Cardiorenal interaction:

perspectives from the kidney

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Abstract -- The incidence of chronic renal failure in combination with cardiovascular events is increasing and the co-existence of the diseases leads to an extremely bad prognosis and often lethal outcome. The combination of cardiac and renal dysfunction, *i.e.* the cardio-renal interaction, leads to amplified progression of failure of the individual organs. This was also studied in an experimental rat model where a myocardial infarction (MI) was induced in unilateral nephrectomized rats and several cardiac, renal and neurohumoral parameters were measured. This study confirmed that MI enhances progressive renal damage in this experimental rat model, evidenced by increased levels of proteinuria and focal glomerulosclerosis.
In this review, I tried to find the underlying mechanisms of the cardio-renal interaction. Therefore, the main consequences of MI were described, which include inflammation, hemodynamic changes and activation of the renin-angiotensin system (RAS). In addition to this, the consequences of unilateral nephrectomy on the residual kidney were described, including reduced glomerular filtration rate (GFR), hypertrophy of the contralateral kidney and slightly higher protein excretion levels.
Since the RAS exerts multiple effects on both the heart and kidneys, and inhibition of the RAS via angiotensin converting enzyme-inhibitors (ACEi) have contributed greatly to the treatment of cardiac and renal failure, the RAS seems to be the most evident link in the cardio-renal interaction. This provides great perspectives for the future to conduct further research on the cardio-renal interaction.

1. Introduction

The incidence of chronic renal failure in combination with cardiovascular events is increasing and the co-existence of the diseases leads to an extremely bad prognosis and often lethal outcome. The combination of renal and cardiac failure is often named the cardio-renal interaction. Combined cardiac and renal dysfunction leads to amplified progression of failure of the individual organs (Bongartz et al., 2005). The clinical importance of this problem is becoming more apparent these days, since many patients suffering from chronic kidney disease are presented with cardiovascular disease.
Population studies in the last ten years have shown that in both patients with end-stage renal disease and patients suffering from mild to moderate impairment of renal function, cardiovascular mortality is very high (Henry, 2002). It has become clear that 90% of patients suffering from chronic kidney disease did not survive long enough to even progress to end-stage renal disease, but instead died prematurely from cardiovascular events (Hostetter, 2004; Schrier et al., 2007).
The problem in this clinical observation is that records of heart function from patients suffering from renal disease often are not available. This leads to problems in drawing conclusions from clinical cases, as we can not be certain that organ failure in patients with renal disease is because of detrimental effects of cardiovascular events, *e.g.* myocardial infarction, or if it was already present before this happened.
To address the question pre-clinically, Van Dokkum et al. investigated in 2004 if impaired heart function could aggrevate a mild state of chronic renal function loss in rats. For this purpose, Van Dokkum et al. introduced a myocardial infarction (MI) in a unilateral nephrectomized rat model and studied several cardiac, renal and neurohumoral

parameters (Van Dokkum et al., 2004). This study confirmed that MI enhances progressive renal damage in this experimental rat model.
To this point, the underlying mechanism of this cardio-renal interaction is not clear. To find out which factors are responsible for the marked predisposition of chronic kidney disease patients, the problem needs to be addressed pre-clinically using animal models, as Van Dokkum et al. did. The best animal model in this case appears to be the rat, considering the suitability of the rat as a model for humans in addition to the practical advantages such as low housing costs (Bhindi et al., 2006). Research on animals makes it possible to perform sequential research for clinical problems.
The aim of this review was to study the possible mechanisms underlying the increased risk of cardiovascular events in chronic kidney disease. To do this, I first reviewed the injurious effects of MI, the number one player in cardiovascular events. Secondly, I described the effects of unilateral nephrectomy on the function of the residual kidney and finally, I interlinked the effects of the diseases on both organs and tried to come to a conclusion on the cardio-renal interaction. Finding the underlying mechanisms in this problem may have important implications for therapeutic intervention in patients with chronic kidney disease.

