome is often described in heart failure patients and it represents the deterioration of renal function in the context of heart failure. When it occurs, the prognosis of these patients is affected by the combination of these pathologies. The treatment for cardiorenal syndrome should be applied individually in order to achieve the improvement of the patient’s clinical status, the preservation of the heart and kidney function and a better outcome. Along with traditional therapies (diuretics, inotropes), which often develop resistance, the beneficial effect of new therapeutic options (ultrafiltration, vasopressin and adenosine antagonists) is being evaluated in different trials.

Keywords: cardiac insufficiency, renal insufficiency, cardiorenal syndrome

These types of CRS are in fact five different syndromes from an epidemiologic, clinical and therapeutic point of view. Often different components, from the different types of CRS, interact with one another. In this article we will refer mostly to the first two types (cardiorenal syndromes).

Renal dysfunction associated with heart failure leads to a severe prognosis. According to some studies, this association increases the mortality rate in these patients with up to 20%²-⁴.

The physiopathological mechanisms which intermediate the disequilibrium present in CRS is presented in Figure 1, according to the Guyton model⁵.

In daily practice, the diagnosis of CRS is based on the existence of an association between heart failure and the onset, or exacerbation, of a renal dysfunction. Current diagnostic elements include the increase of serum creatinine levels by more than 30% compared to initial levels, reducing the diuresis with adequate doses of diuretics, the aggravation of heart failure signs and symptoms, or the absence of regression of hemodyna-

Table 1. The classification of cardiorenal syndromes

<table>
<thead>
<tr>
<th>CRS type</th>
<th>Primary affliction</th>
<th>Secondary affliction</th>
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<tbody>
<tr>
<td>1. Acute Cardiorenal S.</td>
<td>Acute heart failure</td>
<td>Acute renal lesion</td>
</tr>
<tr>
<td>2. Chronic Cardiorenal S</td>
<td>Chronic heart failure</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>3. Acute Renocardiac S.</td>
<td>Acute renal lesion</td>
<td>Acute heart failure</td>
</tr>
<tr>
<td>4. Chronic Renocardiac S.</td>
<td>Chronic renal failure</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>5. Secondary S.</td>
<td>Systemic disease</td>
<td>Heart and renal failure</td>
</tr>
</tbody>
</table>

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The development of resistance to diuretics can be considered a bad prognostic indicator in patients suffering from chronic heart failure. There are numerous mechanisms involved in this process. Two types of diuretics resistance were described: short and long term resistance. The first appears after the administration of a single first dose due to neurohormonal activation. Long term resistance develops after long term treatment with loop diuretics, inducing modifications in the renal structure, such as epithelial cell hypertrophy in the distal tubules, increasing Na reabsorption and decreasing diuresis.

A summary of the mechanisms involved in the development of resistance to diuretics is illustrated in Table 3.

**CRS management**

Considering the complex and heterogeneous physiopathology of CRS, patient management is a real challenge. Up to the present time, there is no treatment ensuring guaranteed success because each patient has his/her own personal history, risk profile and a combination of comorbidities. The medication used for the treatment of CRS is illustrated in Table 4.

**Optimizing the treatment for heart and renal failure**

The best means to control CRS is to prevent it from occurring. This implies adapting heart failure therapy to hemodynamic and clinical conditions, to the presence of associated diseases and to the use of therapeutic agents capable of preserving or improving the renal function. The patient requires permanent hemody-
mic monitoring, especially in case of arterial hypotension and a limitation of the sodium input to less than 2g, as well as a fluid intake limitation to less than 1000 ml/24h, in case the patient presents hyponatremia. It is necessary to monitor weight, ionogram, serum values for urea and creatinine, GFR, diuresis. A serial echocardiography monitoring is also useful. The use of bioimpedance vector analysis has significant prognostic results, positively correlating itself with the BNP values in heart failure. This could prove useful in the management of these patients, to maintain hemodynamic stability and an optimal volemic control.

NEUROHORMONAL MEDICATION

There are therapies used in heart failure which have proved their importance in the increase of survival, which target mostly the neurohormonal modifications. Such therapeutic schemes include beta blockers, ACE inhibitors and aldosterone antagonists.

a) Although the use of ACE inhibitors is frequently avoided, or interrupted, in order to prevent the alteration of the renal function, the increase of creatinine levels after initiating a treatment with ACE inhibitors can actually identify a subgroup of patients which will have a maximum benefit from their use. This requires careful monitoring of the renal function and blood pressure. In addition to all of these, interrupting the use of ACE inhibitors for this group of patients leads to the increase of the mortality risk. The effects of ACE inhibitors in the treatment of heart failure with associated renal failure are difficult to evaluate, because the extended studies which assessed their effects did not include patients with altered renal function.

