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Origins of Cardiorenal Syndrome and the Cardiorenal Connection

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1. Introduction

In recent years, the relationship between the heart and the kidneys in disease has received increasing attention from the clinical and scientific medical community. This was initiated by epidemiological observations in the late 1990's of increasing patient numbers with concurrent heart and kidney problems, and the association with a significantly higher mortality ratio. This has led to intense discussions about the value of the recognition of cardiorenal disease on the one hand, and the existence of a specific "cardiorenal syndrome" on the other hand.[1-10]

The idea of specific interaction between heart and kidneys is not new. There are numerous examples and anecdotes that show that people in the past from various societies considered the heart and the kidneys to have a special relationship.

1.1 Heart and kidneys in ancient times

The Egyptian "Book of the Dead" (1600-1240 B.C.), which served as a reference work to assist the deceased in the afterlife, is one of the first known texts that mentions the heart and kidneys in parallel:

"*Homage to thee, O my heart! Homage to you, O my kidneys!*".[11]

The heart and the kidneys were the only organs left inside the body during the process of mummification. The heart was weighed against the feather of truth by the jackal-headed Anubis (Figure 1), but the exact role of the kidneys for the passage into afterlife is uncertain. Blood vessels are well preserved in mummies, and there is evidence that cardiovascular disease affecting both the heart and the kidneys were not uncommon.[12]

Eknoyan[13] researched the Bible and found that:

> "[T]he kidneys are mentioned five times in the Bible as the organs examined by God to pass judgment on a person. They are mentioned either before or after but always in parallel with the heart, as for example, "*I, the Lord, search the heart, I try the reins, even to give every man according to his ways, and according to the fruit of his doings*" (Jer. 17:10), and, "*Examine me, O Lord, and prove me; try my reins and my heart*" (Psalms 26:2)."

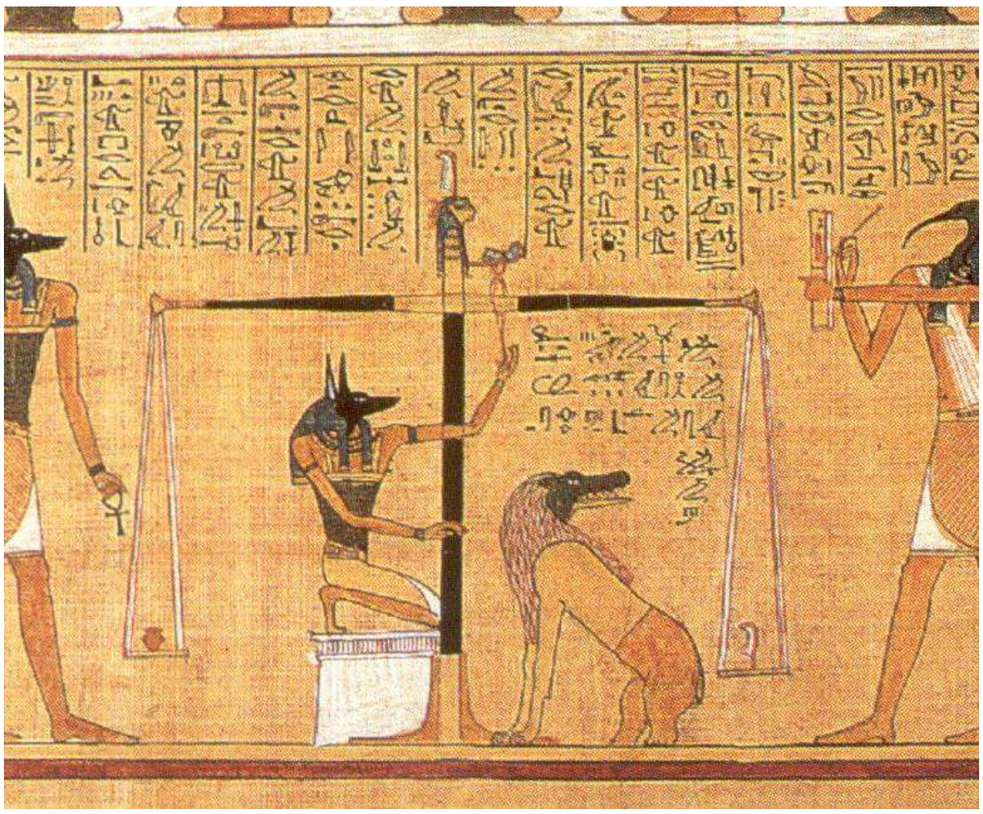

Fig. 1. The weighing of the heart against the feather of truth. This papyrus was found in the tomb of the scribe Hunefer in Thebes. It dates from the 19th Dynasty, about 1285 BC. It can be seen in the British Museum.

