

A re-appraisal of volume status and renal function impairment in chronic heart failure: combined effects of pre-renal failure and venous congestion on renal function

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Abstract The association between cardiac failure and renal function impairment has gained wide recognition over the last decade. Both structural damage in the form of systemic atherosclerosis and (patho) physiological hemodynamic changes may explain this association. As regards hemodynamic factors, renal impairment in chronic heart failure is traditionally assumed to be mainly due to a decrease in cardiac output and a subsequent decrease in renal perfusion. This will lead to a decrease in glomerular filtration rate and a compensatory increase in tubular sodium retention. The latter is a physiological renal response aimed at retaining fluids in order to increase cardiac filling pressure and thus renal perfusion. In heart failure, however, larger increases in cardiac filling pressure are needed to restore renal perfusion and thus more volume retention. In this concept, in chronic heart failure, an equilibrium exists where a certain degree of congestion is the price to be paid to maintain adequate renal perfusion and function. Recently, this hypothesis was challenged by new studies, wherein it was found that the association between right-sided cardiac filling pressures and renal function is bimodal, with worse renal function at the highest filling pressures, reflecting a severely congested state. Renal hemodynamic studies suggest that congestion negatively affects renal function in particular in patients in whom renal perfusion is also compromised. Thus, an

interplay between cardiac forward failure and backward failure is involved in the renal function impairment in the congestive state, presumably along with other factors. Only few data are available on the impact of intervention in volume status on the cardio-renal interaction. Sparse data in cardiac patients as well as evidence from cohorts with primary renal disease suggest that specific targeting of volume overload may be beneficial for long-term outcome, in spite of a certain further decrease in renal function, at least in the context of current treatment where possible reflex neurohumoral activation is ameliorated by the background treatment by blockers of the renin–angiotensin–aldosterone system.

Keywords Chronic heart failure · Renal function · Renal hemodynamics · Salt · Volume status · Dietary sodium

Introduction

The association between cardiac failure and renal function impairment has gained wide recognition over the last decade. The interest in the association is fuelled by the independent predictive role of renal function impairment for prognosis, with a worse prognosis in subjects with worse renal function [1]. This has raised ample interest in the nature of the renal function impairment in chronic heart failure and fuelled the hypothesis that specific renal protection may be of benefit in chronic heart failure.

Both renal hemodynamic factors and structural renal abnormalities contribute to renal function impairment in chronic heart failure. In subjects where chronic heart failure is due to ischemic cardiac abnormalities, generalized vascular damage including renal arteriosclerosis is relatively common. In this concept, renal and cardiac

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impairment can be considered to be partly due to common effects of the process of atherosclerosis on the heart and on the kidney. In non-ischemic heart failure, such as due to myocarditis, the kidneys can be considered as intrinsically normal, at least initially, and the renal function impairment appears to be more directly reflective of the cardiac hemodynamic impairment [2].

Hemodynamic factors are traditionally considered a main driving force in the renal function impairment in heart failure. A reduction in cardiac output leads to impairment of renal perfusion. The latter leads to renal sodium retention, as a compensatory response to restore renal perfusion pressure. In principle, this is an adequate homeostatic response that increases cardiac filling pressure and hence cardiac output according to the Frank–Starling curve of the heart, with consequently restoration of renal perfusion and renal function toward normal values. In heart failure, however, the association between cardiac filling pressure and cardiac output is disturbed, so the restoration of cardiac output is obtained at the expense of an abnormal rise in cardiac filling pressure, contributing to the congestive state. In this classical concept, the congestive state is the price to be paid for restoration of renal perfusion and hence renal function. Recent findings shed new light on the association between chronic heart failure, the derangements in hemodynamics and volume status, and renal function impairment and warrant a different appraisal of the role of renal perfusion impairment, the congestive state, and renal impairment in chronic heart failure, as will be reviewed below.