Most of these studies had an exclusion threshold of 2 mg/dL for the serum creatinine. Even when renal failure was present, ACE inhibitors demonstrated the reduction of proteinuria and long term benefits regarding survival.

b) Beta blockers represent a heterogeneous class of drugs which have beneficial effects on the evolution of heart failure when renal dysfunction is associated. This is due to the higher levels of plasmatic norepinephrine, compared to individuals with a normal renal function. This prompts the enquiry as to what beta blocker is the most appropriate to be used in CRS; metoprolol and carvedilol are eliminated through the liver, leaving open the opportunity to be administered in unmodified doses, whereas bisoprolol is eliminated through both the liver and the kidneys, necessitating an adjustment of the dose to the renal function.

DIURETIC TREATMENT

Diuretics have represented for a long time the initial and essential component in the management of patients suffering from heart failure. They also represent an important element in the elimination of volemic overload in CRS, but they must be used judiciously, under careful monitoring of the renal function and of the volemic status.

Diuretics increase neurohormonal activity, the activity of plasmatic renin and aldosterone and the plasmatic levels of norepinephrine and arginine-vasopressin. They also increment peripheral vascular resistance and indirectly deteriorate left ventricle function. By cumulating these effects, diuretics increase the mortality risk.

The first therapeutic measure is to administer intravenously a loop diuretic for a better effect on a renal level. It is often necessary to double the dose when an appropriate diuretic effect is not obtained. It can be administered in a continuous venous perfusion, with doses adjusted to the severity of the renal dysfunction, for 2-4 hours. Some authors have observed the increase of urinary output, the decrease of the frequency of ototoxicity and a shorter period of admittance. This practice was not confirmed by the randomized prospective trial The Diuretic Optimization Strategies Evaluation (DOSE), which included 308 patients with acute decompensated heart failure. DOSE did not reveal significant differences in the evolution of patients after receiving diuretic treatment in bolus, compared to those who received the treatment through continuo-

Table 4. The medication used for the treatment of CRS

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Diuretics</td>
<td>Acute and chronic CRS</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>Chronic CRS</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Chronic CRS</td>
</tr>
<tr>
<td>Aldosterone antagonist diuretic</td>
<td>Chronic CRS</td>
</tr>
<tr>
<td>Vasodilators: Nitroglycerine, Nesiritide</td>
<td>Acute CRS and hypertension</td>
</tr>
<tr>
<td>Inotrope positive: Dobutamine, Milrinone, Levosimendan</td>
<td>Acute CRS and hypotension</td>
</tr>
<tr>
<td>Vasopressin antagonists: Tolvaptan</td>
<td>Acute CRS</td>
</tr>
<tr>
<td>Vasopresina: Tolvaptan</td>
<td>Acute CRS</td>
</tr>
<tr>
<td>Adenosine antagonists: Rolofylline</td>
<td>Acute and chronic CRS</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Acute and chronic CRS</td>
</tr>
<tr>
<td>Synthetic natriuretic peptide CD - NP</td>
<td>Acute CRS</td>
</tr>
<tr>
<td>Soluble guanylate cyclase activators</td>
<td>Acute CRS</td>
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</table>

CRS - cardiorenal syndrome, ACE inhibitors - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers
us endovenous perfusion. As a result of administering high doses of diuretics, as opposed to the administration of low doses, a transitory deterioration of the renal function could be observed. This had no adverse effects regarding the patient’s prognosis\textsuperscript{21}. Another option taken into study when hypoalbuminemia is associated considers the combined use of furosemide with low sodium albumin. A furosemide - albumin complex is formed, increasing the disponibility of the diuretic by maintaing it in the vascular stream\textsuperscript{22}.

**ULTRAFILTRATION**

Ultrafiltration is a treatment option which is increasin-gly used in the treatment of CRS. It successfully eliminates the liquid excesses in cases with severe heart failure, associated with refractory hydrosaline retention and resistance to optimal diuretic treatment. Ultrafiltration is a mechanical process which consists of removing isotonic liquid and low molecular weight molecules from the circulatory system, based on a pressure gradient and using a semi permeable membrane. In a classic manner a central venous catheter is required, especially for patients with edema, but modern methods allow the use of the cubital vein and the use of a low flow catheter\textsuperscript{23}. Its effects include the decrease of the right atrial pressure and the downgrade of the pressure blocked in the pulmonary capillaries, without a significant impact on the cardiac output and stroke volume\textsuperscript{24}. Ultrafiltration eliminates a larger quantity of water and sodium compared to diuretics, without neurohormo-nal activation, allowing the elimination of approxima-tely 3-4 liters of liquid per session. Because of the ben-efits observed in the treatment of CRS patients a large number of studies were dedicated to the evaluation of the efficiency of ultrafiltration in their treatment. RA-PID CHF studied liquid elimination and the evolution of some patients admitted for CRS, finding better results in cases where ultrafiltration was used, rather than a classic treatment\textsuperscript{25}.