In Hebrew lore the kidneys owned the status as the organs which give the heart advice and counsel, and which symbolize the innermost sources of thought and desire, those hardly accessible to man but tested by God.[14]

1.2 Heart and kidneys in Traditional Chinese Medicine

No less lyrical, albeit more clinical descriptions are found in China, where the heart and the kidneys are described in various medical texts. In Traditional Chinese Medicine (TCM), the kidney represents water and is considered a 'yin' organ whereas the heart represents fire and is a 'yang' organ.[15] In TCM, the kidney not only regulates the urinary system, but also controls the reproductive, endocrine and nervous system. It stores Jing, which is considered a vital life force responsible for development and reproduction. The heart rules the blood vessels and blood supply to the organs, but also stores the "spirit", reflected in a person's mental, cognitive and intellectual abilities.

Dr. Shen Jin'ao writes in his book "Dr. Shen's Compendium of Honoring Life (*Shen Shi Zunsheng Shu*)" from 1773:

> "The heart resides in the vessels. It rules the kidney network, not via a controlling position in the restraining circle of relationship between the organ networks [where the kidney actually restrains the heart], but simply because it is the general master of all

> organ networks. Before the heart fire can harmoniously blend with the kidney water, however, the kidney water must be sufficient. Otherwise the heart fire will flare out of control, and all kinds of heart and kidney ailments will arise."

In the 5 Elements network of Chinese medicine (Figure 2) a disorder called "heart and kidney failing to link" (*xin shen bu jiao*) is presented, resulting in a variety of symptoms ranging from restlessness and palpitations to dizziness, and dark, scanty urination or nocturia.[16] If both kidneys and heart are weakened, there may be palpitations, shortness of breath, dizziness, darken complexion, purple lips and nails, sensitivity to low temperatures, urinary difficulty, edema that is more apparent in the lower limbs, and a bulky tongue. If the kidneys and heart are in disharmony, there may be palpitations, dream-disturbed sleep, forgetfulness, dizziness, thirst, red cheeks, night sweats, lumbar and knee soreness, nocturnal emission, and a red tongue.

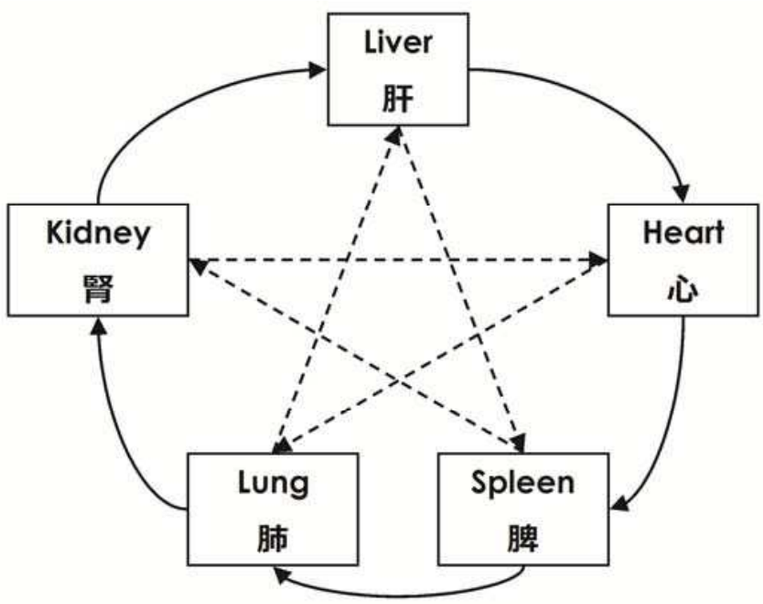

Fig. 2. The Five Elements theory of TCM and the relationships between the organs, with generation (solid arrows) and restriction cycles (dashed arrows).