Role of the kidney in the homeostasis of circulating volume

An adequate response of the kidney to changes in perfusion pressure and volume status is a central factor in the normal homeostasis of circulating volume that involves a coordinated response of the vascular and tubular part of the nephron. Under normal circumstances, the auto-regulatory capacity of the glomerular microcirculation allows filtration capacity to remain constant over a wide range of pressures, thus ensuring stable and continuous excretion of metabolic waste products despite changes in volume status and blood pressure. Meanwhile, the tubular component of the homeostatic response ensures stability of sodium and volume balance by adapting proximal and distal tubular sodium reabsorption. These adaptive glomerular and tubular changes occur in response to altered renal perfusion pressure, as well as in response to changes in volume status without changes in renal perfusion pressure. Thus, renal adaptive capacity allows the body to maintain circulatory homeostasis over a widely different range of sodium and

fluid intake and provides our evolutionary defense against volume depletion by blood loss and dehydration.

Renal response to perfusion impairment

During impairment of renal perfusion pressure, glomerular filtration rate (GFR) is maintained by a two-step hemodynamic adaptation. First, pre-glomerular (afferent) vasodilatation occurs by the afferent myogenic response, reflecting the classical auto-regulation response of the kidney that serves to maintain both glomerular flow and pressure, and hence filtration, with an additional regulation of afferent tone by the tubuloglomerular feedback loop. Briefly, the latter mechanism works as follows: renal perfusion decline leads to compensatory tubular sodium reabsorption and therefore to a reduction in distal tubular sodium delivery, which is sensed by the macula densa. Lower distal sodium delivery decreases adenosine concentration and therefore adenosine- α 1 receptor activity, causing afferent vasoconstriction, commonly known as tubuloglomerular feedback. When faced with a further fall in perfusion pressure, post-glomerular (efferent) vasoconstriction occurs as the next resort of the auto-regulatory response. This ensures preservation of filtration pressure in glomerular capillaries at the expense of a further fall in perfusion. Thus, the proportion of renal perfusion effectively filtered, the filtration fraction (FF) is increased, as a distinguishing feature of increased efferent vascular tone. Increased activity of the renin–angiotensin–aldosterone system (RAAS), elicited by the decreased renal perfusion pressure, plays an important role in the renal hemodynamic and tubular response to perfusion impairment. First, the efferent vasoconstriction is mainly mediated by angiotensin II. Concomitant intra-renal production of vasodilator prostaglandins precludes inadvertent vasoconstrictor effects of angiotensin II on the afferent arteriole that could threaten filtration pressure under these circumstances. Second, the concomitant increase in tubular sodium reabsorption is mediated by angiotensin II, by direct tubular effects as well as by an increase in aldosterone. The ensuing renal sodium retention is facilitated by the concomitant decrease in natriuretic peptides. Angiotensin II furthermore contributes to maintenance of blood pressure by its vasoconstrictor effects on the systemic vascular bed.

The role of renal perfusion impairment in chronic heart failure

In chronic heart failure, whether with reduced or preserved ejection fraction, considerable impairment of renal perfusion occurs due to the decrease in cardiac output. Even if cardiac index is only mildly impaired, the perfusion

impairment can be considerable [3, 4]. The reduction in renal perfusion is the main determinant of the impairment in renal function that is usually observed in heart failure [5]. It would be logical to assume that the reduction in renal perfusion and renal function is proportional to the decrease in cardiac output. However, the association between cardiac index and renal function has been notoriously difficult to demonstrate. In several studies, improvement in cardiac index or improvement in pulmonary wedge pressure did not adequately predict improvement in renal function in heart failure patients [6–9]. To understand this seeming discrepancy, it is important to realize that the association between cardiac output and impairment of GFR is not mono-dimensional.