2. (Patho)-physiology of MI and its consequences

In patients with end-stage renal failure, cardiovascular disease is very common and accounts for 44 percent of overall mortality in this group (Herzog et al., 1998). Herzog et al. showed that the group of patients on dialysis who have acute MI have a high mortality rate and poor long-term survival. Not only patients with end-stage renal failure have an increased risk on cardiovascular events, but even patients with mild renal impairment. What effects do cardiovascular events, or more specifically, does MI have on chronic kidney disease?
To answer this question, we need to assess short-term and long-term effects of acute MI on the vascular bed and systemic functions. These changes in hemodynamics are likely to have an influence on kidney function as cardiac, endothelial and kidney functions seem to be interlinked (Van Dokkum et al., 2004).

2.1. Inflammation

A myocardial infarction occurs when a coronary artery becomes occluded. Due to oxygen deprivation, necrosis in cardiomyocytes is induced. This necrotic loss of cardiomyocytes stimulates the complement cascade of the immune system and initiates an inflammatory response (Lambert et al., 2008).

2.1.1. Neutrophils and macrophages

The inflammatory response consists mainly of neutrophil and monocyte infiltration at the site of injury, to which they are drawn by adhesion molecules and chemoattractant cytokines (chemokines). Adhesion molecules and chemokines are expressed by the endothelial cells of the vasculature, which comprises the border of the infarct site (Sun, 2009). The monocytes extravasate into the injured tissue and differentiate into macrophages. This conversion of monocytes into macrophages is initiated by monocyte adherence to the extracellular matrix, thereby inducing the expression of certain

cytokines such as tumor necrosis factor α (TNFα), platelet derived endothelial cell growth factor, transforming growth factors α and β (TGFα and –β), interleukin-1 (IL-1) and insulin-like growth factor (Lambert et al., 2008).
Macrophage infiltration into the left ventricle regulates several wound healing events. Accumulation of monocyte-derived macrophages for example, increases fibroblast accumulation necessary for scar formation, and endothelial cells necessary for angiogenesis regulated through the expression of growth factors and chemokines. In addition, macrophages may increase expression of anti-inflammatory cytokines such as IL-10, thereby inhibiting the inflammatory response and suppressing injury (Ren et al., 2003). The role of macrophages in the wound healing process thus occurs at multiple levels.

2.1.2. Cytokines

The cytokines expressed by the extracellular matrix during MI comprise pro-inflammatory cytokines, such as TNFα, interleukin-1 beta (IL-1β) and IL-6. These cytokines are usually underexpressed in the normal heart, but it has been shown that they are upregulated in both animals and human models during MI (Pasqui et al., 2010). IL-6 and TNFα mediate the reduction in contractility in the infarcted heart. This may be an adaptive response to decrease the energy demand of the myocardium (Nian et al., 2004). In 2010, Pasqui et al. demonstrated that patients with post-ischemic left ventricular remodeling had an increased production of TNFα in comparison with patients who did not undergo left ventricular remodeling, and also in comparison to controls.
On the long term, patients with left ventricular-remodeling showed lower expression of the anti-inflammatory cytokine IL-10 in comparison to controls and non-remodeling patients. This took place from 1 until 6 months after reperfusion (Pasqui et al., 2010). IL-10 is an anti-inflammatory cytokine and suppresses production of pro-inflammatory cytokines such as TNF-α, which implicates that lower expression of IL-10 may elongate the inflammatory response. Lower IL-10 expression may have a protective role, as ventricular remodeling is part of a compensatory mechanism, but if ventricular remodeling continues it can easily result in ventricular dilatation which eventually leads to chronic heart failure.

2.1.3. Adhesion molecules

Other important players in the inflammatory response are adhesion molecules. The main adhesion molecules present after MI are selectins, vascular cell adhesion molecule-1 (VCAM-1) and inter-cellular adhesion molecule-1 (ICAM-1). Adhesion molecules are expressed by activated endothelium and play significant roles in cell adhesion and leukocyte rolling (Haverslag et al., 2008). Expression of E-selectin *e.g.*, is regulated by TNF-α and IL-1 and is responsible for the initial tethering and rolling of leukocytes. This is followed by firm adhesion through the interaction of integrins on the leukocytes with VCAM-1 and ICAM-1, which are responsible for the migration of leukocytes through the endothelial cells and extravasation into inflammatory sites (Voinea et al., 2005).
Together, the adhesion molecules are responsible for part of the inflammatory response and thus are upregulated after MI. Expression of selectins and integrins remains high as pro-inflammatory cytokines are persistently expressed in the post-infarction phase.

