

Mechanisms of Chronic Heart Failure Development in End-Stage Renal Disease Patients on Chronic Hemodialysis

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Summary

More than 50 % of end-stage renal disease (ESRD) patients treated by chronic hemodialysis die from cardiovascular diseases, including congestive heart failure (CHF). The incidence of CHF is rising in both general and ESRD population. However, the mechanisms, which lead to the development of CHF in dialyzed patients, differ considerably. First, there are several factors leading to increase of the left ventricular afterload: volume overload between dialyses, hypertension, increased arterial stiffness, anemia, vascular access flow (arteriovenous fistula) and sympathetic activation. Second, hypertension, left ventricular hypertrophy, anemia and frequently present coronary artery disease worsen myocardial oxygenation. The combination of these factors explains the high incidence of CHF in dialyzed patients and their roles are reviewed in this article.

Key words

Heart failure • Dialysis • Volume overload • Pressure overload

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Prevalence, mortality, morbidity

More than 50 % of end-stage renal disease (ESRD) subjects treated by chronic hemodialysis die from cardiovascular diseases (Collins 2003). Congestive

heart failure (CHF) is present in more than one-third of new dialysis patients (Stack and Bloembergen 2001) with an incidence of 71/1000 person-years. This figure is substantially greater than the incidence of acute coronary syndromes in ESRD patients (29/1000 person-years in US Renal Data System (USRDS) Morbidity and Mortality Study Wave 2) (Trespalacios *et al.* 2003). CHF contributes significantly to mortality and morbidity and also worsens the quality of life. For instance, the median overall survival of ESRD patients with CHF is reported to be 36 months compared with 62 months in patients without CHF (Harnett *et al.* 1995). Fewer than 15 % of dialysis patients are alive 3 years after hospitalization for CHF (Trespalacios *et al.* 2003).

By definition, CHF is a state in which the heart is unable to pump blood at a rate appropriate to the requirements of the metabolizing tissues or can do so only at an elevated filling pressure (Zipes *et al.* 2005). CHF in ESRD patients differs from CHF states in subjects with preserved renal function by several factors. Interdialytic volume overload and vascular access flow are specific only for ESRD. Therefore, hemodialysis also contributes *per se* to the development of CHF. During continuous worsening of chronic kidney disease, nephrogenic hypertension develops. This is the source of pressure overload, especially in patients with inadequate hypertension control. Most important mechanisms of CHF in ESRD patients treated by hemodialysis are discussed below. We did not include the problems associated with peritoneal dialysis nor kidney transplantation to keep this review more transparent.

Increased left ventricular mass (hypertrophy) (LVH) is the most frequent cardiac abnormality diagnosed in patients starting hemodialysis (present in about 80 %) (Foley *et al.* 1995, Herzog *et al.* 1998). LVH is an independent and strong risk factor for cardiovascular morbidity and mortality in both normal population (Levy *et al.* 1990) and in ESRD patients (Silberberg 1989). In the latter population, LVH is principally due to an increased demand in the left ventricular minute work resulting from volume/flow and pressure overload (Meeus *et al.* 1989). Two forms of the left ventricular hypertrophy – eccentric and concentric – could be present and are relatively equivalent in prevalence in dialysis population. Eccentric hypertrophy results from volume overload leading to cardiac myocyte drop-out: there is myocyte to arteriolar capillary mismatch. Concentric hypertrophy is typically the result of hypertension and increased afterload and is exacerbated by anemia, hyperparathyroidism, and high angiotensin II concentrations. In experimental renal failure, LVH was associated with reduced capillary density and subsequent interstitial fibrosis (Mall *et al.* 1990, Amann *et al.* 1990). The latter is probably a reason of diastolic and later also systolic dysfunction of the left ventricle present in LVH. While in general population hypertension is the most frequent cause of the left ventricle hypertrophy, in ESRD patients, the correlation between left ventricle mass and blood pressure is weak. Experimental and clinical studies have shown that hypertrophy develops even in normotensive ESRD subjects (London *et al.* 1987).

Schematically, factors contributing to the development of CHF include those increasing preload and decreasing the myocardial perfusion or oxygenation of the left ventricle (Table 1). Left ventricular afterload is increased by some and decreased by other mechanisms (Fig. 1).