Another piece of traditional Chinese Medicine text gives a pretty accurate description of the symptoms of cardiorenal failure:

> "When the kidney fails to evaporate fluid which then floods and ascends to depress the function of heart 'yang' there may be clinical manifestations such as oedema, chills and cold limbs, accompanied by palpitations, shortness of breath and stuffiness in the chest, indicating retained water affecting the heart."[17]

1.3 Cardiorenal disease in the European Middle Ages

In Western society, during the Middle Ages, heart disease per sé was not very well described in medical doctrines, although the heart was considered the source of the *spiritus vitalis*. Medieval doctors viewed the outward appearance and excretions of the whole body

or body parts as a reflection of one's state of health, and as such the symptoms of congestive heart failure were approached as separate clinical entities.[18] The examination of urine was however a widely used diagnostic tool. As one of the first Western "cardio-nephrologists", Gentile da Foligno (Gentilis de Fulgineo; 1272? – 1348) considered heart disease as one of the major inflictions modulating the color and output of urine in his commentary on *De pulsibus* (About Pulses) composed by Aegidius Corboliensis (Figure 3).[19]

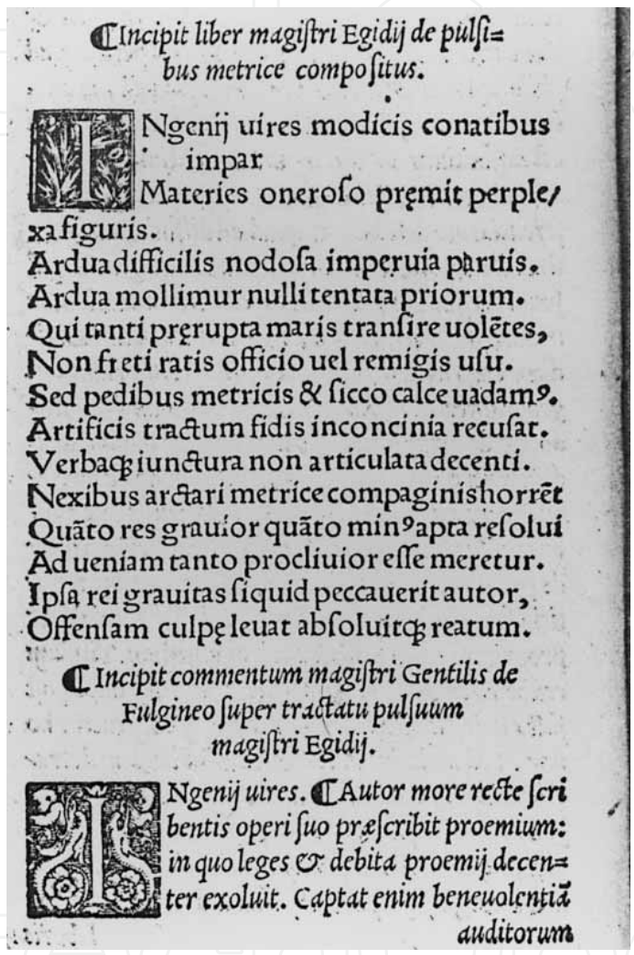
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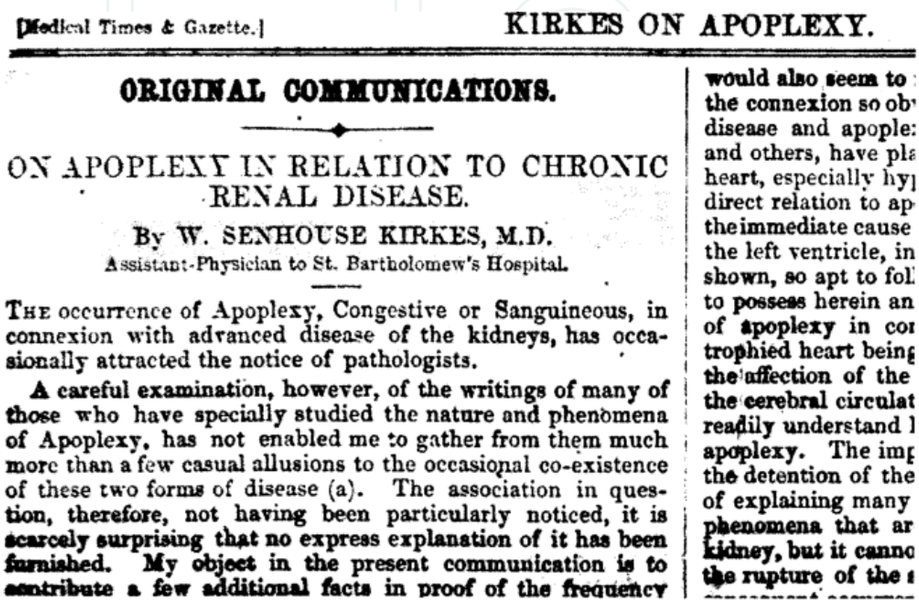
Fig. 3. First page of *De pulsibus.* Town Library, Foligno. Reproduced from ref. [19].