2.2. Hemodynamic changes after MI

Necrotic cardiomyocytes are replaced by fibroblasts in an inflammatory reaction to preserve cardiac function. Fibroblasts are cells from the connective tissue and are the primary reactor cells that synthesize extra cellular matrix and coordinate scar formation after MI (Squires et al., 2005).

In 1978, Fishbein et al. described the acute changes in a rat model, where MI was induced by occluding the left coronary artery. Rats were killed one to 21 days following the occlusion, and the hearts were excised for histological study. It was shown that in all hearts, wavy fibers were present after 72 hours, and after 21 days there was persistent prominence of fibroblasts with increased deposition of collagen. This indicates the formation of scar tissue. The deposition of collagen continued until the entire necrotic zone was replaced. In these scar tissue areas however, the ventricular wall becomes thin and does not contract properly, which leads to impaired cardiac function (Mummery, 2005). This cardiac remodeling thus has implications for the hemodynamics on the long term.

2.2.1. Acute hemodynamic changes

The acute phase of heart failure following MI results from the decreased cardiac contractility. The function of the heart as a pump is diminished and therefore the heart is insufficient to eject the normal stroke volume. As a consequence of the decreased stroke volume, cardiac output and mean arterial blood pressure (MABP) levels fall. More blood is left behind in the heart and therefore, the end-diastolic volume and arterial pressures are raised. The reflex mechanisms to maintain normal cardiac output and sufficient cerebral blood flow overrule reflexes triggered by atrial stretch receptors detecting the increased end-diastolic volume (Dampney, 2007). The reduction of cardiac output elicits compensatory homeostatic responses that are mediated by neurohumoral mechanisms, induced by increased activation of the sympathetic nervous system. Activation of the sympathetic nervous system results in systemic vascular resistance, which has implications for the systemic blood flow. This increased systemic vasoconstriction is responsible for reduced blood flow to several vascular beds, including the kidney (Cody et al., 1988; Hirsch et al., 1990).

2.2.2. Left-ventricular remodeling

The loss of contractility as a result of cardiac remodeling after MI accounts for an augmented load that is placed on the myocardium. The use of compensatory mechanisms to maintain systemic perfusion despite this reduced load, may lead to morphological changes of the heart after a certain time. To determine the mechanism involved in ventricular remodeling and hence ventricular dysfunction, Pfeffer et al. obtained pressure-volume relationships of the infarcted left ventricle of rats during both the early and late phases of ventricular infarction. Pfeffer et al. concluded that the structural remodeling of the left ventricle after MI is a time-dependent process. It involves not only the region of necrosis, but also the residual normal myocardium. The reconstruction of the myocardium consists of different processes each being dominant at different time points in the post-infarction phase. These processes include scar formation at the site of infarction, chamber and ventricle volume enlargement and myocyte hypertrophy.

In the early phase after MI, edema and vascular congestion may take place as a result of infarct expansion. A few days after that, a collagen network is laid down after resorption of necrotic tissue, forming scar tissue. During scar tissue formation, cavitary volume increases in order to restore stroke volume (Pfeffer et al., 1991).
In the more chronic phase after MI volume enlargement may continue, but to a harmful extent. The ongoing cardiac remodeling results in left ventricle dilatation, which is believed to be one of the most powerful predictors of cardiac death. This is the most important conclusion of a large clinical study which included 605 patients (White et al., 1987). The degree to which the heart enlarges after MI therefore, seems to have important implications for survival.

