Contents

List of Abbreviations

AT II	: Angiotensin II AT II : Angiotensin II
ACE	: Angiotensin Converting Enzyme
ACS	: Acute Coronary Syndrome
ADH	: Anti Diuretic Hormone
AHFS	: Acute Heart Failure Syndrome
AKI	: Acute Kidney Injury
ANP	: Atrial Natriuretic Peptide
ARBs	: Angiotensin Receptor Blockers
ARF	: Acute Renal Failure
ATN	: Acute Tubular Necrosis
BNP	: B type Natriuretic Peptide
CHF	: Congestive Heart Failure
CKD	: Chronic Kidney Disease
CNP	: C type Natriuretic Peptide
CO	: Cardiac Output
CRRT	: Continuous Renal Replacement Therapy
CRS	: Cardiorenal Syndrome
Cys C	:Cystatin C
DNA	: Deoxy ribo Nucleic Acid
EF	: Ejection Fraction
ESC	: European Society of Cardiology
eNOS	: endothelial Nitric Oxide Synthase
GFR	: Glomerular Filtration Rate

List of Abbreviations (Cont.)

HF	: Heart Failure
HFSA	: Heart Failure Society of America
IAP	: Intra Abdominal Pressure
ICU	: Intensive Care Unit
KIM 1	: Kidney Injury Molecule 1
NA	: Noradrenaline
NGAL	: Neutrophil Gelatinase Associated Lipocalin
NO	: Nitric Oxide
NPs	: Natriuretic Peptides
NSAID	: Non Steroidal Anti Inflammatory Drugs
NYHA	: New York Heart Association
PCWP	: Pulmonary Capillary Wedge Pressure
RAAS	: Renin Angiotensin Aldosterone System
RF	: Renal Failure
SCr	: Serum Creatinine
V1 receptor	: Vasopressin receptor
VC	: Vasoconstriction
VD	: Vasodilatation
VEGF	: Vascular Endothelial Growth Factor
WRF	: Worsening Renal Functions

List of Figures

Novel Biomarkers, Pharmacologic and Non-Pharmacologic Therapy of Cardiorenal Syndrome in ICU

Essay

Submitted for the Partial Fulfillment of Master Degree in Intensive Care Medicine

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الدلالات الحيوية الحديثة و العلاج الدوائى وغير الدوائى لمتلازمة القلب و الكلى فى وحدة الرعاية المركزة

رسالة

توطئة للحصول على درجة الماجستير في الرعاية المركزة

مقدمة من

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٢٠١٤

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Introduction

Very often intensive care specialists are confronted with patients who have concomitant heart as well as kidney failure. Cardiovascular disease is the leading cause of death consisting of 43.6% of all deaths in patients with end-stage renal disease (ESRD). Both decrease in glomerular filtration rate (GFR) and proteinuria are independent risk factors for the development of cardiovascular disease **(Sarnak *et al.*, 2003).**

Some patients with severe renal artery stenosis clinically manifest as acute congestive heart failure due to volume and pressure overload **(Gottlieb *et al.*, 2002).** On the other hand, there has been a tremendous increase in the incidence of kidney dysfunction while on treatment for cardiac failure with angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and diuretics to reverse congestion in patients who are have fluid overload **(Nohria *et al.*, 2003).**

Further, acute decompensated heart failure, cardiac ischemia, and arrhythmia may lead to acute impairment of kidney function through renal arterial under filling and a drop in renal blood flow secondary to low cardiac output. Investigative and therapeutic procedures such as

percutaneous coronary intervention, coronary artery bypass surgery, or fibrinolytic therapy can also lead to impaired kidney function **(Best *et al.*, 2002).**

The coexistence of kidney and heart failure in the same individual carries an extremely bad prognosis **(Yancy *et al.*, 2006).**

The exact cause of deterioration of kidney function and the mechanism underlying the initiation and maintenance of this interaction are complex, multifactorial in nature, and still not completely understood **(Heywood, 2004).**