Mechanisms of CHF

Volume overload between dialyses

Most subjects with ESRD have insufficiently low or even no diuresis, which leads to water retention. Excessive water is removed during dialysis sessions by ultrafiltration. Nevertheless, dialysis is usually performed only 2-3 times per week and body water accumulates and fluctuates between the dialysis sessions. This fluctuation plays a role in the development of the left ventricular hypertrophy, which in turn predisposes to CHF (London

Table 1. Factors leading to the increase of preload and to the worsening of myocardial oxygen supply.

| | |
|------------------------------------|---|
| \uparrow Preload | Interdialytic volume overload Anemia Vascular access flow Inflammation |
| \downarrow Cardiac oxygen supply | Coronary artery disease Anemia Hypertension LV hypertrophy |

2003a,b). The ultrafiltration rate is targeted to reach so called dry weight of the patient. There are several methods of dry weight calculation. To simplify, dry weight is the minimal tolerated weight – without clinical signs of dehydration. Inappropriate calculation of the dry weight leads to chronic volume overload (Charra 2007).

Overhydration between the dialyses contributes to the pathogenesis of LVH in ESRD by its effects on blood pressure control and also by induction of volume overload (London 2003a,b). The internal dimensions of the left ventricle, stroke volume, and end-diastolic pressure are directly related to circulating blood volume (Chaignon *et al.* 1981). Body fluid volume reduction during dialysis sessions induces a decrease in left ventricle diameter and cardiac output, and there is a direct correlation between interdialytic body weight changes and LV mass, as well as stroke volume (Harnett 1993). LV mass correlates with the concentrations of atrial natriuretic peptides, which are influenced by extracellular fluid volume (Zoccali *et al.* 2001). Regression of the left ventricular dimensions and LVH can be achieved by ultrafiltration and reduced salt intake in hemodialysis patients (Ozkahya *et al.* 1998). Indeed, patients treated by daily dialysis have lower and steadier levels of brain natriuretic peptide (BNP), the marker of heart failure and overhydration (Odar-Cederlof *et al.* 2006). A similar LVH reduction was associated with better blood pressure control, decrease in extracellular fluid volume, and with lower volume fluctuation in patients on daily dialysis (Fagugli *et al.* 2001).

Anemia

Anemia is a frequent condition even in milder stages of chronic renal disease, mainly due to decreased synthesis of erythropoietin. Non-hemodynamic mechanisms of body adaptation to anemia include

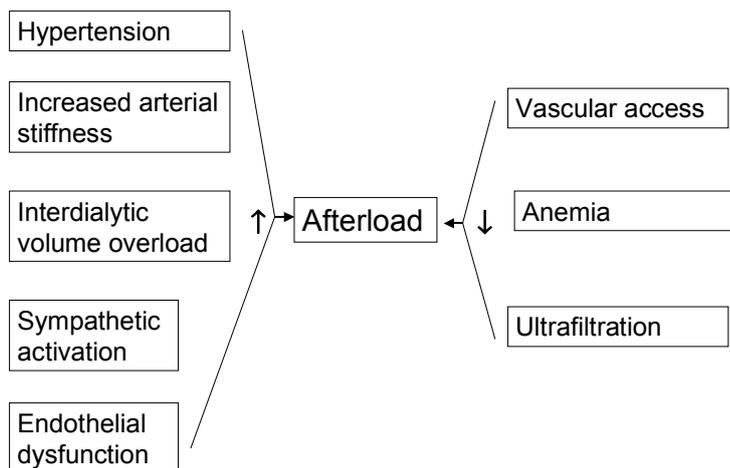


Fig 1. Factors influencing left ventricle afterload. Afterload increasing mechanisms are listed in the left side of the figure, afterload lowering factors on the right side.

increased oxygen extraction in tissues, mediated by increased 2,3-diphosphoglycerate levels. Mechanisms of hemodynamic compensation of anemia are complex: 1) reduced afterload due to a decrease in systemic vascular resistance, 2) increased preload due to an increase in venous return, and 3) increased left ventricular function attributed to increased sympathetic activity and inotropic factors. Increased left ventricular performance can result from an increased preload (Frank-Starling mechanism) and from changes in inotropic state in relation to high sympathetic activity or inotropic factors (Muller *et al.* 1991). In chronic anemia, typical for ESRD, long-lasting flow/volume overload and increased cardiac work lead to progressive cardiac enlargement and to the left ventricular hypertrophy (Parfrey *et al.* 1991). The alterations in cardiac function are accompanied by simultaneous remodeling of the large conduit arteries (London *et al.* 1996). Indeed, in dialysis patients, anemia is associated with LVH, left ventricular dilatation, congestive heart failure, increased hospitalization rate, and increased mortality (Foley *et al.* 1996a,b, Ma *et al.* 1999, Madore *et al.* 1997).