Another study conducted on patients with acute heart failure was the UNLOAD trial. Patients who underwent ultrafiltration lost more weight than those who were given diuretics, but without any statistically significant differences concerning the reduction of dyspnea or the improvement of the renal function. However, the lot of patients treated with ultrafiltration had a lower re-admittance rate after 90 days from the initial admission\textsuperscript{26}.

The indications of ultrafiltration in the treatment of heart failure are limited in day to day practice to patients with edema syndromes refractory to optimal doses of diuretics, or in cases with aggravating renal failure. Due to the high costs it implies and the need for a better patient surveillance, new studies are needed to evaluate ultrafiltration from the perspective of cost-efficiency, moment of administration (clinical context, the gravity of the organ dysfunction) and protocol (type of treat-ment, rhythm and period of administration). The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS) study is currently in progress and tries to answer some of these questions. The patients included in this controlled and randomized trial have been hospitalized for acute, destabilized heart failure and developed cardiorenal syndrome. Serum creatinine and weight were monitored for any modifications at 96 h after admission. Considering the already existing proof, ultrafiltration should be considered and used as first line therapy in CRS.

**Vasodilatation treatment**

Vasodilatation treatment determines the rapid reduc-tion of the ventricular filling pressure, central venous pressure and myocardial oxygen consumption, improving cardiac function.

a) Nitroglycerin is frequently used in heart failure to reduce pulmonary congestion. The reduction of venous pressure could be benefic in CRS by reduc-ing the renal venous pressure. However, the benefits to overall survival and renal function improvement deriving from the use of nitroglycerin in CRS are not yet known.

b) Nesiritide is a recombined BNP (brain natriuretic peptide) which induces vasodilatation with the reduction of cardiac afterload and preload, increasing the cardiac output\textsuperscript{27}. Several clinical studies have confirmed anterior favorable results on hemodynamic parameters and have also shown symptomatic improvement. When nesiritide was compared to an inotrope intravenous medication or to vasodilatation therapy, a symptom improve-ment and increase of diuresis were observed.

Wang’s study was the first to explore the effects of nesiritide on the renal function, in patients with proven cardio-renal dysfunction. The expectations were not matched by the results. This study concluded that nesiritide had no effect on the glomerular filtration rate, renal plasma flow and urine volume or sodium excretion\textsuperscript{28}. Although the initial hypothesis was not con-firmed, the study does not exclude all possibilities for this agent to play a role in the treatment of heart failure symptoms.
Recently, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF) trial included over 7000 patients with acute, decompensated heart failure. The patients included in this study received standard heart failure therapy associated with nesiritide in a continuous perfusion, or placebo. It concluded that nesiritide can be safely administered without adverse effects regarding the renal function or mortality and that it lead to a minor improvement concerning the dyspnea. There are other studies which have tested the effects of nesiritide administered in a single dose per week, evaluating this type of treatment for high risk patients, Fusion II. However, these studies did not prove any significant improvements in the quality of life, or survival. The Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE) trial is currently in progress. It includes patients with acute heart failure, treated with 3 different types of drugs: diuretic treatment, optimal when associated with nesiritide, low doses of dopamine and placebo. At the same time, the efficiency and the study profile of this therapy was studied on patients with acute heart failure.

**POSITIVE INOTROPIC AGENTS**

Such agents like dopamine, dobutamine, phosphodiesterase inhibitors and levosimendan are used in the treatment of CRS in order to facilitate diuresis, preserving or improving the renal function due to their capacity to increase the cardiac index and renal perfusion. Low doses of dopamine (lower than 5 µg/kg/min) were often used in order to improve renal function, but it appears that this effect is owed mostly to the increase of the cardiac output, rather than a local effect. Clinical studies have been conducted on the effects of dopamine and they have not revealed any clinical benefit. Also, in a study performed on patients with acute renal failure it was noticed that dopamine can actually worsen the renal perfusion.

