The Cardio-Renal Syndrome (CRS)

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Summary
The presence of impaired kidney function during heart failure and vice versa is a frequent occurrence. This situation is defined “Cardio-Renal Syndrome”.
In the Cardio-Renal Syndrome (CRS) are included 5 different sub-syndromes defined on the basis of the organ primitively responsible: Acute Cardio-Renal Syndrome (Type 1), Chronic Cardio-Renal Syndrome (Type 2), Acute Reno-Cardiac Syndrome (Type 3), Chronic Renal-Cardiac Syndrome (Type 4) and Secondary Cardio-Renal Syndrome (Type 5).
The physiopathologic mechanisms underlying CRS are still partially obscure, but a key role seems to be played by the Renin-Angiotensin-Aldosterone axis.
Therapeutic strategies involved in CRS treatment include the use of diuretics, ACE inhibitors, Angiotensin Receptor Blockers and β-Blockers, emphasizing the role of a proper use of medication indicated for the treatment of cardiac decompensation.

Key words: Cardio-renal syndrome, Reno-cardiac syndrome, Acute decompensated heart failure, Acute heart failure, Chronic heart failure, Acute kidney injury, Acute renal failure, Chronic renal failure

The presence of a new-onset of renal failure, or the aggravation of a pre-existing one within the ambit of an acute or chronic heart failure exacerbation is frequently found in daily cardiologic clinical practice. It also frequently occurs as a contemporary and progressive cardiac involvement in the development of cadres of renal failure.

Existing relationships between the two diseases had not been fully elucidated for a long time, although it soon became evident that the simultaneous involvement of the two apparatuses conditioned the prognosis in a pejorative sense.

Frequent detailed evidence in literature found a definite classification to this effect in the specific ‘consensus’ conference held in Venice in 2008, which enabled the definition of clinical pictures and physiopathological shared areas within the ambit of the Cardio-Renal Syndrome (CRS).

Classification of the CRS
General definition: The cardio-renal syndrome is a physiopathological disorder of the heart and kidneys in which the acute or chronic dysfunction of one organ induces acute or chronic dysfunction in the other.

In the sense defined above 5 subtypes can be identified:
- **Type I Acute Cardio-Renal Syndrome**: acute worsening of cardiac function that determines renal dysfunction;
- **Type II Chronic Cardio-Renal Syndrome**: chronic abnormalities in cardiac function that determines renal dysfunction;
- **Type III Acute Reno-Cardiac Syndrome**: acute worsening of renal function that determines cardiac dysfunction;
- **Type IV Chronic Reno-Cardiac Syndrome**: chronic abnormalities of renal function that determine a cardiac dysfunction;
- **Type V Secondary 'Cardio-Renal Syndrome**: simultaneous cardiac and renal dysfunction caused by an acute systemic condition.

**Acute Cardio-Renal Syndrome (CRS Type 1)**
This condition occurs when an acute deterioration of cardiac function determines an "Acute Kidney Injury (AKI)" and / or Acute Renal Failure (ARF).
The spectrum of acute cardiac conditions that may contribute to a worsening of renal function in the sense of the development of cardio-renal acute syndrome (CRS Type 1) includes:
- Acutely decompensated heart failure (ADHF),
- Acute coronary syndrome (ACS),
- Cardiogenic shock,
- Low-flow syndrome following cardiac surgery.

Also attributable to this type of renal impairment is the nephrotoxic effect due to contrast medium, widely used in diagnostic tests indicated in acute cardiac conditions that give rise to CRS type 1.
Acute impairment of renal function, as evidenced by an increase greater than 0.3 mg / dl of baseline serum creatinine, occurring in a variable percentage of 27-40% of patients with acute heart failure and / or acute coronary syndrome.
The development of a CRS type 1 causes a significant deterioration in morbidity and mortality as well as prolonged hospitalization.

**Chronic Cardio-Renal Syndrome (CRS Type 2)**
It is a very common situation, which occurs when chronic renal failure develops during cardiac impairment (CRF). Approximately 63% of patients with chronic congestive heart failure presents a picture of Chronic Renal Failure (Stage 3-5), with values of glomerular filtrate (GF) inferior to 60 ml/min/m².
The definition of "chronic cardiac impairment" includes many different heart conditions:
- Chronic heart failure,
- Atrial fibrillation,
- Congenital cyanotic heart disease,
- Constrictive pericarditis,
- Chronic ischemic heart disease.