First, renal perfusion and hence GFR can be affected by pre-existing renal arteriosclerosis. Second, the renal auto-regulatory capacity can maintain GFR in spite of renal perfusion impairment, by tubuloglomerular feedback and afferent vasodilatation, and by increased RAAS activity and consequent efferent vasoconstriction. This adaptive mechanism is readily apparent when renal perfusion is measured concomitantly with GFR, from the increase in FF that is usually present in patients with chronic heart failure. Accordingly, when only data on (estimated) GFR are available, the association between cardiac index and renal changes is obscured. It is only in advanced heart failure, when renal perfusion is severely impaired, that FF decreases sharply, probably because renal perfusion is maintained at the expense of locomotor muscle perfusion initially [10] and not until heart failure advances, will renal perfusion decrease below the lower threshold of auto-regulatory capacity [5]. Renal auto-regulation itself may become impaired due to decreased availability of nitric oxide [11], which impairs tubuloglomerular feedback. Decreased nitric oxide availability, caused by endothelial dysfunction, is not only seen in heart failure but also in diabetes mellitus, inflammation, and atherosclerosis. In such a situation, GFR becomes strongly dependent on blood pressure that is, understandably, very low as well with consequently a sharp further decrease in GFR [5]. It should be noted that currently most patients with chronic heart failure are treated by RAAS blockade for its cardio-protective effects. RAAS blockade, however, impairs the efferent contribution to auto-regulatory capacity and thus can aggravate the GFR impairment. The latter can, to a certain extent, be considered to be a price to be paid for the cardio-protective effects of the RAAS blockade.

The above described sequence of events represents the pre-renal component of the GFR impairment in chronic heart failure and corresponds to the renal changes that occur in other pre-renal conditions, such as severe dehydration and volume depletion. Accordingly, when renal

perfusion is restored by volume repletion, renal function will improve. The major difference between pre-renal failure due to pure volume deficit and renal function impairment in chronic heart failure is, obviously, the congestive state. In patients with pure volume deficit, volume repletion is the single effective treatment, whereas in chronic heart failure, volume repletion measures can be expected to worsen the congestive state.

In the clinical management of heart failure, therefore, the usual concept on volume management is that of a trade-off: measures to improve congestion, diuretics and dietary sodium restriction will do so at the expense of a further decrease in renal function. Vice versa, when severe renal function impairment prompts for accepting a positive volume balance by reducing diuretics or a more liberal sodium intake, the improvement in renal function occurs at the expense of worsening congestion.

Association between the congestive state and renal function

Until recently, it was assumed that the congestive state as such did not impact on renal function, despite a few very old studies [12–14] that suggested an adverse effect of high venous pressure on renal function. Several studies, however, recently demonstrated an association between venous congestion and worse renal function, in various populations with cardiac impairment from different origin with both reduced and preserved ejection fraction.

A large retrospective analysis in 2557 patient from our center that underwent right heart catheterization showed that central venous pressure (CVP) is associated with estimated GFR (eGFR) in a bimodal fashion, with the highest eGFR at a CVP of approximately 3 mmHg and a progressively lower eGFR in subjects with CVP above 5–6 mm Hg, comprising approximately one-third of the population. Remarkably, is shown in Fig. 1, this bimodal association was independent of cardiac index, demonstrating that the adverse impact of high CVP on eGFR was not merely due to the patients with high CVP being a subset in a very poor condition including worse cardiac output. In fact, the decrease in eGFR at higher CVP was, if anything, steeper in subjects with a relatively preserved eGFR. Elevated CVP was also an independent predictor for mortality [15]. Not only directly measured CVP was found to be related to renal function. In a separate study in 2647 patients with systolic heart failure, presence of congestive symptoms, such as peripheral edema, elevated jugular venous pressure, orthopnea, and ascites were associated with worse eGFR and, moreover, with mortality [16].

