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PATHOPHYSIOLOGICAL MECHANISMS AND DRUGS LEADING TO DECREASE IN RENAL FUNCTION IN CONGESTIVE HEART FAILURE

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Summary. *Literature review shows that elevated serum creatinine (or diminished creatinine clearance) is frequent in patients with heart failure (40%) and prognostically bad as it indicates an independently manifold increased mortality. In addition, even renal function worsening during hospitalization (increase in serum creatinine by approximately 30 micromol/L or higher) is not a rare finding (every 4 patients with heart failure) and is an independent marker of bad outcome. The pathophysiological mechanisms involved are numerous: dehydration (including the overdiuresis-induced one), the worsening of cardiac function (including negative inotropes), too much of vasodilatation (drug-induced, i.e. Amlodipine), nephrotoxic drugs, etc. Due to methodological reasons, large heart failure trials have not included enough patients with diminished renal function, as far more of them can be found in "real-life" conditions (epidemiologically). Thus, conclusions of large trials have not proved fully applicable but should be made so by means of trials including a representative number of patients suffering from both cardiac and renal failure. In our country, the knowledge on the issue of decreased renal function in heart failure patients is far from satisfactory, which necessitates further education. Drugs and their doses should be carefully selected and adjusted to individual findings, nephrotoxic medicaments should be avoided, and all useful drugs should be administered. Each of the five basic drugs (beta blockers, ACE inhibitors, spironolactone, aspirin, statins) for heart insufficiency (primarily induced by ischemic heart disease) seems to improve prognosis (including. life span prolongation) even in patients with diminished renal function.*

Key words: *Congestive heart failure, renal function worsening, pathophysiological mechanisms, drugs*

Introduction

The aim of the paper is to review major drugs and mechanisms leading to the **worsening** of renal function in patients with congestive heart failure (CHF). Although commonly used in CHF, drugs like beta-blockers, which improve CHF prognosis substantially, are, thus, beyond the scope of this paper. In addition, Digitalis, Erythropoetin, Heparin, etc. have not been shown to diminish renal function and, although important, will not be discussed. Non-steroidal anti-inflammatory drugs and Gentamycine, well-known nephrotoxic drugs, will not be reviewed either, because they are not administrated in CHF therapy.

Importance of the Problem

The available literature shows that elevated serum creatinine (or diminished creatinine clearance- CrCl) is frequent (40%) in patients with CHF (1-4). Elevated serum creatinine is ***prognostically bad*** in CHF, as it leads to manifold increased mortality, irrespective of the symptoms' severity (1-19). In addition, even the worsening of renal function during hospitalization (increase in serum creatinine by approximately 30 micromol/L) is not a rare finding (25% patients with CHF) and is an independent marker of bad outcome.

At presentation, CHF has been observed to significantly modify the prognostic value of creatinine in acute myocardial infarction (AMI). The adjusted hazard ratio for one-year death associated with elevated creatinine compared with normal creatinine has been estimated at 3.89 in patients without CHF and 1.92 in patients with CHF. A *threshold* of serum creatinine below which there is no association between serum creatinine and prognosis *has not been identified* (20).

Basic Aspects

Renal function is a dynamic process, which may either worsen or improve in a relatively short period of time (21). Prerenal azotaemia, in which the integrity of the renal tissue is preserved, is an appropriate physiological response to renal hypo-perfusion and can com-

plicate any disease characterized by either *true hypovolaemia* or *reduction in the effective circulating volume*, such as low cardiac output, systemic vasodilatation, or intrarenal vasoconstriction. Hypovolaemia leading to a fall in systemic blood pressure activates several neurohumoral vasoconstrictive systems, which act in concert to maintain blood pressure and preserve cardiac output and cerebral perfusion. Gradual dilation of **pre**glomerular arterioles is mediated within the kidney via generation of angiotensin of the vasodilating products of arachidonic acid (*prostaglandin I2*) and of *nitric oxide.* In the lower zone of auto-regulation, concomitant vasoconstriction of the **post**glomerular arterioles, mainly under the influence of angiotensin II, maintains a constant glomerular capillary hydrostatic pressure. Drugs that interfere with the auto-regulation of renal blood flow and glomerular filtration rate (GFR) can provoke acute prerenal failure (22).