Since the coexistence of chronic cardiac impairment in chronic kidney disease is not uncommon, it can be difficult to define which condition is pre-existing and, in this sense, an accurate anamnestic reconstruction is extremely valuable.

In this subtype (CRS Type 2), the coexistence of two pathological conditions, renal and cardiac, also worsens prognosis, both in terms of increased morbidity and in the sense of an increased mortality risk, therefore renal failure can be considered a negative prognostic factor in the independent assessment of the evolution of a framework of heart failure.

**Acute Reno-Cardiac Syndrome (CRS Type 3)**
CRS Tyoe 3 is identifiable in the situation where an acute deterioration of renal function (ARF) results in damage and / or acute cardiac dysfunction.
The boundaries of this condition are still partially undefined, since it is only possible to rely on occasional and unsystematic reports. Typical clinical conditions consist in:
- Drug-induced acute renal disease,
- Acute renal failure after major surgery (cardiac and non),
- Acute nephritic syndromes,
- Rhabdomyolysis.

This type of CRS also refers to acute renal failure from medium contrast (CI-AKI), especially if not determined by diagnostic tests aimed at evaluating a preexistent heart disease, which otherwise would identify a type 1 CRS. These conditions of AKI are frequently accompanied by the development of acute coronary syndrome, arrhythmias, acute decompensation and EPA.

**Chronic Renal-Cardiac Syndrome (CRS Type 4)**

Type 4 CRS consists of the condition in which primitive chronic renal failure (CRF) contributes to the deterioration of cardiac function (e.g. cardiac remodeling, left ventricular diastolic dysfunction, left ventricular hypertrophy) with an increased risk of acute cardiovascular events (myocardial infarction, stroke, acute heart failure).

The presence of chronic renal failure in this group of patients determines a mortality rate 10-20 times higher than in a comparable population by age and sex, but without IRC. Observational and population studies have largely documented a rising trend in morbidity and mortality from cardiovascular disease with the passage to worsening stages of renal dysfunction (from stage 1 to stage 3).

An inverse relationship emerges between renal function and negative cardiovascular outcome for high-risk cohorts, the creatinine clearance is a short-term predictor of poor outcome (cardiovascular death or myocardial infarction).

This negative correlation, if basically pre-existent, could be further compounded by a kind of fear, or "therapeutic nihilism" attitude towards persons with renal insufficiency, in which less attention is devoted to modifying traditional cardiovascular risk factors, as a result of a less aggressive therapeutic approach for fear of a further deterioration of renal function associated with the use of drugs.

**Secondary Cardio-Renal Syndrome (CRS Type 5)**

Type 5 CRS is characterized by an acute or chronic systemic disease that causes simultaneous cardiac and renal dysfunction.

Examples of this can be found in sepsis, SLE, amyloidosis, diabetes mellitus, sarcoidosis. The co-existence of aggravating conditions, such as diabetes and/or hypertension, may increase the severity of the impairment of the two organs.

The physiopathological characteristics of condition have not yet been well defined, but it has its own current epidemiological logic.

**Physiopathology of CRS**

Physiopathological mechanisms supporting the simultaneous involvement of cardiovascular and renal functions in the manifestation of CRS are complex and have not yet been fully elucidated. In Heart Failure, the impairment of systolic and/or diastolic blood pressure leads to a series of adjustments that are configured in the decrease of cardiac output, stroke volume, and finally in reduced circulating volume (Fig. 1).

The decrease in arterial circulating blood volume is taken up by arterial baroreceptors and causes neurohormonal activation that produces compensatory mechanisms aimed at correcting the state of
relative hypovolemia and restoring proper tissue perfusion. In this sense, activation of the reninaangiotensina-aldosterone system (RAAS), the sympathetic nervous system (SNS), endothelin system and arginine-vasopressin causes water retention, mediated by sodium-retentive vasoconstriction, and counterbalanced by the activation of vasodilatory natriuretic hormone (natriuretic peptide) systems and cytokines (prostaglandins, bradykinin, NO)\textsuperscript{18, 19}. Under normal conditions, these mechanisms act unanimously in maintaining vascular tone and normalize cardiac output and tissue perfusion.