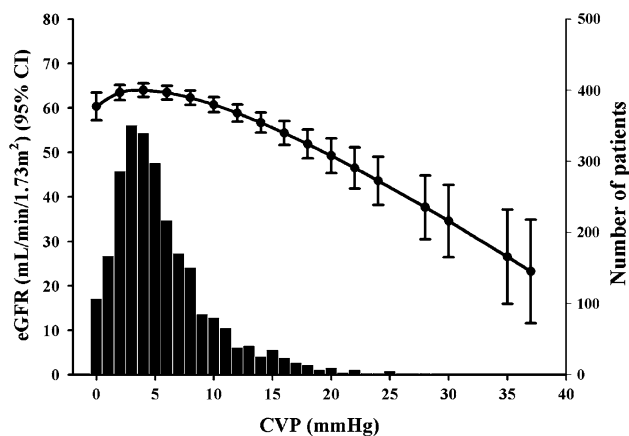


Fig. 1 Distribution of central venous pressure and curvilinear relationship between central venous pressure and estimated glomerular filtration rate in 2557 patients that underwent right heart catheterization at the uMCG between 1989 and 2006. Curve is adjusted for age, gender, and cardiac index. (from: Damman et al. ref 15)

The separate contributions of congestion and perfusion impairment

The separate contributions of renal perfusion impairment and congestion were analyzed in a population of patients with predominantly right-sided heart failure due to primary or secondary pulmonary hypertension, screened for lung transplantation at our center. Their work-up included renal hemodynamic measurements as well as right-sided heart catheterization. In this population with a mean true GFR of 73 ml/min/1.73m², renal blood flow and right atrial pressure were the only determinants of GFR on multivariate analysis, with a worse GFR in subjects with lower renal blood flow and higher right atrial pressure. Remarkably, elevated right atrial pressure did not affect GFR in subjects with preserved renal blood flow, whereas it was associated with a significant further reduction in GFR in subjects in whom renal blood flow was impaired (Fig. 2) [17]. This leads to the concept that venous congestion or backward failure impairs GFR only, or preferentially, when forward failure is concomitantly present.

The mechanisms of the adverse effect of high venous pressure on renal function are incompletely elucidated. Animal studies, in a canine model, where induction of volume overload was associated with a rise in renal interstitial pressure along with a decline in renal perfusion and renal function, suggest that elevated venous pressure may translate into inappropriate elevation of renal interstitial pressure as a possible mechanism [18].

In addition, it has been shown that venous congestion and associated endothelial stretch increase the production of pro-inflammatory cytokines [19], such as tissue necrosis factor- α , which are associated with sodium retention, renal hypertrophy, and nephropathy [20, 21]. Additional

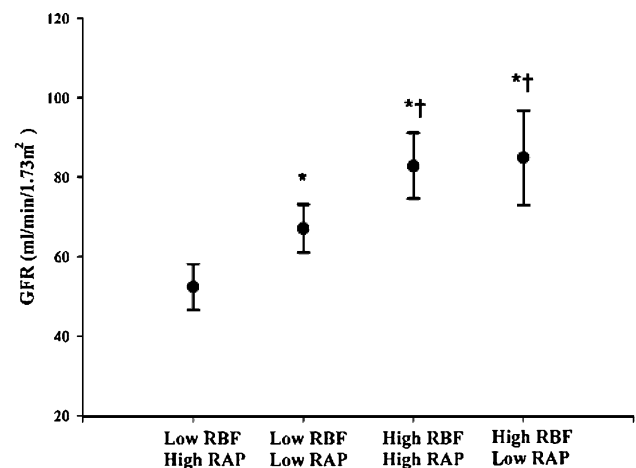


Fig. 2 Relative contributions of right atrial pressure (RAP) and renal blood flow (RBF) on glomerular filtration rate (GFR, Y-axis, ml/min/1.73 m²) Error bars represent 95% CI. * $P < 0.001$ for difference with high RAP, low RBF. + : $P < 0.01$ for difference with low RAP, low RBF. (from: Damman et al. ref 17)

production of reactive oxygen species may reduce nitric oxide availability, leading to peripheral and systemic vasoconstriction [22]. This does not only increase cardiac filling pressure via increased central blood volume but also reduces renal perfusion.

