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Review

The severe cardiorenal syndrome: 'Guyton revisited'

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The incidence of cardiac failure and chronic renal failure is increasing and it has now become clear that the co-existence of the two problems has an extremely bad prognosis. We propose the severe cardiorenal syndrome (SCRS), a pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organ, so that cardiovascular morbidity and mortality in this patient group is at least an order of magnitude higher than in the general population. Guyton has provided an excellent framework describing the physiological relationships between cardiac output, extracellular fluid volume control, and blood pressure. While this model is also sufficient to understand systemic haemodynamics in combined cardiac and renal failure, not all aspects of the observed accelerated atherosclerosis, structural myocardial changes, and further decline of renal function can be explained. Since increased activity of the renin–angiotensin system, oxidative stress, inflammation, and increased activity of the sympathetic nervous system seem to be cornerstones of the pathophysiology in combined chronic renal disease and heart failure, we have explored the potential interactions between these cardiorenal connectors. As such, the cardiorenal connection is an interactive network with positive feedback loops, which, in our view, forms the basis for the SCRS.

Introduction

Cardiovascular disease is a profound problem in chronic renal failure (CRF), with 43.6% of all deaths in patients with end-stage renal disease (ESRD) due to cardiac causes.[1] Death from cardiac causes is 10–20 times more common in patients with CRF than in matched segments of the general population.[2] In ESRD, the prevalence of left ventricular hypertrophy (LVH) and coronary artery disease are ~75 and 40%, respectively.[3] About half of ESRD-patients will suffer from myocardial infarction (MI) within 2 years after initiating dialysis therapy, and mortality in these patients is high.[4] Even a slightly decreased kidney function correlates with a substantial increase in cardiovascular disease risk and higher mortality, independently of other known risk factors.[5–10] A recent statement from the American Heart Association[11] determined that both proteinuria and a decline in glomerular filtration rate (GFR) are independent risk factors for the development of cardiovascular disease, and highlighted our lack of knowledge on the pathophysiology of this syndrome. Impaired renal function is also associated with adverse outcomes after acute coronary syndromes,[12] percutaneous coronary intervention,[13] coronary artery bypass surgery,[14] or

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fibrinolytic therapy.[15] The incidence of heart failure as cause of death was inversely related to GFR.[16,17]

Another major concern is the incipient epidemic of CRF.[18] Not only the prevalence of ESRD increases, but also the number of patients with moderate renal dysfunction.[19] An epidemic of heart failure is also in progress, due to increasing age and better survival after MI.[20] The risk for developing CRF in heart failure has not been defined clearly, but renal dysfunction is often observed in heart failure patients,[21] and is associated with adverse prognosis.[22] The frequency of the combination of heart failure and CRF will thus increase and inescapably come with high morbidity and mortality. The mechanisms that cause decline of kidney function and its repercussions are, however, still poorly understood. In this review, we would like to explore potential pathophysiological interactions that lead to strong interactions between cardiovascular and renal disease.

The severe cardiorenal syndrome

The strong connection between renal and cardiovascular disease has revived interest in the complex interactions between heart and kidneys. The late Arthur Guyton extensively described normal physiological interactions between the control of extracellular fluid volume by the kidney and the systemic circulation by the heart (*Figure 1*). The framework of reasoning about the control of extracellular fluid volume (ECFV) and systemic haemodynamics, the concept of total body autoregulation, as well as the renal control mechanisms for sodium excretion with their 'infinite gain',[23] are of invaluable importance. A recent monograph on volume control in haemodialysis treatment has applied the