Acute inhibition of cyclo-oxygenase (type I or II) by non-steroidal anti-inflammatory drugs (NSAIDs) can reduce GFR and the renal blood flow in specific clinical situations, such as:

– *atherosclerotic* cardiovascular disease in patients *older* than 60 years;

– pre-existing *chronic* renal insufficiency (serum creatinine >180 micromol/L); and

– conditions of renal *hypoperfusion* such as those in sodium depletion, diuretic use, hypotension, and sodium-avid states such as cirrhosis, nephrotic syndrome, and CHF (22). Renal function is usually impaired in severe CHF, and this, together with the shift in the dose response curve to the right, requires at least doubling the usual loop diuretic dose in most patients.

GFR declines with age and declines more steeply with age among patients with CHF. This change is reflected as a rise in blood urea nitrogen with age. CHF is not only a disease of the elderly, it is a disease of the *very elderly*. In the CHF register, the number of patients over 85 years of age was more than twice that of patients between 65-69 years of age. A total of 34,587 elderly CHF patients were studied, of whom more than half had coronary heart disease, more than half had a history of hypertension, and renal insufficiency was more common with advancing age. *Blood urea nitrogen* increased with *age* but *creatinine did not*. Creatinine remained unchanged, probably due to the competing age-related decline in creatinine as a result of muscle mass decline and a rise in creatinine as a result of glomerular filtration decline. Left ventricular (LV) ejection fraction (EF) was <40% in only 50.4% patients in whom it was assessed. Patients with CHF constitute a heterogeneous group and appear to differ substantially from patients enrolled in clinical trials. The results of these clinical trials must not be generalized to older patients. An evidence-based guidance for treatment in the context of multiple co-morbid conditions, poor renal function, and CHF with preserved LV systolic function is urgently needed (23).

Left Ventricular Systolic Dysfunction and Prerenal Azotemia

No clear relationship between hypotension or the severity of LV systolic dysfunction and the worsening of renal function (WRF) has been found (24). It is noteworthy that LVEF was not a predictor of WRF and that, among patient subgroups with mild, moderate, and severe LV systolic impairment, as well as those with normal LVEFs, the number of patients who developed WRF was similar. These findings are consistent with those of Weinfeld *et al.*, who showed no correlation between renal deterioration and cardiac output, filling pressures, or baseline systemic vascular resistance in a study of 48 CHF patients (25). It seems likely that other endogenous vascular factors, including endothelin, nitric oxide, prostaglandin, natriuretic peptides, and vasopeptidase inhibitors may affect renal perfusion independently of central chemo-dynamics. Co-morbid conditions or the treatments utilized may also play a critical role in the development of WRF (24).

In the Second Prospective Randomized study of Ibopamine on Mortality and Efficacy (PRIME II) trial, in which participants had advanced New York Heart Association (NYHA) class III to IV CHF and LVEFs of <35%, the calculated CrCl was the most powerful predictor of mortality (11). The adverse prognostic influence of renal dysfunction is *independent* of atherosclerotic burden and *LV systolic function* (3). The *elderly* are at high risk for renal insufficiency due to the age-related decrease in kidney function, as well as other factors, such as concomitant hypertension, diabetes, and vascular disease (17). Patients who developed renal insufficiency had lower baseline body weight and higher baseline serum creatinine, required higher doses of loop diuretics, and were more likely to be treated with thiazide diuretics than controls. Of 282 women with CHF and documented preserved systolic function, *over half of them* had renal insufficiency: 41% with CrCl 40 to 60 ml/min and 15% with CrCl <40 ml/min. O*ver one-half* of 190 women with documented depressed systolic function had renal insufficiency: 35% with CrCl 40 to 60 ml/min and 23% with CrCl <40 ml/min (4).

Impaired renal function is *not related to LVEF*, and *is associated with increased levels of N-terminal atrial natriuretic peptide*, suggesting that factors other than reduced cardiac output, such as neurohormonal activation, may be involved. The observed relation between mild renal insufficiency and CHF is not entirely due to diminished cardiac output secondary to systolic dysfunction. Similar associations between renal insufficiency and CHF were observed in the Cardiovascular Health Study, in which 55% of patients had normal systolic function and 80% had normal or only mildly reduced systolic function (26). In a cross-sectional analysis from the Strong Heart Study, mild renal dysfunction and older age were the strongest predictors of CHF despite normal LVEF-s (27).