The OPTIME study investigated the use of milrinone for patients suffering from chronic heart failure. It showed that patients in advanced stages of the disease do not have an improved prognostic if they follow this treatment. Inotrope medication can be introduced in the treatment of patients suffering from CRS only in cases in which renal failure develops secondary to low cardiac output. The medication will be administered on short term and under careful monitoring due to the risk of developing arrhythmia. It does not represent a routine treatment for patients suffering from chronic or acute heart failure because it increases the mortality risk and has multiple adverse effects on the heart.

The ROSE study, previously mentioned, proposes the optimization of heart failure therapy, wishing to administer low doses of dopamine in acute heart failure.

**The treatment of anemia**

The cardiorenal-anemia syndrome was extensively described in the literature. It develops as a result of the combination between heart failure and renal failure, through plurifactorial mechanisms. In its turn, anemia can exacerbate heart failure and CRS. Thus, a new concept appeared considering a new syndrome, with a different pathology than the one associated with classic CRS and with a diverse impact on patients’ morbidity and mortality.

The treatment of anemia with erythropoietin demonstrated a favorable impact on the cardiac function, increasing left ventricular ejection fraction and physical performance. However, the correction of the anemia must be only partial, because an aggressive correction is accompanied by a high rate of adverse effects. Alpha darbepoetin also demonstrated a favorable effect in the treatment of patients suffering from heart failure. The RED-HF trial studies the effects of long term administration of alpha darbepoetin to patients with left ventricular dysfunction.

**FUTURE DIRECTIONS IN THE STUDY AND TREATMENT OF CARDIORENAL DYSFUNCTION**

In order to develop new approaches to this syndrome there are several ongoing research projects, testing new therapies. Other options include the early introduction of dialysis and ultrafiltration; in severe cases, left ventricular devices and intra aortic counter pulsation balloons can be used for short term management of these patients.

a) Vasopressin antagonists: anti diuretic hormone, also known as arginin vasopressin (AVP), is secreted when the circulatory volume decreases, or when hyperosmolarity occurs. It exerts its effect through three kinds of receptors, of which the V2 receptors are located in the kidney, more precisely in the distal and collecting tubules. AVP acts at this level causing vasoconstriction and water reabsorption. AVP serum levels can be low in heart failure with hypotension and low sanguine circulatory volume. A class of drugs called vaptans was developed in order to antagonize the effects of AVP, increasing water excretion by enhancing the
clearance of water and increasing serum sodium levels, useful especially in hyponatremic states\textsuperscript{43}. The ACTIV study focused on the effects of administering tolvaptan in acute heart failure. It was observed that patients treated with tolvaptan presented a more rapid weight loss and an increased urinary debit compared to those who have received the standard treatment, without modifications to serum creatinine values at discharge\textsuperscript{44}. A more ample study, EVEREST, confirmed the data already known from ACTIV, but did not demonstrate any prognostic benefits from long term administration of tolvaptan in acute heart failure\textsuperscript{45}.

d) Soluble guanylate cyclase activators (cinaciguat, atisigicquat) can be used in the treatment of heart failure to reduce systemic vasoconstriction by increasing the vasodilatation effect of nitric oxide, thus preventing the development of resistance to nitrates, which usually appears in heart failure\textsuperscript{55}. An experimental study showed the reduction of the preload and afterload, with the increase of the cardiac output in a heart failure model\textsuperscript{56}. The observed renal effect was the preservation of glomerular filtration, possible because of the effects on renal resistance.

e) The intrarenal administration of medication can be an alternative to the classic administration of drugs in CRS, in order to increase the local concentration and inducing local renal effects, with less systemic exposure and side effects. By administering fenoldopam (a dopaminergic agonist) or nesiritide locally, in the renal arteries the renal metabolization occurring when the drug is administered intravenously is by-passed, inducing less systemic side-effects\textsuperscript{48,57} refI. Phosphodiesterase V inhibitors are also in study as a possible therapy, administered in association with BNP in order to offer a new vision of CRS physiopathology and to establish a new therapeutic combination, with influence in the treatment and prevention of heart failure\textsuperscript{58}. Sympathetic renal denervation can have a potential role in the prevention and management of cardiorenal syndrome, without having any clinical or experimental trials to confirm the therapeutic effects of this procedure.

**CONCLUSIONS**

According to the presented facts we can safely affirm that the onset of cardiorenal syndrome is a bad, but frequent development in the evolution of chronic heart failure. Understanding the mechanisms involved in the development of CRS is rudimentary at best, lacking efficient therapies. The treatment of heart failure is
nowadays mostly the same as it was a few decades ago, especially from the point of view of cardiorenal interactions. Our hope is that new and efficient therapies will be developed in order to prevent this challenging syndrome.

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