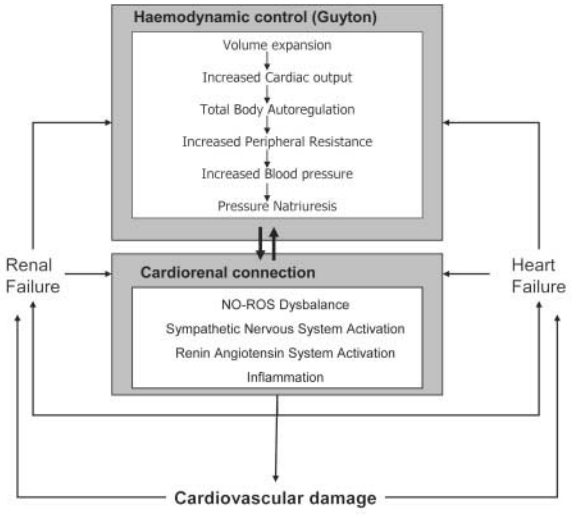

Figure 1 Pathophysiological basis of the severe cardiorenal syndrome. The model of Guyton explains heart–kidney interaction with respect to extracellular fluid volume, cardiac output, and mean arterial pressure. When one of these organs fails, a vicious circle develops in which the renin–angiotensin system, the NO–ROS balance, the sympathetic nervous system, and inflammation interact and synergize, here called the cardiorenal connection.

Guytonian rules to explain and treat cardiovascular disease.[24] Nevertheless, pathophysiological mechanisms underlying this reciprocal relationship between the heart and kidneys are still enigmatic. We propose the severe cardiorenal syndrome (SCRS), a pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organ to lead to astounding morbidity and mortality in this patient group.[25] SCRS is a syndrome with accelerated and extensive cardiovascular disease that has distinct properties not occurring in conditions that affect either organ alone.

In the heart, the consequence of the SCRS is in part due to the described accelerated atherosclerosis in the form of coronary artery stenosis.[26–28] Similarly, LVH is an almost invariable finding, in both clinical and experimental uraemia, in the absence of significant haemodynamic stimuli.[29,30] Rather, the interplay between renal failure and cardiovascular disease reflects an inappropriate remodelling process. The SCRS also involves myocardial micro-angiopathy, manifested in the intramyocardial arterioles by wall thickening and reduced lumen diameter as a consequence of hypertrophy of smooth muscle cells.[31] Clinically, the narrowed lumen diameter may interfere with the already reduced coronary perfusion reserve. The intramyocardial capillaries of uraemic rats exhibit decreased capillary density,[32] which increases the oxygen diffusion distance and may further impair the ability of the myocardium to withstand episodes of hypoxia.

Pulse wave velocity (PWV) is a reflection of the elastic properties of 'windkessel' arteries and a high PWV has been recognized as a prognostic factor for cardiovascular events. Uraemia affects PWV by functional (angiotensin, volume expansion)[33] and structural (vascular calcification) derangements. The aggressiveness of the calcification process is almost exclusively observed in severe CRF and ESRD,[34] and is present not only in the large arteries but also in coronary plaques of CRF patients.[35–37]

Finally, heart failure can lead to excessive and inappropriate activation of the renin–angiotensin system (RAS),[38] which has been implicated in many ways in the progression of renal disease.[39] Thus, combined renal and cardiac disease invokes a number of forces that are specific for this combination and synergistically aggravate renal and cardiac disease.

Components of the cardiorenal connection contributing to the SCRS

Central in Guyton's model are the kidney, as regulator of ECFV, and the RAS with its corresponding extensions (aldosterone, endothelin) and its antagonists [natriuretic peptides, nitric oxide (NO)]. The model is sufficient to explain the changes in ECFV, blood pressure, and cardiac output in combined heart and renal failure. However, can we also explain the accelerated atherosclerosis, cardiac remodelling and hypertrophy, and progression of renal disease observed in the SCRS (*Figure 1*)?

In this respect, we have recently proposed an extension to the Guytonian model of volume and blood

pressure control called the Cardiorenal Connection (CRC).[25] Over the past decades, actions have been described by the regulators central in Guyton's model which do not directly control haemodynamics, but affect other aspects of cardiac and renal function. In dissecting the pathophysiological events in the SCRS, we try to couple actions of the regulators of Guyton's model to their extended actions on structure and function of heart and kidney. We propose the RAS, the balance between NO and reactive oxygen species (ROS), inflammation, and the sympathetic nervous system (SNS) as actual connectors in the CRC (*Figure 1*). We envisage that derangement of one connector of the CRC leads to a vicious circle in which the other connectors become disturbed as well and synergize, ultimately resulting in cardiac and renal functional derangement and structural damage. Accordingly, renal failure and heart failure would lead to the SCRS via common pathophysiological mechanisms: the CRC. The following sections describe evidence on the pathophysiological mechanisms and interactions between connectors of the CRC.