1.4 Heart-kidney interactions in the late 19th and early 20th century

During the Industrial Revolution the medical sciences expanded and scientific methods became more and more reliant on experiments and observation. Richard Bright (1789–1858) and Ludwig Traube (1818–1876) both documented that cardiac hypertrophy was a common anomaly resulting from chronic renal disease.[20, 21] Traube refers in his writings to William Senhouse Kirkes (1822 – 1864) who reviewed 14 autopsy cases of with apoplexy and diseased kidneys, of which only one did not have an enlarged heart (Figure 4).[22] He concludes that:

> "... I believe that the affection of the kidneys is the primary disease... [it] has among its most frequent and permanent accompaniments an hypertrophied condition of the left

ventricle ... of the various explanations of this pathological fact the most probable perhaps is that which regards the blood as so far altered from its normal constitution ... as to move with less facility through the systemic capillaries, and thus to require increased pressure, and consequently increased growth of the left ventricle, to effect its transmission."


[Medical Times & Gazette.] KIRKES ON APOPLEXY.

ORIGINAL COMMUNICATIONS.

ON APOPLEXY IN RELATION TO CHRONIC RENAL DISEASE.

By W. SENHOUSE KIRKES, M.D.
Assistant-Physician to St. Bartholomew's Hospital.

THE occurrence of Apoplexy, Congestive or Sanguineous, in connexion with advanced disease of the kidneys, has occasionally attracted the notice of pathologists.

A careful examination, however, of the writings of many of those who have specially studied the nature and phenomena of Apoplexy, has not enabled me to gather from them much more than a few casual allusions to the occasional co-existence of these two forms of disease (a). The association in question, therefore, not having been particularly noticed, it is scarcely surprising that no express explanation of it has been furnished. My object in the present communication is to contribute a few additional facts in proof of the frequency

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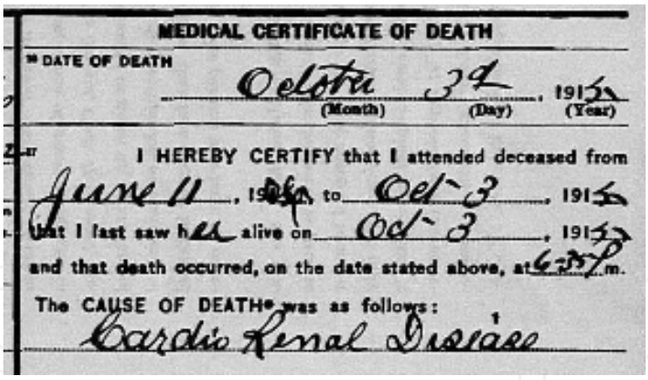
Fig. 4. Beginning of Kirkes' publication in the Medical Times & Gazette, 1855.

In a lecture delivered at the University College in London in 1913, Thomas Lewis[23] speaks about "paroxysmal dyspnoea in cardio-renal patients" and after a very interesting review of the clinical and pathological findings of multiple cases, he concludes:

> "We come to this standpoint-that the clinical or anatomical distinction between cardiac and renal asthma, is no certain one. Asthma occurring, in patients who show on the one hand prominent cardiac lesions, on the other hand prominent renal lesions, may or may not be due to a single cause."