The association between renal function and mortality did not differ with respect to preserved or depressed systolic function. Renal insufficiency was found predictive of mortality in women with both preserved and depressed systolic function (independent of systolic function) (4). The baseline renal function, uncontrolled hypertension, and history of diabetes mellitus or CHF were independent predictors of WRF (28,29).

The predictors of WRF included:

- a history of diabetes mellitus or CHF;
- systolic blood pressure > 160 mm Hg; and
- creatinine level > 221.0 micromol /L on admission.

The admission hematocrit level > 45% was associated with a lower risk. The admission creatinine level between 132.6 and 221.0 micromol/L showed a strong tendency to significance, but hypotension (defined as systolic blood pressure < 100 mm Hg) was not associated with development of WRF (21).

Renal Insufficiency and Ace Inhibition

The beneficial effect of unloading the failing heart by reducing the systemic outflow resistance is opposed by a potentially harmful effect of unloading the kidney by preferentially reducing the outflow resistance of the glomerulus (30). An acute rise in serum creatinine level after inhibition of the renin angiotensin system occurs in patients with HF primarily due to renal hypo-perfusion and volume depletion secondary to aggressive diuresis, low cardiac output, or both (31).

A difference in the association between renal insufficiency and mortality among users and nonusers of ACE inhibitors was observed. Women with creatinine clearance 40 to 60 ml/min using ACE inhibitors had no increased risk of death, compared to those with CrCl < 60 ml/min. By contrast, women with CrCl 40 to 60 ml/min who did not use ACE inhibitors had a twofold risk of death, compared with those with CrCl < 60 ml/min. The risk of death also differed among users and nonusers of ACE inhibitors with CrCl < 40 ml/min (4).

However, development of functional renal insufficiency is unlikely and is a rare cause for withdrawing ACE inhibitors when certain **precautions** are considered:

(1) The initial dose of an ACE inhibitor has to be reduced with increasing severity of CHF (the titration period thereafter should be monitored carefully);

(2) An increase in serum creatinine not exceeding 30% of the basal value may be taken as evidence for a beneficial action of the drug, which in addition to altering cardiac function alters kidney function (when the increase in serum creatinine is considered to be of clinical significance, it seems wise to reduce the dose of diuretics first - thereby neuroendocrine stimulation can be attenuated and the dependency of renal filtration from angiotensin II-induced efferent vasoconstriction can be reduced); and

(3) Co-administration of the inhibitors of prostaglandin synthesis (e.g., acetylsalicylic acid) appears to be associated with a higher risk of impairing renal function: the decrease in glomerular filtration rate is more pronounced and the compensatory increase in renal plasma flow following ACE inhibition is no longer observed (30).

A Long-term treatment with ACE inhibitors, however, has been shown to reduce renal disease progression (32,33). Patients with diabetic nephropathy given the ACEI lisinopril showed a 1-9% fall in GFR 1 month following the treatment initiation. Within the period 1 month-5 years, GFR remained stable with no further decline. The mean arterial pressure registered in this study ranged from 99 to 105 mmHg. After an average of 5 years of ACEI therapy, patients were withdrawn from ACEI treatment, and clonidine was substituted to maintain blood pressure control. GFR returned to the levels not different from the baseline within 1 month of ACEI termination, despite similar blood pressure control. This study further supports the assumption that while GFR may be reduced acutely, the rate of progression of renal disease can be markedly blunted with ACEIs. In addition, these initial ACEI -associated declines in GFR are reversible and partially independent of systemic arterial pressure (31).

Clinical trials of ACE inhibitors for treatment of patients hospitalized with AMI have excluded patients with moderate to severe renal insufficiency, thereby limiting a possible generalization of the results of these trials to patients with elevated serum creatinine (20). However, among patients with mild renal insufficiency, treatment with ACE inhibitors reduces mortality and nonfatal cardiovascular events (34). Therefore, in patients with elevated serum creatinine in the setting of AMI, the cardio-protective effects of ACE inhibitors may offset deleterious effects on renal function (20).