The RAS

Activation of the RAS by low renal perfusion pressure or blood flow serves as a defence against under-perfusion of vital organs, such as in haemorrhage. In heart failure, this response can take a devastating downhill course: volume retention due to the haemodynamic and reabsorptive actions of angiotensin II (Ang II) develops[40] with further congestive heart failure as a consequence. Unfortunately, inappropriate activation of the RAS is also one of the characteristics of renal failure.[41]

Besides the (dys)regulation of ECFV and vasoconstriction, one of the most deleterious actions of the RAS in the CRC is activation of NADPH-oxidase by Ang II, resulting in formation of ROS.[42] This has been documented in endothelial cells, vascular smooth muscle cells,[43] renal tubular cells,[44] and cardiomyocytes.[45] Interesting observations in this context are raised NADPH-oxidase activity in hearts of patients with end-stage heart failure[46] and increased NADPH-oxidase-mediated ROS release in glomeruli of Dahl salt-sensitive rats with heart failure, which could be attenuated by angiotensin-converting enzyme (ACE) inhibition.[47] Moreover, ACE inhibition has been shown to increase NO bioavailability in patients with coronary artery disease, possibly related to reduced vascular oxidative stress or increased extracellular superoxide dismutase (SOD) activity.[48]

Ang II, potentially acting via changes in the cellular redox state, is implicated in vascular inflammation via the nuclear factor kappa B (NF-κB) pathway, which induces production of chemotactic and adhesion molecules.[49,50]

The RAS interacts with the SNS by complex mechanisms.[51] It has been found that the stimulus for the sympathetic hyperactivity observed in renal failure arises from the failing kidneys[52] and that increased sympathetic outflow in CRF could be controlled with ACE-inhibition.[53,54] Blocking Ang II signalling reduced SNS hyperactivity after MI in rats, attenuating ensuing development of heart failure.[55] Interactions of the RAS with the other cardiorenal connectors are shown in *Figure 2A*.

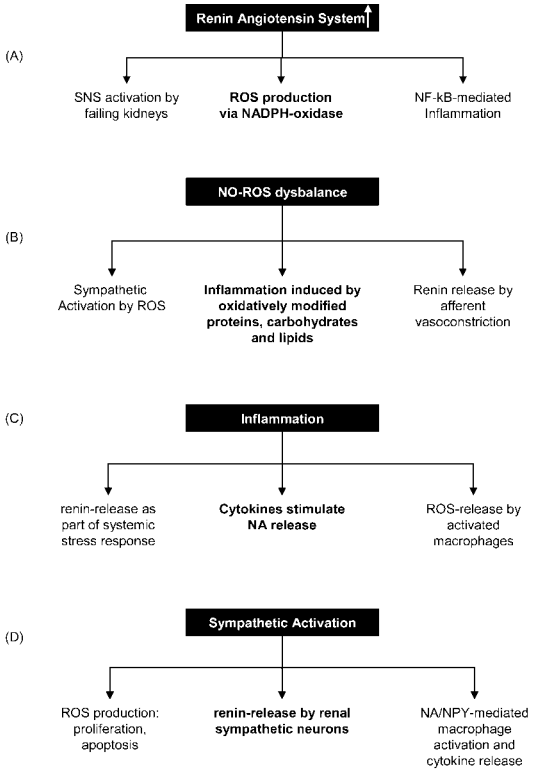

Figure 2. (*A*) Angiotensin II (Ang II) affects the other cardiorenal connectors: SNS activation in kidney failure, generation of ROS, and NF-κB mediated pro-inflammatory gene expression. (*B*) Imbalance between NO and ROS is a central event in cardiovascular diseases. In the cardiorenal connection, this balance may influence sympathetic nervous activity, release of renin and angiotensin, and promote inflammation by oxidative modification of substances. (*C*) Persistent inflammation has been found in both renal and heart failure. By altering ROS functioning, and promoting ROS and noradrenaline (NA) formation, inflammation contributes to the positive feedback loops in the cardiorenal connection. (*D*) Sympathetic nervous activity is 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, generates ROS, and induces inflammation. NPY: neuropeptide Y.