Fundamentally, the heart and the kidneys are the organs which are richly vascular (kidneys are more vascular than the heart). In addition, both organs are supplied by sympathetic and parasympathetic innervations. These two organs are acting in tandem to regulate blood pressure, vascular tone, diuresis, intravascular volume homeostasis, peripheral tissue perfusion, and oxygenation **(Bongartz *et al.*, 2005).**

They have endocrine functions with interdependent physiological hormonal actions regulated by arterial natriuretic peptide, a vasodilator secreted from the heart, and rennin angiotensin - aldosterone system (RAAS). Also, vitamin D3, erythropoietin, and renalase are all secreted

from the kidneys and are capable of cellular and humoral signaling. Dysfunction of either of the two organs can cause dysfunction of the other. Changes in the RAAS, the imbalance between nitric oxide (NO) and reactive oxygen species (ROS), the sympathetic nervous system, and inflammation are the cardiorenal connectors to develop cardiorenal syndrome **(Bongartz *et al.*, 2005).**

These connectors together decrease the sensitivity of erythropoietin and are responsible for renal anemia that also aggravates the clinical conditions of cardiac failure **(Putten *et al.*, 2008).**

In 2007, The National Heart, lung and Blood Institute defined the cardiorenal syndrome as "a state in which therapy to relieve congestive heart failure symptoms is limited by further worsening renal functions" more broadly described as"moderate or greater renal dysfunction in a patient with decompensated heart failure during treatment.

Recently, the bidirectional nature of the heart-kidney interaction and the vast interrelated derangements that can take place in cardiorenal syndrome proposed that the recent definition of cardiorenal syndrome should be modified into categories whose labels reflect the likely primary and secondary pathology and time frame. Emerging biomarkers

may be used for early recognition and intervention because of this interrelation of these two organs. Accordingly the definition was proposed as "pathophysiological disorder of the heart and kidney in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ **(Ronco *et al.*, 2008).**

Cardiorenal syndrome, a poorly understood clinical entity, needs more widely accepted definition and pathogenesis, and its challenging management needs to be looked into. Yet, it has remained a source of debate.

Aim of the Work

The aim of this work is to provide a review on pathophysiology of Cardiorenal syndrome and its subtypes and an overview on the recent lines of management of this syndrome.

Chapter (1)

Pathophysiology of Cardiorenal Syndrome

Combined heart and kidney dysfunction is common. A disorder of one of these two organs often leads to dysfunction or injury to the other. This is the pathophysiological basis for the clinical entity defined cardiorenal syndrome (CRS).Generally defined as a condition characterized by the initiation and/ or progression of renal insufficiency secondary to heart failure, the term CRS should also be used to describe conditions of renal dysfunction leading to heart dysfunction (renocardiac syndrome) **(Ronco *et al*., 2008)**.

The absence of a clear definition contributed in the past to a lack of clarity with regard to diagnosis and management. The common view is that a relatively normal kidney is dysfunctional because of a diseased heart **(Bongartz *et al.*, 2005)**.

This concept, however, has been challenged and the most recent definition includes a variety of conditions, either acute or chronic, where the primary failing organ can be either the heart or the kidney. Such advances in the definition and classification of CRS enabled the

characterization of the complex organ crosstalk and have proposed specific prevention strategies and therapeutic interventions to attenuate end organ injury **(Ronco *et al.*, 2009)**.

A major problem with previous terminology was that it did not allow identification of the pathophysiological interactions occurring in the different types of combined heart/kidney disorder **(Karmer *et al.*, 1999)**.

Hypotheses for the Pathophysiology of Cardiorenal Failure

Evolutionary mechanisms designed to maintain constant blood volume and organ perfusion under continuously changing conditions are clearly responsible for CRS. Unfortunately, when primary cardiac or renal dysfunction develops, the renin-angiotensin-aldosterone system (RAAS), pressure sensing baroreceptors, cellular signaling, and sympathetic nervous system mechanisms turn from friend to foe. Attempting to understand the nature of these normal physiological mechanisms changing from a friend to an enemy is a key to developing a multimodal approach to preserving function in both organs.