Haemodynamic acute renal failure *caused by ACE inhibitors* or by angiotensin-II-receptor blockers develops in patients with stenosis of the renal artery in a solitary kidney or with bilateral renal-artery stenosis. Renovascular disease has been found in 34% of elderly people with heart failure, but patients with hypovolaemia, severe chronic heart failure, polycystic kidney disease or intra-renal nephrosclerosis without renal-artery stenosis are also at risk. The frequency of acute renal failure induced by ACE inhibitors varies between 6% and 23% in patients with bilateral renal artery stenosis and increases to 38% in patients with unilateral stenosis in a single kidney. Prerenal azotaemia can be corrected if the extrarenal factors causing the renal hypo-perfusion are reversed. When not corrected, persistent renal hypo-perfusion will ultimately lead to ischaemic acute tubular necrosis (22). Much less is known about angiotenzin receptor blocker's (ARB) influence upon WRF in CHF. Because of the similarities in the effects of ACE inhibitors and ARBs in CHF, it seems logical to use ARBs carefully in CHF patients with low blood pressure and other clinical situations known to induce WRF until we have more valid information on this issue.

Renal Insufficiency and Diuretics

The overall prescription rate for **loop diuretics** has not been found to differ between patients with WRF and control subjects on the day before WRF. However, loop diuretic doses were significantly higher in patients with WRF. Net increase in dose from admission to the day before WRF was 92 mg in patients with WRF and 64 mg in patients without it**.** The association between higher loop diuretic doses and development of WRF is not readily explainable. Diuretic delivery to the tubules is dependent on renal function in patients with CHF. Elevated doses of diuretics are required for patients with impaired renal function. In patients with advanced CHF, the natriuretic response to loop diuretics is reduced to one third to one fourth of normal. It is possible that a specific subgroup of patients with CHF is chronically resistant to diuretics and therefore requires even higher dosages for acute de-compensation and that this group is particularly prone to the development of WRF. This hypothesis is supported by the average creatinine level on admission being significantly higher in patients with WRF. An alternate explanation is that higher loop diuretic doses may have led to more aggressive diuresis, thereby increasing the risk for WRF (21).

However, no differences in filling pressures among patients with HF in whom WRF developed during a net diuresis of at least 2 kg of fluid during HF hospitalization (25). A likely conclusion is that differences in amounts of diuresis do not contribute significantly to WRF. The data on higher diuretic use and development of WRF suggests that it is **most likely that this is not related to over-diuresis** but, rather, to **higher doses in patients resistant to diuretics** (21).

CHF often causes prerenal azotaemia that may lead to diuretic resistance. **Diuretic resistance** in the edematous patient has been defined as a clinical state in which diuretic response is diminished or lost before the therapeutic goal of relief from edema has been reached. The *major causes of diuretic resistance* include:

- *functional renal failure (prerenal azotaemia);*
- hyponatremia,;
- altered diuretic pharmaco-kinetics; and
- sodium retention caused by counter-regulatory mechanisms intended to reestablish the effective arterial blood volume (35).

Hyponatremia is frequently associated with reduced diuretic efficacy due to diminished distal tubular sodium delivery and secondary hyperaldosteronism. Hyponatremia may be due to treatment with diuretics, especially thiazides but, more often, it is due to underlying severe CHF leading to stimulation of thirst, as well as a non-osmotically stimulated vasopressin system that impairs excretion of free water. *ACE inhibition is often successful* in treating refractory edema in patients with diuretic resistance, resulting in a loss of body weight, a decrease in serum creatinine level, and an amelioration of hyponatremia. The underlying mechanisms for these beneficial effects include improvement of cardiac performance and suppression of angiotensin-II–mediated stimulation of thirst, vasopressin release, and tubular sodium re-absorption. Another diuretic combination involves the addition of spironolactone to a regimen that includes a loop diuretic and an ACE inhibitor. The rationale is that during long-term ACE inhibition, aldosterone secretion is no longer suppressed ("*aldosterone escape*"), thereby contributing to sodium retention. Small doses of spironolactone (e.g., 12.5 to 25 mg daily) effectively block aldosterone action when given in addition to a loop diuretic and an ACE inhibitor (35).