However, in terms of heart failure, the same mechanisms act by perpetuating vicious circles that waver, finally, in a state of chronic renal hypoxia, inflammation and oxidative stress which alone can alter cardiac and renal structure and function\textsuperscript{20}. The activation of SRAA determines renal hypoxia, vasoconstriction, intraglomerular hypertension, glomerulosclerosis, tubulointerstitial fibrosis and proteinuria\textsuperscript{21}, proteinuria\textsuperscript{21, 22}. Similarly the activation of the SNS involves proliferation of smooth muscle cells and adventitial fibroblasts in the intrarenal vascular walls\textsuperscript{23}. An attempt to attribute the responsibility of renal impairment to initial hemodynamic components, or modify the therapy in the course of acute heart failure has produced controversial and ultimately inadequate explanations, both because responsibility for the changes in cardiac output has not been identified, inasmuch as kidneys are able to tolerate decreases in cardiac index up to 1.5 L/min/m\textsuperscript{2}\textsuperscript{24, 25}; and also because renal failure can occur under conditions of both low as well as preserved tissue perfusion\textsuperscript{20, 25}. The only hemodynamic variable involved is the right atrial pressure (or central venous)\textsuperscript{26}.

Transrenal perfusion pressure is calculated from the mean arterial pressure minus the central venous pressure: therefore even a modest reduction in blood pressure if accompanied by a state of congestion, entails a clear impairment of renal perfusion pressure\textsuperscript{27, 28}; this condition can aggravate pre-existing renal impairment or determine acute impairment of renal function which, in addition to neuro-hormonal mechanisms triggered by the failure, aggravates conditions for compensation of cardiac and renal function in a vicious cycle.

To the above listed conditions must be added the direct effect of uremia in determining Uremic Heart Disease, a peculiar cardiomyopathy, which adds to and somewhat overlaps already compromised pre-existing cardiac conditions\textsuperscript{31}.

**Therapy**

To date, no one has identified and defined a specific therapeutic direction in the treatment of the cardio-renal syndrome.

Current evidence indicates that an optimal treatment of acute and chronic SCC, with an appropriate use of drugs proven to be effective (ACE-I, Angiotensin receptor inhibitors, beta-blockers, diuretics, ... ) is the best therapy possibile\textsuperscript{30} (Tables 1-2). In practical terms, **a) the introduction of therapy with an ACEI or ARB, must not cause alarm because of an expected increase of up to 33\% in the initial values of serum creatinine.** Further and more substantial increases should suggest careful monitoring of the state of the patient’s hydration, an eventual concomitant use of drugs interfering with the SRAA (NSAIDs), as well as recommending a thorough study of the renal vessels.

b) When using **diuretic therapy** in the presence of CRS with advanced renal impairment (FG _30
ml/min/m²), the class of drugs of choice consists of loop diuretics (furosemide, torasemide) whose dosage should be gradually increased to attain the expected result, with a careful check of the water balance between the introduction and diuresis, in order to prevent the onset of a condition of hyponatremia, aggravating the condition of failure.

Untrainfiltation techniques, although yet to be clearly defined both for distinct and niche populations, are of secondary importance. Finally, the most crucial health facilities consist of constant suspicion and careful research of signs that lead to timely diagnosing renal impairment in all conditions of acute or chronic heart failure and/or ischemic heart disease.

Finally, a routine determination of FG value (with the formulas MDRD or Cockcroft-Gault is sufficient). Convenient calculators are easily available online (e.g. http://www.mdcalc.com) to provide enlightening information. To integrate a possible error of GFR estimate calculated, under conditions of severe ARF, the assessment of the rate of progression (slope) of creatinine values is revealing.

Bibliography
Fisiopatologia dello scompenso

**Fig. 1**

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<th>Terapia dello scompenso: raccomandazioni di Classe I</th>
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<td><strong>Beta-Bloccanti</strong></td>
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<td><strong>Antagonisti Aldosterone</strong></td>
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<td><strong>Diuretici</strong></td>
<td>Tutti i pazienti con segni o sintomi di congestione</td>
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Tab. 1 - Da: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008[9].
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<th>Terapia dello scompenso: dosaggio dei farmaci</th>
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Tab. 2 - Da: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008[1].