Alfred Stengel[24] proposed a definition of "cardio-renal disease" (Figure 5) when he wrote in 1914:

> "The clinician encounters many cases, mainly in persons of middle age or older, in which evidences of cardiac weakness and other circulatory disturbances, such as high pressure, are associated with signs of failure of renal function or urinary indications of renal disease. When this combination of symptoms is of such character that the observer cannot readily assign to either the cardiovascular system or to the kidneys the preponderance of responsibility, the term "cardio-renal disease" is often employed. The term, therefore, comprises cases of combined cardiovascular and renal disease without such manifest predominance of either as to justify a prompt determination of the one element as primary and important and the other as secondary and unimportant."


MEDICAL CERTIFICATE OF DEATH

DATE OF DEATH October 3d, 1915
(Month) (Day) (Year)

I HEREBY CERTIFY that I attended deceased from June 11, 1915, to Oct 3, 1915
that I last saw her alive on Oct 3, 1915
and that death occurred, on the date stated above, at 6:35 P.M.

The CAUSE OF DEATH was as follows:
Cardio Renal Disease

Fig. 5. Example from a 1915 Death Certificate from Massachusetts. From Rudy's List of Archaic Medical Terms at http://www.antiquusmorbus.com/English/Heart Stroke.htm

The observations on the cardiac consequences of chronic kidney disease were later expanded, and Gouley[25] was coined the term "uremic myocardiopathy" in 1940 and in 1944 Raab[26] proposed that cardiotoxic substances accumulate in uremia. Rössle,[27] and Langendorf and Pirani[28] later showed that interstitial widening and fibrosis were common in hearts of patients dying from uremia.

1.5 The Cardiorenal Syndrome in modern times

The advent of the Cimino-shunt and the development of hemodialysis (HD) as the mainstay treatment for end-stage renal disease (ESRD) resulted in further increasing interest in the structural and functional cardiac status of HD patients.[29-32] The full extent of the problem of cardiovascular disease in chronic kidney disease (CKD) and ESRD patients was then charted in the 1990's, showing that a large proportion of patients starting dialysis already suffers from cardiac abnormalities and dysfunction and that survival of these patients after a myocardial infarction (MI) was dismal.[33-35] In 2003, a statement from several councils from the American Heart Association (AHA) was published in Hypertension and Circulation underscoring the problem of increased cardiovascular risk in CKD, and the lack of knowledge on pathophysiology.[36] This was followed by two seminal papers published in the New England Journal of Medicine showing the exponentially increased risk for adverse outcome with decreasing kidney function, in "normal" patients but even more so after they had experienced a myocardial infarction.[37, 38] At the same time, the scientific and clinical community became increasingly aware of the effect of decreased kidney function or kidney damage on the prognosis of patients with heart failure.[39-41] Interestingly, in a study on the predictive value of 10 different biomarkers in over 3000 patients from the Framingham Heart Study, levels of brain natriuretic peptide and urinary albumin-to-creatinine ratio most strongly predicted major cardiovascular events.[42] One patient study even suggested that the decline of renal function is accelerated after an acute MI.[43] These epidemiological associations resulted in a strong clinical suspicion that the combination of heart and kidney disease is associated with accelerated disease progression and adverse outcome.

2. The Severe Cardiorenal Syndrome and the Cardiorenal Connection

The epidemiological data, the AHA statement, and our own clinical observations of cardiorenal failure in patients led us to propose the "Severe Cardiorenal Syndrome" (SCRS)

as a separate disease entity with the "Cardiorenal Connection" (CRC) as the putative pathophysiological model.[44] We defined the SCRS as a condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organ, leading to grossly increased cardiovascular morbidity and mortality. The CRC works in conjunction with the hemodynamic control model of heart-kidney interactions as stipulated by the late professor Guyton (Figure 6).