Guidelines for CHF recommend taking **spironolactone** in addition to ACE inhibitors and beta-blockers (36,37). A randomized controlled trial Randomized Aldactone Evaluation Study (RALES) on the use of spironolactone in heart failure patients reported a low risk of renal insufficiency (0%). Others studies observed that a rise in creatinine > 4.0 mg/dL occurred in 0.3% of CHF patients on spironolactone. The patients who experienced renal insufficiency had a *preexisting renal impairment* and were more likely to be treated with potential *nephrotoxic agents*. Patients developing renal insufficiency after the initiation of spironolactone therapy had higher baseline creatinine (0.3 mg/dL) and BUN levels (5 mg/dL). Patients with renal failure were older, had lower body weight, received higher loop diuretic doses, and were more likely to have a history of gout and be treated with thiazide diuretics, beta-blockers, amiodarone, and COX-2 inhibitor therapy (38).

Predictors of hyperkalaemia and azotaemia include:

- age;
- lower LVEF; and
- higher NYHA functional class.

Excessive diuresis might be an *important cause of renal dysfunction* while taking spironolactone. Particular caution should be taken in elderly people with LVEFs below 20%, potassium supplementation should be discontinued, changes in body weight should raise concern, doses in concomitant diuretic regimens may need adjustment, and continuous laboratory monitoring remains inevitable (39).

Patients developing renal insufficiency during spironolactone therapy were found to have lower body weight at the time of drug discontinuation, while the body weight of controls did not change. This suggests that patients experiencing increased creatinine may have developed pre-renal azotaemia *due to diuresis* or dehydration. Alternatively, the observed drop in body weight in the patients developing renal insufficiency may have occurred due to the effects of CHF leading to progressive cachexia. This subgroup of patients demonstrated *loop diuretic resistance* compared to controls, as the baseline loop diuretic dosage in these patients was nearly twice that in the other study samples. The effects of spironolactone on serum creatinine and BUN were only partially reversible and remained higher than the baseline values for both groups of cases (38).

One way of dealing with renal dysfunction secondary to spironolactone may be to *reduce* doses of concomitant diuretics.

Calcium channel blocker (CCB) administration was more frequent in WRF cases than in control subjects on the day before WRF (25% vs. 10%, $p < 0.05$). CCB use was higher among patients with low EF but was not statistically significantly different in patients with preserved EF. Both dihydropyridine and non-dihydropyridine CCB use was higher in cases of WRF (13% vs. 6% for dihydropyridine and 13% vs. 5%, for non-dihydropyridine CCB, both $p < 0.05$). More cases with WRF were already on *vasodilators* upon hospitalization (vasodilator use increased from 32% to 46%) as compared to CHF patients without WRF (vasodilator use increased from 33% on admission to 35%, $p < 0.05$). Some CCBs have prominent negative inotropic properties, which may lead to a further decrease in cardiac output in patients with depressed EF, thus explaining these findings. On the other hand, it is possible that patients receiving CCBs may represent a group at higher risk for development of WRF (e.g., patients with rapid atrial fibrillation associated with hemodynamic compromise or uncontrolled hypertension). Another possible explanation can be referred to the vasodilatory effects of CCBs. The use of other vasodilators was also significantly higher in patients on the day before WRF (21). Some direct vasodilators (e.g., minoxidil and prazosin) have been associated with a rise in creatinine concentrations (40). It is possible that there are subgroups of patients with HF in whom aggressive vasodilatation may lead to deleterious renal effects (e.g., patients with uncontrolled hypertension or renal artery stenosis) (21).

The pharmaco-kinetics of many medications is altered in the setting of renal dysfunction. Typical example is **digitalis**, which has been known to accumulate in renal failure frequently enough to produce intoxication (41). In addition, renal dysfunction decreases the clearance of glycoprotein IIb-IIIa inhibitors as well as the **low-molecular-weight heparins** and the direct thrombin inhibitors. Inadequate dose adjustment of these medications in the setting of renal dysfunction may result in excessive anticoagulation and bleeding complications that may offset any potential therapeutic benefits (20).

Patients with reduced creatinine clearance rates were more likely to develop aggravated renal deterioration and poor outcomes despite similar baseline creatinine level (25). Nonetheless, another study provides firm support for using increases in serum creatinine to predict adverse outcomes regardless of the "actual" renal function. Furthermore, serum creatinine levels are less expensive than assessments of creatinine clearance, and they are more clinically useful for monitoring short-term fluctuations in renal function (24).