In patients on dialysis, treatment of anemia with erythropoietin alters both the function and the structure of the left ventricle. It decreases the stroke volume and heart rate, and decreases the cardiac output and left ventricular work (Fellner *et al.* 1993). Older studies showed optimistic data of mortality risk decrease (Moecks 2000). Recent studies compared the lower and higher target hemoglobin values (10.5-11.5 g/dl and 13.0-13.5 g/dl, respectively). They failed to show any benefit of higher target hemoglobin value except for better quality of life (Drueke *et al.* 2006, Singh *et al.* 2006). In a meta-analysis, patients in the higher target value group had higher mortality (Phrammintikul *et al.* 2007). It was

speculatively explained by increased rate of thromboses, including infarctions as a result of both higher hematocrit, and by some direct effects of erythropoietin favoring inflammatory states.

Hypertension and arterial wall stiffness

Chronic kidney disease could be both the reason and the result of hypertension. This is probably a source of the very high hypertension prevalence in ESRD subjects. For example, in our previous study, more than 70 % of 258 subjects coming for vascular access examination into our department from the whole country suffered from hypertension (Malik *et al.* 2007). In non-ESRD patients, several studies have repeatedly confirmed that the treatment of high blood pressure decreases both cardiac and particular cerebrovascular events in patients with diabetes (Schrier *et al.* 2002) as well as in those without diabetes (Hansson *et al.* 1999). Similarly, decreasing blood pressure has been shown to prevent progression of renal disease (Bakris *et al.* 2000). A new light was brought by a series of subsequent studies, which were meta-analyzed by the project "INDIANA" (Boutitie *et al.* 2002). It has been shown that lowering diastolic blood pressure is protective until a certain level and then the risk of all-cause mortality rises again: J-shaped curve. The authors have revealed a J-point at a diastolic blood pressure of 84 mmHg. There are several possible explanations of this phenomenon and two of them seem to be particularly important. First, subjects with low blood pressure suffer probably from more severe cardiac disease (heart failure and/or coronary artery disease). Second, the decrease of the diastolic blood pressure leads to the increase of pulse pressure and the increment in pulse pressure may be responsible for the "J"-like relation (Berl and Henrich 2006).

The ill effects of hypertension are usually attributed to the reduction in the internal diameter of arterioles, resulting in a peripheral resistance increase. Blood pressure is the easiest measurable index of opposition to left ventricular ejection (afterload). In fact, the appropriate term to define the arterial factors opposing LV ejection is the aortic impedance, which depends on: 1) the peripheral resistance, 2) the viscoelastic properties of the aorta and central arteries, and 3) the inertial forces represented by the mass of the blood in the aorta and left ventricle (Nichols and O'Rourke 2005). Peripheral resistance, as a determinant of mean blood pressure, sets the general level at which the pressure wave will fluctuate. The amplitude of this fluctuation (pulse pressure) is influenced by the viscoelastic properties of the aorta and large arteries and by the characteristics of the left ventricular ejection (stroke volume and ejection velocity). The viscoelastic properties of the aorta can be described in terms of compliance, distensibility and stiffness (Meeus *et al.* 2000). Stiffening of arterial walls can increase the afterload independently of peripheral resistance. Clinically, high aortic stiffness is suspected in patients with high pulse pressure. The latter can occur in case of diastolic pressure decrease, systolic pressure increase, or both. Arterial stiffening leads to faster pulse wave velocity, which, after the reflections at the level of the peripheral arteries, returns earlier to the aorta, amplifies aortic and even ventricular pressures during systole (aortic valve is still open) and reduces aortic pressure during diastole (Safar *et al.* 1990). Vicious circle continues by further stiffening of arteries. Arterial stiffening is also a result of metabolic disturbances (see below).