2.2.3. Long-term changes in hemodynamics
Several hemodynamic changes on the long-term were observed by Nager et al, in 1967. Nager et al. were the first to describe changes in the circulation 4 months after MI. Instead of focusing only on the importance of cardiac output after cardiac infarction, Nager et al. emphasized the importance of stroke volume, which they believed to be a more representative measurement of ventricle function altogether. It was shown that patients with stroke volume above 60ml represented good cardiac function, and patients with stroke volume between 40 and 60ml and below 40ml represented moderately impaired and poor cardiac function, respectively. The level of stroke volume generally reflected clinical features shown by the patients, in respect to cardiovascular physical signs and ventricular dysfunction (Nager et al., 1967).

2.3. The renin-angiotensin system (RAS)
The reduction in cardiac output after MI elicits increased activation of the sympathetic nervous system. Activation of the sympathetic nervous system has various effects, including effects that eventually result in reduced renal blood flow and hence glomerular filtration rate.

2.3.1. Circulating angiotensin II
The reduced renal blood flow promotes production and secretion of the neurohormone renin. Renin in turn induces the conversion of angiotensin I to angiotensin II, mediated by angiotensin converting enzyme (ACE), and thus increases circulating angiotensin II levels (Sun, 2009). The most important role of circulating angiotensin is maintaining cardiovascular homeostasis. It has been demonstrated in many ways that angiotensin II is a potent vasoconstrictor and that it initiates water and salt retention in the kidney, which together increase blood volume. Moreover, angiotensin stimulates the release of aldosterone from the adrenal cortex, which stimulates reabsorption of sodium and thus further enhances sodium retention. Meanwhile, water retention in the kidney is reinforced by increased levels of antidiuretic hormone (ADH), produced by the arterial baroreceptors in response to decreased baroreceptor activity. This is initiated by the fall in MABP and works via the increased sympathetic activity. In addition to water retention, ADH augments vasoconstriction. (Dampney, 2007). Increased blood pressure is subsequent to this rise in blood volume and systemic vasoconstriction. Hypertension may be very harmful in the post-infarction phase since the heart has a reduced pump function

and elevated afterload (consequent to hypertension) further diminishes stroke volume (MacGregor et al., 1974).

2.3.2. Tissue-dependent angiotensin II

In addition to circulating angiotensin, there is tissue-dependent angiotensin as well. Angiotensin II is produced *de novo* in the injured myocardium, under the influence of inflammatory-induced renin-production in the myocardium itself (Sun, 2009). The existence of tissue RAS was reviewed by Grinstead and Young, who described the different evidential features of myocardial production and activity of renin and angiotensinogen, the presence of angiotensin in the heart, the localization of ACE in myocardial endothelium and intracardial conversion of angiotensin I to angiotensin II (Grinstead and Young, 1992). Not only the well-known endocrine properties of circulating angiotensin II are therefore met, but various paracrine and autocrine properties on local tissue cells as well, for example the induction of ventricular hypertrophy.

2.3.3. Angiotensin II and heart failure

Indirectly, angiotensin II stimulates the release of catecholamines and thereby augments vascular tissue responses to sympathetic activity (Hirsch et al., 1990). The sodium-retaining effects of increased sympathetic nerve activity and renin-angiotensin system activation, may contribute in an important way to the development of heart failure (Dargie et al., 1987). About 30 years ago, it was demonstrated that indeed MI is attended by stimulation of the renin-angiotensin system. This was shown by Dargie et al. in 1987, through the activation of plasma neurohormones in patients after acute MI. It was also suggested that patients with the highest neuroendocrine stimulation had more complications and a poorer prognosis (Dargie et al., 1987).

2.4. Conclusion

MI induces an inflammatory response at the site of injury through the complement cascade, induced by necrotic cardiomyocytes. During this response, upregulated production of pro-inflammatory cytokines (TNFα, IL-1β, IL-6) as well as anti-inflammatory cytokines (IL-10) is seen. Pro-inflammatory cytokines mediate reduction in contractility of the infarcted heart to decrease energy demand, whereas circulating angiotensin II, also highly upregulated during MI, exerts inotropic effects on the myocardium by increasing contractility. However, since cardiac output is known to decrease after MI, the inflammatory cytokines seem to have the upper hand in this case.