Of course, each nephrotoxic drug (e.g., Gentamycine) may worsen the renal function in CHF, too, probably even more.

One of the important reasons for the decrease in kidney function is CHF worsening. Thus, CHF diminishes renal function and prognosis and, in turn, renal insufficiency worsens CHF (vice versa).

Mechanisms by which Impaired Renal Function Worsens CHF

Increased vulnerability to CHF in subjects with impaired renal function has been suggested by several mechanisms, including

- accelerated hypertension;
- activation of the sympathetic and renin-angiotensin systems;
- volume expansion due to impaired sodium excretion;
- left ventricular hypertrophy; and
- proatherogenic effects (9,27,42-44).

Is there a causal relation between reduced renal function and CHF, or is renal insufficiency only a marker for the presence of co-morbidities or disease severity?

Deterioration in renal function may reflect the effects of co-existing conditions, such as diabetes mellitus, hypertension, or atherosclerosis, which directly affect both the heart and the kidneys. Mild renal insufficiency has been associated with the elevated levels of proinflammatory and procoagulant markers. Although it is one of the possible mechanisms, however, promotion of atherosclerosis is unlikely to account for the entire association between mild renal insufficiency and CHF. The association between decreased renal function and risk of CHF remained highly significant after control of coronary heart disease and other atherogenic risk factors, such as diabetes and hypertension, and there were no clear differences in associations observed in stratified analyses.

A primary effect of renal insufficiency on the development of CHF is supported by several plausible mechanisms, including

- activation of the sympathetic and renin-angiotensin systems;
- arterial stiffening;
- sodium and fluid retention leading to increased filling pressures;
- worsening or secondary hypertension; and
- ventricular hypertrophy and dilation (17).

Chronic renal dysfunction is accompanied by:

- high levels of homocysteine;
- increased oxidation of low-density lipoproteins;
- diminished nitric oxide production (which may result in accelerated atherosclerosis and poor outcomes after myocardial infarction);
- hypertension;
- anemia and hypervolemia contributing to left ventricular hypertrophy (which is an important risk factor for death resulting from cardiovascular disease);
- conventional cardiovascular disease risk factors;
- older age;
- higher prevalence of co-morbid disease at admission; and

- lower likelihood to undergo coronary revascularization during hospitalization (compared with patients with normal serum creatinine) (20).

Renal disease may be a *marker* for concomitant cardiovascular risk factors such as

- diabetes mellitus;
- hypertension; and
- dyslipidemia.

On the other hand, it has been postulated that renal disease exerts an *independent* effect on cardiovascular mortality due to:

- systemic inflammation;
- oxidative stress;
- abnormal lipid metabolism;
- hyperhomocysteinemia, or alterations in serum; and
- fibrinogen levels (45).

Thus, CHF impairs renal function, which – in turn – further promotes CHF, leading to a vicious circle and poor prognosis.

Currently, guidance for clinicians caring for patients who have CHF and renal insufficiency is lacking, as no clinical trials have focused on treatment of these patients, and persons with renal insufficiency are poorly represented in clinical trials. More research in this high-risk population is needed, particularly to guide the dosing and administration of potentially beneficial medications like ACE inhibitors and other treatments, including angiotensin receptor blockers and spironolactone, as renal insufficiency worsens (4).

Conclusions

1. Elevated serum creatinine (or diminished creatinine clearance) is frequent in patients with heart failure (in 40%) and it is prognostically bad in CHF, because it leads to an independently manifold increased mortality.

2. Even the worsening of renal function during hospitalization (increase in serum creatinine by approximately 30 micromol/L) is not a rare finding (every 4 patients with heart failure) and is an independent marker of a bad outcome.

3. Surprisingly, literature overview has suggested no clear relationship between hypotension or the severity of left ventricular systolic dysfunction and the occurrence of either renal failure or the worsening of renal function.

4. ACE inhibitors – particularly at high doses - may decrease renal function in prone CHF patients. On the other hand, if used with caution, they are capable of improving a long-term prognosis in such patients.

5. Calcium channel blockers may diminish renal function in congestive heart failure, which is not surprising because all of them are contraindicated in heart insufficiency, except amlodipine and felodipine.

6. Diuretics (both loop and spironolactone) should be carefully titrated according to the clinical response, with close monitoring of renal function.