Vascular pathology, coronary artery disease

Several vascular pathologies play a role in patients suffering from ESRD. These include 1) atherosclerosis, 2) arteriosclerosis, and 3) vascular calcifications and remodeling.

Atherosclerosis develops rapidly in ESRD patients. Uremia produces specific atherogenic factors, e.g. secondary form of complex dyslipidemia (Madore 2003), calcium-phosphate metabolism alterations (Floege and Ketteler 2004), malnutrition, and activation of inflammation (Madore 2003). These factors are additive to the risk factors present in patients with normal renal function, such as age, hypertension, smoking, diabetes, male gender and insulin resistance (Brunner *et al.* 2005). Although atherosclerosis was considered the only cause

of macrovascular disease, many vascular complications arise in ESRD patients in the absence of clinically significant atherosclerotic disease.

Arteriosclerosis refers to the hardening or stiffening of arteries (or arterioles). It is typically associated with aging and involves the entire arterial tree, although it principally affects the elastic arteries. Unlike atherosclerosis, arteriosclerosis involves both intimal and medial thickening. Arteriosclerosis is associated with vascular hypertrophy characterized by increased wall thickness, lumen enlargement, and increased length of arteries, referred together as remodeling (London 2003a,b).

Histologically, arteries from uremic patients have been reported to have fibrous or fibroelastic intimal thickening; calcification of the internal elastic lamella, medial ground substance and medial elastic fibers; and disruption and reduplication of the internal elastic lamella (Ibels *et al.* 1979). These indicate the predominance of arterial calcification in uremia and provide histological evidence for the loss of elasticity in ESRD. Excessive calcification also affects the cardiac valves.

Tunica media calcification is a common feature in ESRD subjects. Diabetes mellitus is the strongest risk factor, but uremia *per se* has also been shown to contribute. It is due to disturbed calcium/phosphate metabolism – abnormal phosphate homeostasis in the setting of ESRD markedly alters the severity, progression, and extent of vascular calcifications (Vattikuti *et al.* 2004). Vitamin D deficiency, as a result of kidney failure, affects cardiac contractility, vascular tone, cardiac collagen content and cardiac tissue maturation (Achinger and Ayus 2005). Reduced levels of vitamin D, hyperphosphatemia and a tendency towards hypocalcemia lead to the increased production of parathormone and the secondary hyperparathyroidism develops (DeFrancisco 2004). Clinically, so-called calcium/phosphate product is used as a measure of calcium/phosphate metabolism. Detailed description of the mechanisms of vascular calcifications is behind the scope of this review. Higher concentrations of aldosterone, endothelin, angiotensin II or asymmetric dimethylarginine (ADMA, which is an endogenous inhibitor of nitric oxide synthase) also contribute to higher arterial stiffness.

Valvular disease

Valvular calcifications are typical for ESRD patients. They mostly occur in mitral and aortic valve and

are markers of poorer prognosis. Wang *et al.* (2003) found that valvular calcification is an important predictor of all-cause and cardiovascular mortality in peritoneal dialysis patients. They hypothesized, that the poor outcome could be explained by the fact that these patients have the most severe and advanced atherosclerosis. On the contrary, the increased mortality was not explained by the valvular obstruction. Despite the findings of Wang *et al.*, the incidence of aortic valve stenosis increases during last two decades (Michel 1998). It is explained by increasing age of hemodialyzed population, but the disturbances of calcium/phosphate metabolism probably also play a role together with the increased shear of aortic valve due to hyperkinetic circulation. In a general population, aortic stenosis leads to heart failure in its late stage. In ESRD patients, aortic stenosis could contribute to heart failure symptoms earlier.

Mitral valve calcifications lead only rarely to the development of significant regurgitation/stenosis. Valvular regurgitation may be also a result of infective endocarditis. It is more common in patients dialyzed *via* permanent catheter (Kamalakkanan *et al.* 2007).

Vascular access

Surgically created vascular access, either “native” (direct connection of patient’s artery and vein) or with the use of artificial graft, serves for repeated entries into the blood stream during hemodialyses. Adequate flow volume is needed for the hemodialysis procedure and also for longer patency of the access. Generally, forearm accesses have flow 400-800 ml/min, brachial accesses 800-1500 ml/min. Such flow is due to a sudden fall of peripheral vascular resistance just after the access creation together with further maturation of both the feeding artery and outflow vein. This systemic vascular resistance decrease leads to subsequent volume overload and – at least temporarily – to increased cardiac output and left ventricle ejection fraction (Ori *et al.* 1996). Bos *et al.* (1999) studied the effects of vascular access on cardiac oxygen supply and demand using pressure wave analysis. They concluded that access has small effect on left ventricular oxygen demand, but decreases cardiac oxygen supply considerably.