In addition to elevated cytokine levels, adhesion molecule levels are also high. Adhesion molecules play a pivotal role in the inflammatory reaction by mediating leukocyte rolling and adhesion, and are persistently expressed in the post-infarction phase. Since adhesion molecules are expressed by activated endothelium it is not unthinkable that adhesion molecules are expressed by endothelial cells in the kidney as well, in response to the inflammatory parameters that might exert effects elsewhere in the body.

In the inflammatory reaction cardiomyocytes are replaced by fibroblasts forming a collagen layer which replaces the necrotic zone. This new-formed collagen layer, forming scar tissue, is part of the cardiac remodeling process which in the end leads to impaired cardiac function. During the scar tissue formation in the first days after MI, the heart is not sufficient to eject normal stroke volume. To compensate for this, cavitary and

ventricular volumes increase in order to restore stroke volume and thereby provide sufficient blood flow to the brain and other vascular beds. This ventricular remodeling is likely to develop in the more chronic phase after MI eventually leading to ventricular dilatation, which is one of the most powerful predictors of cardiac death. Subsequent to diminished stroke volume is decreased cardiac output. Decreased cardiac output elicits activation of the sympathetic nervous system and in reaction to this, neurohumoral mechanisms take place. These neurohumoral mechanisms lead to systemic vasoconstriction which eventually results in diminished blood flow to the vascular beds, including the kidneys. Another effect of the sympathetic nervous system is the activation of the renin-angiotensin system. Circulating angiotensin II is responsible for the increased water and salt retention in the kidney after MI resulting in a greater blood volume. This together with the vasoconstrictive effects of angiotensin II is responsible for elevated blood pressure and can even lead to hypertension. Hypertension in the post-MI phase can be very dangerous as the pump function of the heart is not optimal and a chain of causation is entered. The activation of the RAS might be the most evident link between cardiac and renal interaction, since it appears to be an interplay between cardiac activation and renal response. This assumption is supported by the fact that several studies suggest that intervention of RAS-activation after MI prevents the progression of renal damage.

Despite of all these injurious consequences of MI, the abnormalities are not attended by lethal injury, and the ischemic myocardium ultimately recovers (Ren et al., 2003). But how than, is it possible that cardiovascular events, such as MI, in patients with mild renal damage often are lethal and account for 44% of mortality in patients with chronic kidney disease?
To answer this question, we need to get insights in the pathophysiology of the renal system. Perhaps renal pathophysiology is sufficient to explain why enhanced kidney damage was seen in unilateral nephrectomized rats when presented with MI. If not, how do the symptoms of these two non-lethal diseases detriment organ function in a way that it becomes lethal?

3. What happens after unilateral nephrectomy, *i.e.* mild renal damage?

Unilateral nephrectomy can be either inherited, as is the case in children born with unilateral renal agenesis, or therapeutically induced in patients who need kidney transplantation (or kidney donors). Over the years, researches have described the consequences of unilateral nephrectomy in children and kidney donors. Since recently, animal models have been used as a model for unilateral nephrectomy to conduct pre-clinical research. It appears that survival in patients with one kidney is very high and that is has little adverse effects. These effects alone do not often result in severe disease processes, and therefore unilateral nephrectomy is seen as a model for mild (chronic) renal damage.

3.1. Glomerular filtration rate and effective renal plasma flow after unilateral nephrectomy

In 1975, Pabico et al. determined the changes brought about by unilateral nephrectomy in glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and functions of the proximal and distal tubules. Pabico et al. used seven healthy kidney donors who had undergone unilateral nephrectomy and who had no evidence of kidney disease. Comparisons of the kidney function before and after unilateral nephrectomy were made using function-values of the remaining kidney compared to 50% of the pre-uninephrectomy values. In this study, a considerable increase in GFR and ERPF was found in the remaining kidney within a relatively short period of time after unilateral nephrectomy.

This increase in GFR and ERPF was also seen by Sugino et al., who reported a marked increase in GFR within hours (Sugino et al., 1967). This increase may be compensatory as only half of the kidney surface and thus half the number of nephrons is left to filtrate. To maintain sufficient filtration, the remaining kidney will enter a state of slight hypertrophy and hyperfiltration. Studies with long follow-ups however, showed that after the short-term increase of GFR, GFR eventually falls. Ibrahim et al. for example, reported that kidney donors 12 years after donation had a GFR that was 76% of the estimated GFR at the time of donation (Ibrahim et al., 2009). After this fall GFR remains stable for over decades (Kasiske et al., 1995).