Implications for treatment: a re-appraisal of volume targeting in chronic heart failure

The evidence that congestion as such is associated with an adverse effect on renal function challenges the trade-off concept that volume repletion, with acceptance of a certain worsening of congestion, will invariably improve renal function. In fact, the curve in Fig. 1 suggests that careful targeting of the congestive state can lead to improvement in renal function in subjects with severely elevated CVP, which would be in line with the aforementioned animal study. It should be noted here that the associations between CVP and eGFR in human populations were cross-sectional and did not include interventions in volume status. In fact, recent data on intervention in volume status in heart failure are scarce.

Targeting volume status can be effectuated by dietary sodium restriction, diuretics, and the combination, whereas in severe heart failure, hyponatremia can prompt for fluid restriction as well. Ultrafiltration can be used as a last resort in patients with severe congestion along with poor cardiac output.

The ESC guidelines on acute and chronic heart failure [23] identify the effect of dietary sodium restriction as one of the gaps in the current evidence. Studies on natriuretic efficacy of diuretics, however, have shown that negative

volume balance is difficult to achieve by diuretics when sodium intake remains high, especially when the kidney is avidly retaining sodium [24]. It seems logical therefore to aim for dietary sodium restriction in patients where diuretic treatment is considered to be indicated. This requires that patients should be educated concerning the salt content of food, as recommended by the guidelines. The latter is important as, first, salt content of the western diet (9–12 g/day) contains approximately double the amount recommended for the general population, i.e., 5–6 g/day, and moreover, 75–80% of dietary sodium intake derives from pre-manufactured food products. In the clinical management of heart failure, the actual adherence to dietary sodium restriction is rarely verified, but it is likely that many patients ingest excess sodium without being aware of it, as has been shown in studies in chronic kidney disease, where dietary sodium intake, as apparent from 24-hour sodium excretion, is approximately similar to the general population, despite efforts to reduce salt intake [25–27].

Use of diuretics is, in different guidelines [23, 28], limited to patients with symptoms of congestion. This conservative use of diuretics is mainly based on two concerns. First, during therapy with diuretics, GFR tends to decline [29], and reduction of GFR in general is a poor prognostic sign. Second, diuretics induce excess neuro-hormonal activation, in particular of plasma renin activity and aldosterone [30], which could adversely affect outcome. However, in the current era, with most patients being treated with RAAS blockade, often in combination with beta-blockade, the significance of the latter may have diminished [23, 28], although concern remains on the direct pro-fibrotic effects of aldosterone on the heart and the kidney [31]. Aldosterone antagonists therefore look promising as reno-protective agents [32], but newer B-blockers may also yield protective effects on renal function [33]. These drugs act via an effect on intrarenal vascular resistance and may therefore affect renal blood flow and thus GFR. Larger trials in heart failure are needed to study their effect on renal function in heart failure.

Recent data, however, warrant a re-appraisal of the impact of volume targeting on GFR in patients with heart failure. It should be noted first that a diuretic-induced decrease in GFR in patients on RAAS blockade reflects reversible renal hemodynamic changes rather than persistent renal damage. This is probably due to the impaired autoregulation under these conditions. Withdrawal of diuretics or restoration of volume status by a liberal sodium intake will restore GFR, as demonstrated in renal patients (Fig. 3). Interestingly, in these renal patients, the treatment-induced decrease in GFR predicts a favorable long-term renal outcome [34], probably because it reflects the efficacy of RAAS blockade apparent from the consequent decrease in filtration pressure. A corresponding finding was recently reported from a