Case reports of hyperkinetic heart failure as a result of high flow access have been published (Jin *et al.* 2006). More commonly, access flow contributes to the development of already present congestive heart failure either clinically silent or overt. Such opinion is supported by the following studies of access creation impact on

heart failure parameters. Ori *et al.* (1996) documented an increase of cardiac output, ejection fraction, cardiac index and of atrial natriuretic peptide and a decrease of plasma renin activity in a small study (10 subjects). Similar findings were observed two weeks after access creation (Iwashima *et al.* 2002), and left ventricle diastolic function worsened after access creation together with the increase of ANP and BNP. We observed a significant increase of BNP levels six weeks after the construction of vascular access with “normal” flow (709±311 ml/min) (unpublished data). Unfortunately, these studies do not demonstrate the long-term effect of access flow on heart failure.

An opposite approach was used by Chemla *et al.* (2007) they monitored the effect of surgical access flow reduction on cardiac output in a group of high access flow patients (3135±692 ml/min). Access age (mean ± SD) at inclusion was 30±17 months and only accesses with flow volume exceeding 1600 ml/min were included. Cardiac output decreased significantly after the surgery together with the access flow. Similar topic (but with the use of a different flow-reducing surgical technique) was studied in a case reported by Murray *et al.* (2004). The most interesting finding in this study was that in high-output states (induced by high flow accesses), the necessary increase in cardiac output to sustain the high access flows must be numerically greater than the actual access flow. This phenomenon was also apparent in the study by Chemla *et al.* (2007) where access flow reduction of about 2 l/min led to cardiac output decrease by more than 3 l/min. We could hypothesize that this numerical imbalance mirrors excessive increase of preload or, in other words, a sign of heart failure.

Other mechanisms

Hemodialysis is associated with repetitive hemodynamic instability and subsequent myocardial ischemia, which may be due to coronary microvascular dysfunction. This process may also be important for the development of heart failure in hemodialysis patients (McIntare *et al.* 2008).

Pericardial effusions are common in ESRD patients, but only rarely significant if chronic dialysis therapy has been established. Various arrhythmias could be present as a result of ionic imbalance. They could contribute to the CHF by impaired left ventricular filling. Sleep apnea is common in ESRD patients (Kimmel *et al.* 1989) and leads to nocturnal hypoxemia. Malnutrition is also common and is associated with higher risk of CHF

(Foley *et al.* 1996b). It could be estimated by the level of serum albumin.

Kidney transplantation leads (sometimes) to the regression of the left ventricular hypertrophy and systolic dysfunction (Parfrey *et al.* 1995). This phenomenon was explained by the decrease of “uremic toxin” levels and the term “uremic cardiomyopathy” is sometimes used to describe the complex non-coronary left ventricular changes in ESRD patients (Gross and Ritz 2008). However, patients treated by hemodialysis do not have real clinical signs of uremia and many so called “uremic toxins” were already discovered – aldosterone, endothelin, angiotensin II, ADMA, parathormone, cytokines, advanced glycation end-products, advanced oxidation protein products, etc. (for review see also Cibulka and Racek 2007).

Research and diagnostic limitations

The research, but also the clinical care, is limited especially by the fact that the steady state of CHF in ESRD patients does not exist. Volume load changes between dialyses could be documented by changing blood pressure, heart rate, vascular access flow, left

ventricle diameter and mass (Paleček *et al.* 2008), by levels of natriuretic peptides etc. It is generally accepted that regular examinations should be performed at least 24 h after last hemodialysis, some authors examine just before the next dialysis.

Conclusions

Congestive heart failure is common in ESRD patients and is associated with substantial morbidity and mortality. It is a result of a complex of mechanisms, some of them occurring solely in ESRD patients. Unfortunately, chronic hemodialysis therapy cannot fully replace functioning kidneys. Detailed understanding of the mechanisms leading to CHF could improve the outcome of ESRD.

Conflict of Interest

There is no conflict of interest.

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