The findings of Kasiske et al. are not in line with these studies. They analyzed 48 reports on people who underwent unilateral nephrectomy and presented the results systematically. They extracted that there was an initial decrease in GFR but this progressed in a small increase in GFR during follow-up in patients with a 50% reduction in renal mass. Elevated effective renal blood flow (ERBF) was found by both Anderson et al. and Indudhara et al., ranging from an increase of 29-30.1% one week after surgery. Anderson et al. reported a 37.2% increase 10 years after surgery (Anderson et al., 1991; Indudhara et al., 1999).

Baudoin et al. assessed the long-term effects of unilateral nephrectomy in children, in a follow-up study of up to 52 years after nephrectomy. In this study renal function, protein excretion and blood pressure was measured in 111 subjects who had surgery before the age of 16 and who had no evidence of kidney failure at the time of the surgery. Baudoin et al. reported well maintained renal function overall, but patients with a follow-up of more than 25 years showed lower renal function, and higher blood pressure, urinary albumin excretion and protein excretion (Baudoin et al., 1993).

3.2. Hypertrophy of the residual kidney

Following nephrectomy, the contralateral kidney increases its mass by approximately 50%. This tissue growth is achieved through increasing volume of the nephrons and glomeruli, *i.e.* hypertrophy of the nephrons and glomeruli. Subsequent to this hypertrophy is elevated glomerular flow and pressure, which lead to increased single-nephron filtration rate. This early compensatory mechanism is responsible for the increased GFR. The hemodynamic hyperfunction caused by structural enlargement of residual nephrons may be harmful over time. This was demonstrated in multiple clinical situations, where glomerular hypertrophy was shown to be associated with glomerular sclerosis, resulting in glomerular degeneration and thus eventually in a reduced number

of nephrons (Hostetter et al., 1995). This was demonstrated in the unilateral nephrectomy ratmodel of Van Dokkum et al. as well (van Dokkum et al., 2004). Several studies have shown that in humans, a reduced number of nephrons is associated with hypertension, renal disease and chronic kidney disease (Brenner et al., 1988; Hegde et al. 2009; Hoy et al., 2005).

3.3. Systemic blood pressure

Long-term renal function and blood pressure in kidney donors was investigated because of the findings that unilateral nephrectomy in rats causes hypertension (Hegde, 2009). Kasiske et al. reviewed that patients with a single kidney showed a small increase in systolic blood pressure which rose further during follow-up. Also a small increase in diastolic blood pressure was reported, however this did not progress during follow-up. Indudhara et al. did not identify one patient with hypertension, elevated creatinine or proteinuria after a 4.5 year follow-up in kidney transplantation donors. Hypertension was also not seen by Prasad et al., who studied the short-term effects of unilateral nephrectomy on the cardiovascular risk profile of living kidney donors (Prasad et al., 2008). In addition, Ibrahim et al. described that the risk of (carefully screened) kidney donors on developing hypertension appeared to be similar to those in the general population (Ibrahim et al., 2009).

3.4. Protein excretion

In the case of proteinuria and albuminuria after unilateral nephrectomy the results of studies conflict. There are studies that show a slight increase in proteinuria after nephrectomy (Baudoin et al., 1993; Kasiske et al., 1995), but several studies argue that there are no significant changes in proteinuria levels compared to the general population (Prasad et al., 2008; Hegde et al., 2009) or an increase that might be similar to the general population, considering natural regression in kidney function and hence progression of proteinuria with age (Kasiske et al., 1995). Vu et al. conducted research on patients with only one (normal) functioning kidney who were diagnosed in the first year of life and studied at age 2, 5 and 10, with some of them having undergone unilateral nephrectomy. Low GFR, hypertension and proteinuria was found in all patients during follow-up.
In their rat model, Van Dokkum et al. also found significantly higher proteinuria levels compared with all controls, increasing from week 6 until in week 16 a stable level was reached (Van Dokkum et al., 2004).