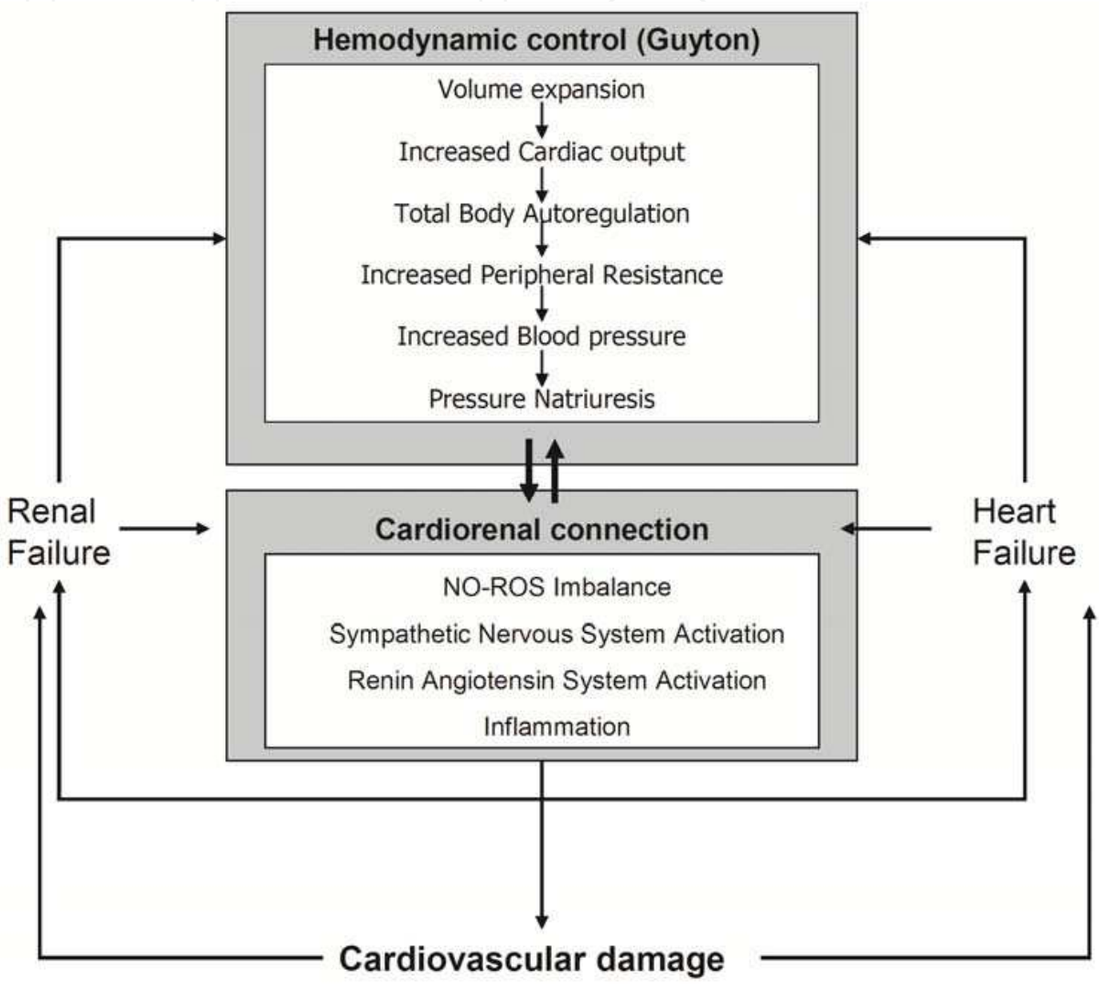


Fig. 6. The cardiorenal connection works extensive to Guyton's model to drive accelerated cardiovascular damage in combined renal and heart failure.

The "cardiorenal connectors" that we put forward were:

- the balance between nitric oxide (NO) and reactive oxygen species (ROS),
- the sympathetic nervous system (SNS)
- the renin-angiotensin system (RAS), and
- inflammation.

We envisioned that both heart and renal failure lead to derangement of the Guytonian model of hemodynamic control, but also results in activation/disturbance of the connectors

of the CRC. The connectors have a modulating effect on hemodynamic control but can also induce cardiovascular damage, thereby mediating further functional deterioration.[44] We proposed that activation of the CRC leads to a vicious cycle in which all the connectors become disturbed, synergize and further activate each other. This ultimately results in worsening of both cardiac and renal damage and failure.