The balance between NO and ROS

NO is important in renal control of ECFV and blood pressure by causing vasodilation, natriuresis, and desensitization of tubuloglomerular feedback.[56] There are now many indications that superoxide has the opposite effect on ECFV control and can contribute to high blood pressure.[57–60] 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. Increased levels of different oxidative stress markers, like F_2-isoprostane[61] and antibodies against oxidized LDL,[62] have been found in dialysis patients. A low antioxidant status is caused by oxidative inactivation, decreased availability of antioxidant vitamins, and removal of water-soluble antioxidants

through the dialysis membrane.[63] Oxidative stress is further increased by interplay between the uraemic state and inflammatory reactions on the dialysis membrane. A relative NO-deficiency in renal failure is caused by reaction of NO with oxygen radicals, as well as by high concentrations of circulating asymmetric di-methyl arginine (ADMA), an endogenous NOS inhibitor.[64] In heart failure, increased oxidative stress has also been demonstrated[46] and decreased antioxidant status was found in rat myocardium after MI, which was associated with progression to heart failure.[65] Interestingly, haemodynamic improvement by captopril and prazosin led to enhanced antioxidant status.[66] Kielstein *et al.*[67] also showed a relationship between reduced renal perfusion, impaired NO-mediated endothelial vasodilation and high concentrations of ADMA in patients with normotensive heart failure, markedly resembling the situation in CRF patients.

Additional potential interactions between the NO–ROS imbalance and other cardiorenal connectors in the SCRS are depicted in *Figure 2B*. Oxidative stress by hydrogen peroxide (H_2O_2) has been shown to increase activity of pre-ganglionic sympathetic neurons *in vivo* and *in vitro* in rats, raising mean arterial pressure and heart rate.[68] Also, renal sympathetic nervous activity in spontaneously hypertensive rats was found to be regulated by vascular superoxide concentrations.[69]

In renal failure, oxidative stress imposes damage on DNA (8-oxo-OH-deoxyguanosine), proteins (carbonyl compounds,[70] advanced oxidation protein products[71]), carbohydrates (advanced glycation end-products[72]), and lipids (oxidized LDL[62]). These substances have pro-inflammatory effects by attracting and activating leukocytes,[73,74] but they can also damage endothelial cells.[75] Oxidative stress is a major initiator of an inflammatory response, resulting in a shift towards production (and activation) of pro-inflammatory cytokines, in particular IL-1, IL-6, and tumour necrosis factor alpha (TNFα).

Although as yet not completely resolved, oxidative damage to the renal tubular or interstitial cells may interfere with feedback systems involved in renin secretion and angiotensin formation in the SCRS. Chronic inhibition of NO synthesis causes upregulation of cardiac ACE and Ang II receptors, possibly mediating inflammatory changes.[76]

Himmelfarb *et al.*[77] have termed oxidative stress the 'elephant', or key-point, in uraemia. Treatments that decrease superoxide production (such as NADPH-oxidase inhibitors), aid in scavenging ROS, or support the function of NO, are intriguing clues that support our concept. One relatively small trial has reported a positive effect of antioxidant therapy on cardiovascular endpoints in patients with renal failure,[78] but more evidence is needed.

Inflammation

Together with increased oxidative stress, inflammation has been designated the other common denominator in uraemia.[79] The combined occurrence of chronic renal insufficiency and high C-reactive protein (CRP) levels has a more than additive effect on the incidence of MI and death.[80] In CRF, circulating levels of CRP[81] and several pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα, are predictors of atherosclerosis.[82,83]

It has been suggested that inflammation will aggravate heart failure. In patients with heart failure, elevated levels of TNF-α and IL-6 have been found in both plasma and myocardium, and are related to progression of the disease.[84,85] Interleukin-18 has also been associated with cardiac dysfunction after MI.[86] The exact role of the activation of inflammatory cells is as yet far from clear; however, in both CRF and heart failure a state of chronic inflammation is present.