7. Heart insufficiency worsens renal function and prognosis and vice versa.

References

1. McClellan WM, Flanders WD, Langston RD, et al. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002; 13: 1928-36.
2. Akhter M, Aronson D, Bitar F, et al. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with de-compensated heart failure. Am J Cardiol 2004; 94: 957-60.
3. Ezekowitz J, McAlister F, Humphries K, et al. for the APPROACH Investigators. The Association among renal insufficiency, pharmaco-therapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. J Am Coll Cardiol 2004; 44: 1587-92.
4. Bibbins-Domingo K, Feng Lin F, Vittinghoff E, et al. Renal Insufficiency as an Independent Predictor of Mortality Among Women With Heart Failure. J Am Coll Cardiol 2004; 44:1593- 600.
5. MacDowall P, Kalra P, O'Donoghue D,. et al. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. Lancet 1998: 352: 13-6.
6. Miller K. Factors influencing selected lengths of ICU stay for coronary artery bypass patients. J Cardiovasc Nurs 1998; 12: 52-61.
7. Zanchetti A. and Stella A. Cardiovascular disease and the kidney: an epidemiologic overview. J Cardiovasc Pharmacol 1999: 33 Suppl 1: S1-6.
8. Hall WD. Abnormalities of kidney function as a cause and a consequence of cardiovascular disease. Am J Med Sci 1999: 317: 176-82.
9. Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000; 35: 681-9.
10. Levin A, Foley R. Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis 2000: 36 Suppl 3: S24-30.
11. Hillege H, Gribes A, de Kam P, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000; 102: 203-10.
12. McCullough P, Soman SS, Shah SS, et al. Risks associated with renal dysfunction in patients in the coronary care unit. J Am Coll Cardiol 2000: 36: 679-84.
13. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001; 38: 955-62.
14. Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. J Am Coll Cardiol 2002; 40: 1801-8.
15. Echemann M, Alla F, S. Briançon S, et al. on behalf of the EPICAL Investigators. Antithrombotic therapy is associated with better survival in patients with severe heart failure and left ventricular systolic dysfunction (EPICAL study). Eur J Heart Failure 2002; 4: 647-54.
16. Mahon NG, Blackstone EH, Francis GS, et al. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol 2002; 40: 1106-13.
17. Chae C, Albert C, Glynn R. et al. Mild renal insufficiency and risk of congestive heart failure in man and women > 70 years of age. Am J Cardiol 2003; 92: 682-6.
18. McAlister FA, Ezekowitz J, Tonelli MR, et al. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004; 109: 1004-9.
19. Silverberg D, Wexler D, Blum M, et al. The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens 2004; 13: 163-70.
20. Walsh C, O'Donnell C, Camargo C, et al. Elevated serum creatinine is associated with 1-year mortality after acute myocardial infarction. Am Heart J 2002; 144: 1003-11.