3.5. Conclusion

The general finding of many studies on patients with one functioning kidney is an initial rise in GFR, ERBF and ERPF, with ERBF and ERPF being the volume of blood respectively blood plasma delivered to the kidney per unit time. These findings however appear to apply only on short-term studies, as other studies reported a decreased GFR after years and even decades. Robitaille et al. suggested that the increase in GFR is an adaptive process which is essentially completed after 3-4 weeks. They found that many years after unilateral nephrectomy, patients had a mean endogenous creatinine clearance (a method to evaluate GFR) that was 74.3% of that of normal controls (Robitaille et al., 1985). Robitaille et al. also described that GFR may moderately and progressively rise

during the first 4 years after unilateral nephrectomy, which may explain the findings of Kasiske et al., who reported an increase in GFR during several years.
After unilateral nephrectomy, the contralateral kidney increases its mass through hypertrophy of the nephrons and glomeruli. This serves a compensatory process as the residual nephrons show hyperfiltration to sustain sufficient filtration rate. As this process continues it may become harmful, since glomerular hyperfiltration is associated with glomerulosclerosis through mechanisms not discussed here. Glomerulosclerosis eventually leads to glomerulo-degeneration.
In some cases unilateral nephrectomy is accompanied by a slight increase in systolic and diastolic blood pressure, with occasionally blood pressure values on the borderline of hypertension. This finding is not in line with animal studies, where rats showed significant increase in blood pressure after nephrectomy. In studies where patients did show increase in blood pressure this may well be due to the fact that blood pressure increases with age. Given that patients are studied during a follow-up of several years, this seems a plausible explanation.

Most reviews conclude that the long-term outlook for patients who underwent unilateral nephrectomy or suffer from unilateral renal agenesis is reasonably good and that stable renal function is expected for up to five decades (Hegde et al., 2009; Kasiske et al., 1995). Unilateral nephrectomy in humans does not seem to reduce life expectancy or produce other adverse outcomes, despite a few harmless compensatory processes. Survival curves are not different from the general population (Hegde et al., 2009).
Hedge et al. state that the physiologic impact of unilateral nephrectomy is related to the mass of kidney tissue removed. This determines the compensatory hemodynamic changes and therefore the remaining kidney (dys-)function. In this review, the problems following unilateral nephrectomy (*i.e.* 50% kidney tissue removal) were taken into account, which therefore can be defined as relatively mild renal damage.

4. The relation between MI compensation mechanisms and renal failure

Increased levels of proteinuria in combination with focal glomerulosclerosis are thought to be the most powerful indicators of renal damage and therefore Van Dokkum et al. concluded that MI accelerates renal dysfunction in rat models with chronic mild renal damage.
In this review, I tried to find the underlying mechanism of this phenomenon. Many studies have showed that unilateral nephrectomy does not have severe adverse effects on kidney function which is also reflected in the increasing number of healthy kidney donors nowadays. However the incidence of chronic renal failure in combination with cardiovascular events is increasing, and co-existence of the diseases leads to an extremely bad prognosis. Therefore, the suggestion that maybe the systemic adaptations occurring after MI play a pivotal role in this seems valid.
MI often results in congestive heart failure, which is long-term damage of the heart. This is the result of a number of events occurring directly and on the longer term after MI. It all starts with the induction of the inflammatory response at the injured site, in response to necrotic cardiomyocytes. During the inflammatory response, cytokine levels are upregulated and may exert effects systemically as well as locally, as cytokines travel through the blood and therefore reach all organs in the body. It may be that this enhances