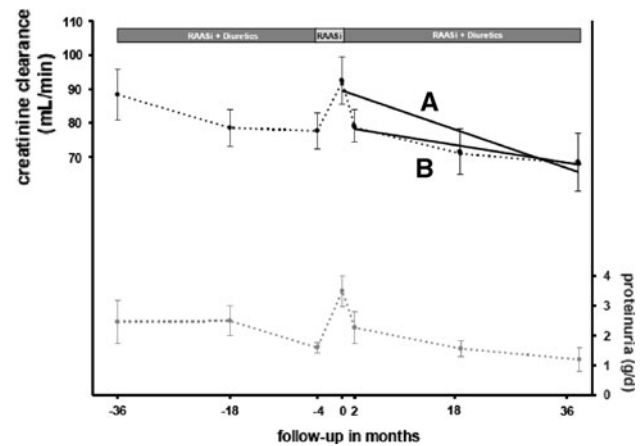


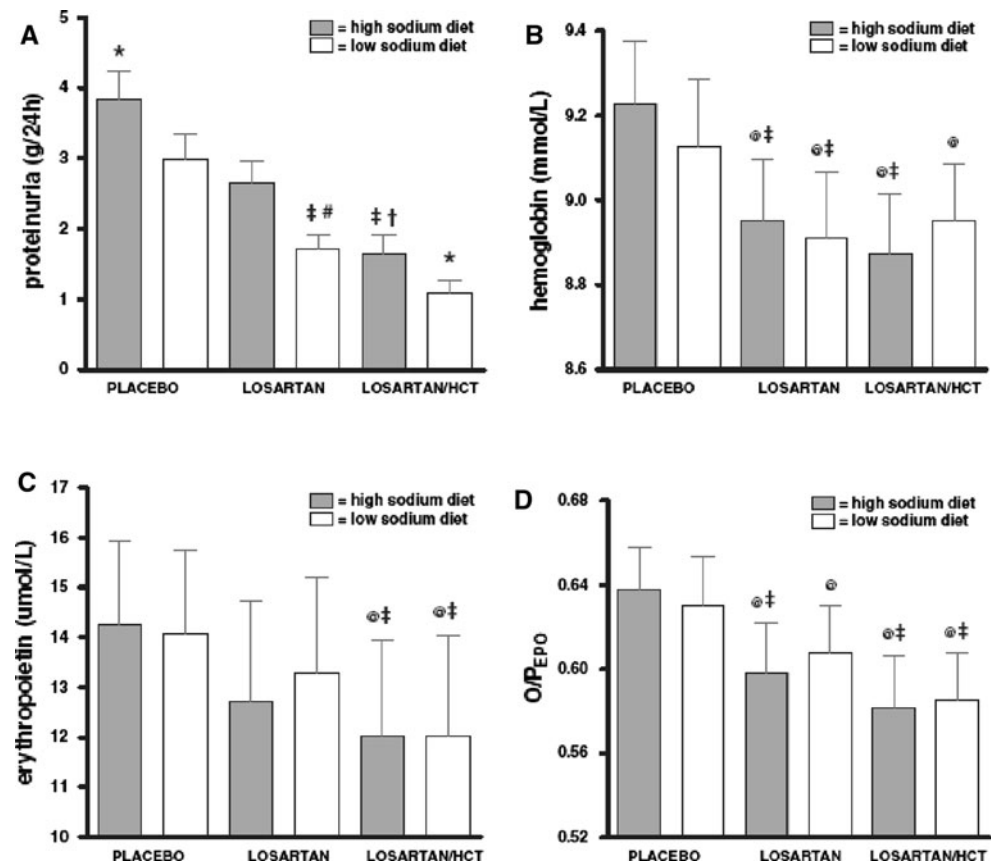
Fig. 3 Graph illustrating the reversibility of diuretic-induced decrease in renal function (creatinine clearance, left Y-axis) and the long-term rate of renal function in renal patients on RAAS blockade (RAASi): dotted lines. At time point -4 , diuretic treatment is withdrawn, with continuation of the RAASi. This results in a rise in renal function, demonstrating the volume dependency of renal function during RAASi, and its reversibility. At re-institution, necessitated by the concomitant rise in proteinuria (*lower dotted line*), creatinine clearance decreases again, with a concurrent decrease in proteinuria. The drawn *lines A and B* represent estimation of rate of long-term renal function loss, without and with taking into consideration the reversible impact of the change in volume status by the diuretic. (from: Slagman et al. ref 34)

well-performed study in decompensated heart failure patients [35], where subjects aggressively treated with diuretics had worse renal function, but 180-day mortality was reduced in these subjects, when compared to subjects treated more conservatively. Worsening of renal function may therefore be accepted upon start of therapy with diuretics or sodium restriction (Fig. 3).