2.1 Summary of the Cardiorenal Connection

A shift in the balance between NO and ROS towards ROS is a central event in many cardiovascular diseases.[45] In the SCRS, the balance between NO and the ROS is skewed towards the latter by increased production of ROS, a low anti-oxidant status, and lower availability of NO.[46] In the cardiorenal connection, this imbalance may influence sympathetic nervous activity,[47] release of renin and angiotensin,[48] and promote inflammation by oxidative modification of substances.[49]

Sympathetic nervous activity is also increased in both renal and heart failure. By affecting the other cardiorenal connectors it can play a significant role in the SCRS. It stimulates renin release from the kidneys,[50] generates ROS which induces vascular wall growth,[51] and induces inflammation.[52]

The RAS is activated in both renal and heart failure [53, 54] and angiotensin II affects the other cardiorenal connectors in different ways. It activates the SNS in both heart and kidney failure,[55, 56] it generates ROS via nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase,[57] and activates pro-inflammatory gene expression via nuclear factor-κB.[58]

Persistent inflammation has been found in both renal and heart failure. By altering the functioning of the RAS,[59] and promoting ROS[60] and noradrenaline formation,[61] inflammation can contribute to the positive feedback loops in the cardiorenal connection. The Severe Cardiorenal Syndrome is thus not a syndrome in which cardiac and renal failure simply co-exist side-by-side. Cardiac and renal failure are intimately linked by the cardiorenal connectors, because failure of either organ can excite the cardiorenal connectors, but the connectors themselves also affect the structure and function of both organs. Logically, the cardiorenal connectors become more pronounced in combined failure.[6]

3. Previous research on the cardiorenal interactions

In a recent comprehensive review in *Circulation,* Bock and Gottlieb[10] state that:

> "…each dysfunctional organ has the ability to initiate and perpetuate disease in the other organ through common hemodynamic, neurohormonal, and immunological/ biochemical pathways." They also write: "…our understanding of the complex physiological, biochemical, and hormonal derangements that encompass the CRS is woefully deficient…".

Despite general acknowledgement of the adverse prognosis of concurrent cardiac and renal disease, many clinicians and researchers are skeptical about the true existence of a specific heart-kidney interaction that goes beyond known physiological interactions. Thus the question was raised whether kidney disease and heart disease simply co-exist or that they indeed worsen each others progression. Clinical studies can not provide the answer to this

question because they are observational, lack histological end-points, and are confounded by selection bias, inconsistent definition of end-points, and medication use. Therefore, further exploration of the mechanisms of cardiorenal interactions must rely on animal studies, in which timing and severity of the disease are controlled, progression of disease can be followed, and histological end-points are assessed.

Much of what we know today on the structural cardiac consequences of chronic kidney disease results from the extensive research in rats with CKD by the group of Kerstin Amann and Eberhard Ritz in the late 80's and early 90's.[62] Despite numerous cardiac changes, in the rat CKD model of subtotal (5/6th) nephrectomy (SNX) cardiac systolic function is generally maintained.[63, 64] Conversely, after MI by ligation of the left coronary artery in rats, renal histological damage or proteinuria is absent although glomerular filtration rate (GFR) may be decreased.[65, 66] Thus, it appears that both organs need to be affected to cause acceleration of damage and failure typical for the CRS. Only two animal studies investigated the effect of 'dual damage' to heart and kidneys, with MI following shortly after a renal insult in rats, with conflicting results.[65, 67] Different models of nephrectomy exist in mice, but these are not as robust as those in rats, with variable changes in renal function and cardiac abnormalities.[68-72]

The renal hemodynamic response to heart failure (HF) induced by pacing in dogs has also been investigated,[73-75] but whether there is histological damage is unknown. Furthermore, there is no proven model of CKD in dogs. Taken together, there is still a paucity of models that investigate the interaction between kidney and heart failure in a chronic set-up with integrated physiological and histological assessment. From the available data, combining the SNX model of CKD and the coronary ligation model of HF appears to be the most robust option to investigate the SCRS.