a possible, already ongoing, inflammatory reaction in the kidney. This inflammatory reaction of the kidney might occur in reaction to the state of slight hyperfiltration the residual kidney enters after nephrectomy.
Scar tissue formed during the inflammatory response in the heart does not have contractile properties like normal cardiac tissue. As a result, cardiac contractility is diminished which leads to decreased stroke volume accompanied by decreased cardiac output. The decreased cardiac output results in a number of compensatory mechanisms. One of the mechanisms is the activation of the sympathetic nervous system. The sympathetic nervous system has various effects on the systemic vascular bed which are mediated by a neurohumoral response. The main effect is systemic vasoconstriction which leads to diminished blood flow to the vascular tissues, including the kidney. Less blood is offered to the kidney and thus renal perfusion is reduced. This is followed by a decreased GFR.
Reduced GFR at its turn may lead to insufficient tissue perfusion and thus lowered oxygen supply, which mismatches the oxygen demand of the hyperfiltrating kidney. Oxygen deprivation leads to ischemic tissue damage and results in an inflammatory response. This inflammatory response is initially meant to protect the kidney from further damage, but in extreme levels it can have detrimental effects instead, causing further damage to heart and kidneys. In line with this thought, Van Dokkum et al. did observe the highest number of macrophages present in the group with mild renal damage and MI, in comparison with the sham- , MI – and unilateral nephrectomy groups. This indicates a marked inflammatory reaction.
In 1988, Cody et al. identified the factors that characterize impaired GFR in patients with congestive heart failure. This was done measuring systemic hemodynamics, vasoactive hormones and sodium and volume status in 34 patients with congestive heart failure. It became clear that patients with the greatest impairment of GFR had the lowest filtration fraction and the highest overall renal vascular resistance. This, in combination with the vasoconstrictive effects of the sympathetic nervous system may cause hypertension. Former research had already established the dominant role of the kidney in the long-term regulation of arterial pressure, and therefore the development of hypertension (Woods et al., 2001). This hypertension is not seen in patients with unilateral nephrectomy alone, but was indeed observed by Van Dokkum et al. in their rat model. Hypertension is further enhanced by activation of the renin-angiotensin system (also activated in response to sympathetic activity). Circulating angiotensin II is responsible for the increased water and salt retention in the kidney after MI resulting in a greater blood volume. An indirect effect of angiotensin II is stimulating the release of catecholamines, thereby augmenting the vascular tissue response to sympathetic activity.
The activation of the renin-angiotensin system might be the most evident link between cardiac and renal interaction, as it appears to be an interplay between cardiac activation and renal response. This link has been established widely through the use of angiotensin converting enzyme-inhibitors (ACEi) in patients with congestive heart failure and renal failure. For many decades, patients suffering from congestive heart failure are prescribed ACEi. ACEi have been demonstrated to attenuate left ventricle dilation and improve survival in both patients and experimental models of heart failure (Hirsch et al., 1990) and because of their additional vasodilator effects, they exert an acute increase in cardiac output and decline in left ventricular filling pressure (Cohn, 1990). In clinical trials

including chronic kidney disease patients, interference of the RAS through ACEi showed blockade on the progression of chronic kidney disease, thereby protecting patients against the progressive loss of renal function (Siragy et al., 2010).
The influence of ACEi on renal impairment in combination with MI, and thus cardiac damage, has only been demonstrated in experimental models. In 2006, Windt et al. first of all confirmed their previous findings that MI induces enhanced progressive renal damage in uninephrectomized rats and, in addition to this, they showed that ACEi are effective agents in the prevention of this phenomenon. This was demonstrated by significantly lower levels of proteinuria, glomerular surface area (hence decreased glomerular hypertrophy) and focal glomerulosclerosis incidence in the rats receiving ACEi therapy. Furthermore, they showed a significantly lower level of renal inflammation and a more favorable outcome of cardiac contractility and left ventricular end diastolic pressure (Windt et al., 2006). This provides great perspectives for the future as it shows a link between renal and cardiac damage and presents a window to conduct further research on the cardio-renal interaction.

5. Limitations

Considering all the articles reviewed it should be noted that many of the studies did show variation in either population, methods for measuring the parameters, and quality of the research. Furthermore, several studies presented results of outcomes of renal or cardiac damage, without taking into account the possibility of mild organ failure before MI or kidney dysfunction. Obviously, this was borne in mind when writing this review, however it might influence the drawn conclusions. The realization that matched control populations and retrospective studies are very important in this field of research may provide more suitable studies in future to make comparisons and draw conclusions on this particular matter.

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