Even more recently, results from the DOSE trial were released, wherein subjects admitted to the hospital with acute decompensated heart failure were treated with either diuretics continuously or via bolus and either normal or high doses. Subjects with higher doses of diuretics fared better subjectively, which was associated with more weight loss and greater urinary output. The greater rise of serum creatinine in this group was completely reversible after 3 weeks [36].

Therefore, data on (estimated) renal function in a decompensated state should be interpreted with caution as worsening GFR may reflect both poor prognosis and proper treatment response, which is associated with good prognosis. Without information on filtration fraction or renal perfusion, which is usually not readily available, eGFR and serum creatinine are therefore poor prognostic markers of renal function during acute decompensated heart failure. Due to these reasons, it has been suggested that blood urea nitrogen/creatinine ratio may be a better prognostic marker in ADHF than serum creatinine or estimated GFR [37].

Fig. 4 Proteinuria and hematological parameters in renal patients during different treatment regimens, during low (open bars) and high (gray bars) sodium diet. Low sodium diet does not affect hemoglobin or EPO level, neither during placebo nor during losartan. Losartan leads to a decrease in hemoglobin level, and hydrochlorothiazide 25 mg/day added to losartan leads to a further decrease in hemoglobin, along with a decrease in EPO level, and the observed/predicted ratio for EPO. (from: Slagman et al. ref 41)



Studies in hypertension and chronic kidney disease provide clues that suggest proper attention for volume targeting will be beneficial in heart failure. This not only applies to amelioration of the congestive state and hypertension but notably also to the potentiation of the effect of RAAS blockade in those conditions [38, 39], with concomitant beneficial effects on hard end points [40]. Considering the main role of RAAS blockade in the clinical management of heart failure, it might be worthwhile to consider a systematic re-appraisal of the role of dietary sodium restriction and diuretics in the management of heart failure, especially in view of the fact that counseling on sodium restriction for a short period may bear significant long-term effects in terms of reductions in cardiovascular mortality [40]. The strategy for volume targeting in heart failure will usually require both dietary sodium restriction and diuretics to be sufficiently effective. As noted above, diuretics are insufficiently effective in the presence of high sodium intake [24]. Whereas the effects of low sodium diet and diuretics exert more or less similar effects on volume status, it should be noted that they may differ in other effects relevant to heart failure patients, such as for instance serum potassium. Of note, in renal patients, recent data showed that diuretic treatment affects EPO production when used in conjunction with RAAS blockade [41] in

spite of a well-preserved renal function, whereas low sodium diet does not (Fig. 4). Considering the prognostic impact of EPO levels in heart failure, and the corresponding treatment regimen, this might bear relevance to heart failure patients as well. Corresponding data for heart failure patients are not available yet, but the data in renal patients suggest that it would be worthwhile to explore not only the effects of volume targeting but also to address whether it matters for long-term outcome by which strategy the volume correction is achieved.

Conclusions

The traditional concept of renal function decline as being merely due to impaired perfusion in heart failure has recently been challenged from several angles. Increasing evidence seems to suggest a strong role for venous congestion in the pathogenesis of renal function impairment in heart failure, in particular when perfusion is impaired as well. Observational and interventional data in cardiac and renal patients suggest that therapy aimed at reducing volume overload may yield beneficial effects on hard end points, despite a reduction in renal function at onset of therapy. Dietary sodium intake is a logical target for

intervention, which requires, however, a better awareness of sodium intake and deliberate efforts to change dietary habits. Results in the general population suggest that counseling on dietary sodium intake improves cardiovascular risk long after cessation of counseling. Reducing sodium intake may prove to be an effective yet cheap intervention. More studies to confirm and optimize the beneficial effects of volume targeting in congestive heart failure are warranted.

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