



REVIEW ARTICLE

Type 4 cardiorenal syndrome



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Abstract The Acute Dialysis Quality Initiative consensus conference proposed a classification of cardiorenal syndrome (CRS), aiming for a better delineation of each subtype. Although the exact pathophysiology of type 4 CRS is not completely understood, the mechanisms involved are probably multifactorial. There is growing evidence that oxidative stress is a major connector in the development and progression of type 4 CRS. Giving its complexity, poor prognosis and increasing incidence, type 4 CRS is becoming a significant public health problem. Patients with chronic kidney disease are particularly predisposed to cardiac dysfunction, due to the high prevalence of traditional cardiovascular risk factors in this population, but the contribution of risk factors specific to chronic kidney disease should also be taken into account.

Much remains to be elucidated about type 4 CRS: despite progress over the last decade, there are still significant questions regarding its pathophysiology and there is as yet no specific therapy. A better understanding of the mechanisms involved may provide potential targets for intervention.

The present review will provide a brief description of the definition, epidemiology, diagnosis, prognosis, biomarkers and management strategies of type 4 CRS, and the pathophysiological mechanisms and risk factors presumably involved in its development will be particularly highlighted.

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PALAVRAS-CHAVE

Síndrome cardiorrenal tipo 4;

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Resumo A definição e classificação de síndrome cardiorrenal foram avançadas pela conferência *Acute Dialysis Quality Initiative*, visando uma melhor compreensão acerca de cada subtipo

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Stresse oxidativo

desta patologia. Embora a fisiopatologia exata não esteja completamente definida, os mecanismos envolvidos na síndrome cardiorenal tipo 4 são potencialmente multifatoriais. Há crescente evidência de que o stress oxidativo é um conector principal no desenvolvimento e progressão desta síndrome. Dada a sua complexidade, pior prognóstico e incidência crescente, a síndrome cardiorenal tipo 4 tem vindo a tornar-se num importante problema de saúde pública. Os pacientes com doença renal crónica estão particularmente predispostos a desenvolver disfunção cardíaca, devido à elevada prevalência de fatores de risco cardiovasculares nesta população, mas a contribuição de fatores de risco específicos da doença renal crónica devem ser tidos em conta.

Muito permanece por esclarecer acerca da síndrome cardiorenal tipo 4: apesar do progresso ao longo da última década, persistem questões importantes relativamente à sua fisiopatologia e ainda não existe tratamento específico. É sublinhada a necessidade de elaborar recomendações científicas para a prevenção e estratégias terapêuticas eficazes para a síndrome cardiorenal tipo 4, sendo que um conhecimento mais aprofundado acerca dos mecanismos envolvidos na síndrome cardiorenal tipo 4 poderão conferir potenciais alvos de intervenção.

A presente revisão irá focar-se na síndrome cardiorenal tipo 4: a sua definição, epidemiologia, diagnóstico, prognóstico, biomarcadores e estratégias terapêuticas serão brevemente descritos, mas uma particular atenção será dada aos mecanismos fisiopatológicos e fatores de risco presumivelmente envolvidos nesta patologia.

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List of abbreviations

CAD	coronary artery disease
CKD	chronic kidney disease
CRS	cardiorenal syndrome
EF	ejection fraction
ER	endoplasmic reticulum
ESRD	end-stage renal disease
FGF2	fibroblast growth factor 2
FGF23	fibroblast growth factor 23
GFR	glomerular filtration rate
HD	hemodialysis
HF	heart failure
IL	interleukin
IS	indoxyl sulphate
LV	left ventricular
NO	nitric oxide
PBUT	protein-bound uremic toxins
PD	peritoneal dialysis
PTH	parathyroid hormone
RAAS	renin-angiotensin-aldosterone system
ROS	reactive oxygen species
SCD	sudden cardiac death
SNS	sympathetic nervous system
TGF- β	transforming growth factor-beta
TNF- α	tumor necrosis factor-alpha
VDR	vitamin D receptor

Introduction

The heart and kidneys are so closely connected that each dysfunctional organ has the ability to initiate and perpetuate injury in the other, through hemodynamic, neurohormonal

Table 1 Classification of cardiorenal syndrome subtypes.

	Description
Type 1	Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acute decompensated HF) leading to AKI
Type 2	Chronic abnormalities in cardiac function (e.g. chronic congestive HF) causing progressive and permanent CKD
Type 3	Abrupt worsening of renal function (e.g. AKI) causing acute cardiac disorder (e.g. acute HF)
Type 4	CKD contributing to decreased cardiac function, cardiac hypertrophy, fibrosis and/or increased risk of adverse cardiovascular events
Type 5	Systemic condition (e.g. sepsis) causing both acute cardiac and renal injury and dysfunction

AKI: acute kidney injury; CKD: chronic kidney disease; CRS: cardiorenal syndrome; HF: heart failure.

Adapted from McCullough et al.⁸ and Ronco et al.⁹

and immunologic/biochemical feedback pathways.^{1,2} To reinforce this crosstalk between heart and kidneys, the concept of the cardiorenal syndrome (CRS) was advanced by the Acute Dialysis Quality Initiative (ADQI), defined as "a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other".³⁻⁹ It has been divided into five subtypes (Table 1), according to the primary organ dysfunction and time frame, as well as the clinical context.^{5,8-10} This classification is not intended to be static: many patients may transition between different CRS subtypes during the course of their disease.¹⁰⁻¹³ The interplay between cardiac

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