3.1 The role of nitric oxide in the Severe Cardiorenal Syndrome

We developed a model of the SCRS based on CKD and depletion of NO availability. The rationale for these investigations was that the pathogenesis of CKD (in the presence of hypertension, diabetes or aging) is associated with low NO availability,[76,77] while experimental SNX induces nephron number reduction in a healthy animal. Furthermore, in SNX, cardiac systolic function generally remains preserved, while in patients left ventricular dysfunction (LVSD) develops during the course of CKD progression.[78]

Reduced NO availability is considered a hallmark of CKD.[46, 79] NO can function as an effector of the CRC by way of its vasodilatory action. It also modulates GFR and tubulo-glomerular feedback.[80] Reduced NO availability will result in tissue damage by oxidative stress. In extension to our proposal of the Cardiorenal Connection,[44] we postulated that the balance between NO and ROS is a key modulator of the other cardiorenal connectors.[81] Many effects of the other CRCs may be mediated by changes in the redox-balance and NO availability.[82, 83]

Also, it has been shown that constitutive NO production supports basal cardiac function.[84] Apart from its role in endothelial dysfunction, NO availability also modulates cardiac contractility, as NO synthase (NOS) inhibition reduces cardiac output, and causes cardiac damage in high doses.[85, 86]

We thus hypothesized that a reduction in NO availability would accelerate the development of cardiac dysfunction. Indeed, treatment with an oral NO synthase (NOS) inhibitor (L-NNA), at a very low dose, induced NO depletion and severe cardiac dysfunction.[87] Furthermore, proteinuria, severe glomerulosclerosis and cardiac interstitial fibrosis were worsened compared to rats with CKD without NOS inhibition. Another remarkable finding was that the effects on cardiorenal dysfunction but also on systemic NO production were irreversible after cessation of the NOS inhibitor, during a 7 week follow-up. A five times higher dose of NOS inhibition in control rats, which caused a similar level of hypertension and NO depletion, induced LVSD that was not as severe as in the CRS rats. Furthermore, all effects on blood pressure, cardiac function and NO availability were completely reversible, and had no effect on kidney structure and function. Combining NOS inhibition with SNX also, worsened kidney injury. The more severe hypertension and direct effects of NOS inhibition may have played a role in this.

We concluded that during CKD development the heart is very sensitive to depression of systemic NO availability. Compared to the normal kidney, the damaged kidney is more sensitive to alterations of NO availability as well, possibly because of a loss of autoregulation.[88] Thus, maintaining adequate NO availability appears to be very important for progression of cardiorenal failure during progression of CKD, and the combination of CKD and NO depletion appears to produce a functional model of the SCRS in which cardiac function is further compromised.

That supplementation of NO is useful as a rescue therapy was shown in a subsequent study, where treatment with the oral tolerance-free NO donor molsidomine (MOLS) significantly improved cardiac diastolic and systolic function, abrogated mortality, and also slightly improved kidney function and injury.[89] The cardiac effect of MOLS appeared to be a combination of reduced cardiac loading and improved contractility and relaxation. Systolic blood pressure was only mildly reduced and GFR was even slightly improved. Thus, MOLS appears to be an attractive and safe therapeutic option for CKD patients suffering from cardiac dysfunction of non-ischemic origin. The pathophysiology of the continuing low NO production in this model is likely very complex and may include low NOS expression or activity, substrate deficiency, high oxidative stress levels, and increased amounts of endogenous NOS inhibitors.[79]

In conclusion, the cardiorenal connection has intrigued scientists and physicians for centuries. The existence of a specific cardiorenal syndrome has been suggested since the start of the 20th century, but has recently gained widespread attention in the scientific literature. We proposed the Severe Cardiorenal Syndrome, in which CKD and HF induce derangements to cause a vicious cycle of cardiovascular damage and progression of failure of both organs. Understanding of pathophysiological mechanisms is expanding and animal models provide an invaluable tool to investigate the bidirectional nature of cardiorenal interactions.

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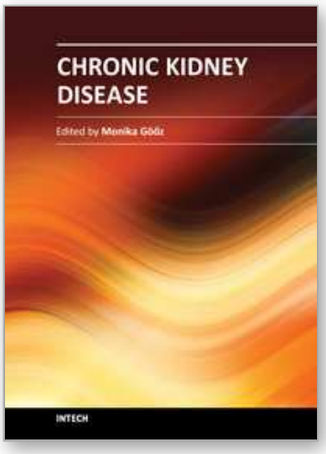

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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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