This low-grade inflammation can cause ROS production by activating leukocytes to release their oxidative contents.[87] In cultured rat vascular smooth muscle cells, IL-6 induced upregulation of the AT_1 receptor and Ang-II mediated production of ROS, providing evidence for a possible link between inflammation and RAS activation.[88] Cytokines may stimulate renin secretion as a component of the systemic stress response, and tubulointerstitial inflammation may have effects on adaptive responses of glomerular haemodynamics to impaired renal function.[89] After MI, IL-1β is produced,[90,91] which has been shown to stimulate noradrenaline release from sympathetic neurons.[92] Interactions between inflammatory factors and the other connectors are depicted in *Figure 2C*.

SNS

By stimulating renin release via renal sympathetic neurons, the SNS contributes to long-term regulation of ECFV and blood pressure. Converse *et al.*[52] were the first to report increased peripheral sympathetic nerve activity in ESRD, which was corrected when the diseased kidneys were removed. The SNS is initially activated in heart failure by the baroreflex to provide inotropic support and preserve cardiac output. However, excessive sympathetic activity can induce cardiomyocyte apoptosis, hypertrophy, and focal myocardial necrosis.[93] Cardiac hypertrophy is partly due to direct actions of catecholamines, as several studies have shown that noradrenaline induces hypertrophy of cultured cardiomyocytes.[94,95] Interestingly, this action involves induction of superoxide.[94,95] Chronically, sympathetic over activity causes beta-adrenoceptor insensitivity in both renal failure[96] and heart failure.[97,98] This can lead to a disturbed baroreceptor reflex, reduction in heart rate variability, and increased susceptibility to arrhythmia. Whether the atherosclerotic process is associated with increased sympathetic activation is unclear. However, sympathetic over-activity can affect lipid metabolism, and beta-blockers have been shown to have anti-atherosclerotic properties.[99,100] There are several indications that the SNS affects the other connectors of the CRC, for instance RAS activation, production of ROS by sympathetic neuroactive substances, and activation of the immune system (*Figure 2D*).

Next to direct sympathetic innervation of the kidneys, renin release can be enhanced because prolonged SNS

over-activity has a growth-promoting effect on the wall of intrarenal blood vessels.[101] This effect has recently been found to be mediated by ROS production.[102] In ischaemia/reperfusion damage in the kidney, H_2O_2 formation by monoamine oxidase enzymes induced a pro-apoptotic cascade in proximal tubular cells.[103] The SNS may induce inflammation by noradrenaline-mediated cytokine production from liver[104] and heart,[105] and beta-blockade after experimental MI diminished myocardial cytokine gene expression.[106] Neuropeptide Y (NPY) is a neurohormone released by sympathetic activation that is involved in the prolonged vasoconstriction associated with stress. It can act as a vascular growth promoter, leading to neo-intima formation and has been associated with carotid artery atherosclerosis.[107] Thirdly, it affects the immune response by altering cytokine release and immune cell function.[108,109] High levels of NPY have been demonstrated after MI and in patients with heart failure.[110] Thus, the SNS can modulate the other cardiorenal connectors.

Conclusion

In this review, we extend the solid framework of Guyton for extracellular fluid volume and blood pressure regulation. Epidemiological data point towards reciprocal connections between the heart and kidneys in disease, encompassed in the SCRS. This connection is, in our opinion, more elaborate than the haemodynamic model of Guyton alone. With the model of the CRC, we hope to unravel the interactions underlying the deleterious consequences of the SCRS by taking into account the extended cardiorenal effects of the RAS, the balance between NO and ROS, inflammation, and the SNS. Oxidative stress and inflammation have been strongly implicated in the SCRS. Although several interventions (e.g. blockade of the RAS and the SNS or physical exercise) have been shown to be effective in reducing oxidative stress and inflammation, at present no effective strategy to directly influence these factors has been devised. Since interactions in the CRC induce positive feedback loops at many points, it is considered likely that multiple interventions are needed to stop the vicious circle. Ideally, when all four factors are taken into account, we will be able to predict the clinical course of most patients with SCRS. Taken further, if all four factors were to be corrected, we would stand a better chance to control the progression of the SCRS more effectively. Because only fragmentary data exist on interactions between the cardiorenal connectors in the setting of the SCRS, experimental and clinical studies are needed to test this model.

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