21. Butler J, Forman D, Abraham W, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J 2004; 147: 331-8.
22. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005; 365: 417-30.
23. Havranek E, Masoudi F, Westfall K, et al. Spectrum of heart failure in older patients: Results from the National Heart Failure Project. Am Heart J 2002; 143: 412-7.
24. Forman D, Butler J, Yongfei Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004; 43: 61-7.
25. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J 1999; 138: 285-90.
26. Kitzman DW, Gardin JM, Gottdiener J, et al. for the CHS Research Group. Importance of heart failure with preserved systolic function in patients >65 years of age. Am J Cardiol 2001; 87: 413-9.
27. Devereux RB, Roman MJ, Liu J, et al. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000; 86: 1090-6.
28. Krumholz HM, Chen YT, Vaccarino V. Correlates and impact on outcomes of worsening renal function in patients >65 years of age with heart failure. Am J Cardiol 2000a; 85:1110-3.
29. Krumholz HM, Abraham WT, Butler J, et al., Stratifying patients hospitalized with heart failure by their risk of developing worsening renal function: a multi-center study. Circulation 2000b: 102: II-878.
30. Dietz R, Nagel F, Osterziel K. Angiotensin-converting enzyme inhibitors and renal function in heart failure. Am J Cardiol 1992; 70: 119-25.
31. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; 160: 685-93.
32. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med 1996: 334: 939-45.
33. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993: 329: 1456-62.
34. Mann JF, Gerstein HC, Pogue J, et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med 2001;134: 629-36.
35. Kramer B, Frank Schweda F, et al. Diuretic Treatment and Diuretic Resistance in Heart Failure. Am J Med. 1999; 106: 90-6.
36. Greenberg B. Treatment of heart failure: state of the art and perspectives. J Cardiovasc Pharmacol 2002; 38: 59-63.
37. Remme WJ, Swedberg K. (Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology.) Comprehensive guidelines for the diagnosis and treatment of chronic heart failure. Eur J Heart Fail 2002; 4: 11-22.
38. Tamirisa K, Aaronson K, Koelling T. Spironolactone-induced renal insufficiency and hyperkalemia in patients with heart failure. Am Heart J 2004; 148: 971-8.
39. Svensson M, Gustafsson F, Galatius S, et al. Hyperkalaemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study. Br Med J 2003; 327: 1141-2.
40. American Hospital Formulary Service and American Society of Health System Pharmacists. Drug information. Bethesda (Md): American Society of Health-System Pharmacists and Lippincott Williams & Wilkins; 2001
41. Piccini J, Zaas A. Cases from the Osler Medical Service at Johns Hopkins University. Am J Med 2003; 115: 70-1.
42. Luke RG. Chronic renal failure - a vasculopathic state. N Engl J Med 1998; 339: 841-3.
43. Amman K. and Ritz E. Cardiac structure and function in renal disease. Curr Opin Nephrol Hypertens 1996; 5: 102-6.
44. Reis SE, Olson MB, Freid L, et al. Mild renal insufficiency is associated with angiographic coronary artery disease in women. Circulation 2002; 105: 2826-9.
45. Naidu S, Selzer F, Jacobs A, et al. Renal Insufficiency Is an Independent Predictor of Mortality After Percutaneous Coronary Intervention. Am J Cardiol 2003; 92: 1160-4.

PATOFIZIOLOŠKI MEHANIZMI I LEKOVI KOJI SMANJUJU FUNKCIJU BUBREGA U INSUFICIJENCIJI SRCA

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Kratak sadržaj: *Pregled literature pokazuje da je povišen kreatinin u serumu (ili smanjeni klirens kreatinina) čest u bolesnika sa insuficijencijom srca (u 40%) i prognostički loš, jer ukazuje na više puta i nezavisno povećan mortalitet. Sem toga, čak i pogoršanje renalne funkcije tokom hospitalizacije (porast kreatinina u serumu za oko 30 micromol/L i više) nije redak nalaz – u svakog četvrtog bolesnika sa insuficijencijom srca – i nezavisan je marker loše prognoze.*
Brojni su patofiziološki mehanizmi bitni: dehidracija (uklj. onu izazvanu prekomernom diurezom), pogoršanje funkcije srca (uklj. negativne inotrope), prejaka vazodilatacija (uklj. onu izazvanu lekovima), nefrotoksični lekovi, itd. Velika istraživanja srčane insuficijencije nisu (iz metodoloških razloga) uključivala dovoljno bolesnika sa smanjenom funkcijom bubrega, jer ih je daleko više nadjeno u uslovima "stvarnog života" (epidemiološki). Stoga zaključci velikih ispitivanja nisu kompletno aplikabilni i trebalo bi ih učiniti takvima putem istraživanja sa respektabilnim brojem bolesnika sa bubrežnom i srčanom insuficijencijom. U našoj zemlji je znanje o problemu smanjene renalne funkcije u pacijenata sa insuficijencijom srca daleko od zadovoljavajućeg, pa je potrebna dalja edukacija. Trebalo bi da pažljivo biramo lekove i njihove doze i striktno ih podešavamo nalazima individualnog bolesnika, da izbegavamo nefrotoksične, a primenjujemo sve korisne medikamente. Svaki od 5 bazičnih lekova za insuficijenciju srca (dominantno uzrokovanu ishemijskom bolešću srca) izgleda da poboljšava prognozu (uklj. produžavanje života) čak i u bolesnika sa smanjenom funkcijom bubrega (beta blokatori, ACE inhibitori, spironolakton, aspirin, statini).

Ključne reči: *Kongestivna insuficijencija srca, pogoršanje funkcije bubrega, patofiziološki mehanizmi, lekovi*