European Heart Journal (2011) **32**, 2476–2478
doi:10.1093/eurheartj/ehr242

EDITORIAL

Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney

Piero Ruggenenti[1,2] and Giuseppe Remuzzi[1,2]*

[1]Mario Negri Institute for Pharmacological Research, Bergamo, Italy; and [2]Unit of Nephrology, Azienda Ospedaliera Ospedali Riuniti, Bergamo, Italy

Online publish-ahead-of-print 23 July 2011

This editorial refers to 'Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial'†, by J.E.A. Blair *et al.*, on page 2563

In a post-hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), Blair and co-workers found that worsening kidney function shortly after hospitalization and in the early post-discharge period independently predicted cardiovascular mortality and re-hospitalizations because of heart failure (HF).[1] These findings confirmed previous evidence that worsening kidney function following hospitalization for decompensated HF is a strong independent predictor of long-term adverse outcomes. An intriguing finding of the above study, however, was that worsening kidney function was also associated with a decrease in body weight and circulating levels of the B-type natriuretic peptide (BNP), changes that reflected an amelioration of fluid congestion and that *per se* were expected to predict improved outcomes in the long term.

To explain this apparent paradox, we have to go back to the old days of Arthur J. Merril who in 1946 measured renal plasma flow and the glomerular filtration rate (GFR) by using the sodium *para*-amino hippurate and inulin renal clearance techniques, in 37 subjects admitted because of HF from different aetiologies.[2] In these patients, the renal plasma flow was reduced to one-third to one-fifth of normal, whereas the cardiac output was rarely reduced below half the resting value. On the basis of these findings, he suggested that in HF there is a specific diversion of blood away from the kidneys, organs which normally receive ~20% of the cardiac output. Despite the large reduction in renal plasma flow, however, the GFR was half to one-third normal. This was explained by a concomitant increase in the filtration fraction, that, according to Merril, reflected a 'high intraglomerular pressure from efferent arteriolar constriction, sustained by enhanced renal renin release'. This was the first demonstration that in compensated HF the reduced renal blood flow caused by circulatory impairment leads to a compensatory increase in the filtration fraction, which preserves the GFR despite decreased kidney perfusion (*Figure 1A*). It is only in more severe, decompensated, congestive HF, with extremely high renal vascular resistances and markedly diminished renal blood flow, that GFR falls without further increase in the filtration fraction.[3] In this setting, an extreme activation of the renin–angiotensin system and of the neurohormonal axis induces a maximized pre-glomerular vasoconstrition whose aim it is to sustain systemic blood pressure and redistribute diminished cardiac output mainly to the brain and heart. These profound haemodynamic changes, however, eventually lead to diminished intraglomerular pressure with reduced glomerular ultrafiltration and GFR, despite enhanced post-glomerular resistances (*Figure 1B*). Moreover, the activation of the neurohormonal axis is associated with an enhanced proximal tubular sodium and water reabsorption in order to increase the plasma volume and sustain cardiac output and renal perfusion.[4] This maladaptive response, however, eventually results in oligoanuria, fluid retention, and worsening of congestion. In this scenario, the only approach is to intensify the use of diuretics. With diuretics, however, amelioration of congestion is only achieved to the detriment of effective arterial volume, with further worsening of arterial underfilling, kidney hypoperfusion, and dysfunction. Thus, worsening kidney function eventually unmasks those patients with more severe HF who require high-dose diuretic therapy to maintain fluid homeostasis. This may explain the paradox observed by Blair and co-workers[1] that in their patients with decompensated HF, worsening kidney function independently predicted worse outcomes, despite improved markers of heart congestion such as decreased body weight and BNP.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +39 35 4213405, Fax: +39 35 319331, Email: gremuzzi@marionegri.it or manuelap@marionegri.it

† doi:10.1093/eurheartj/ehr238

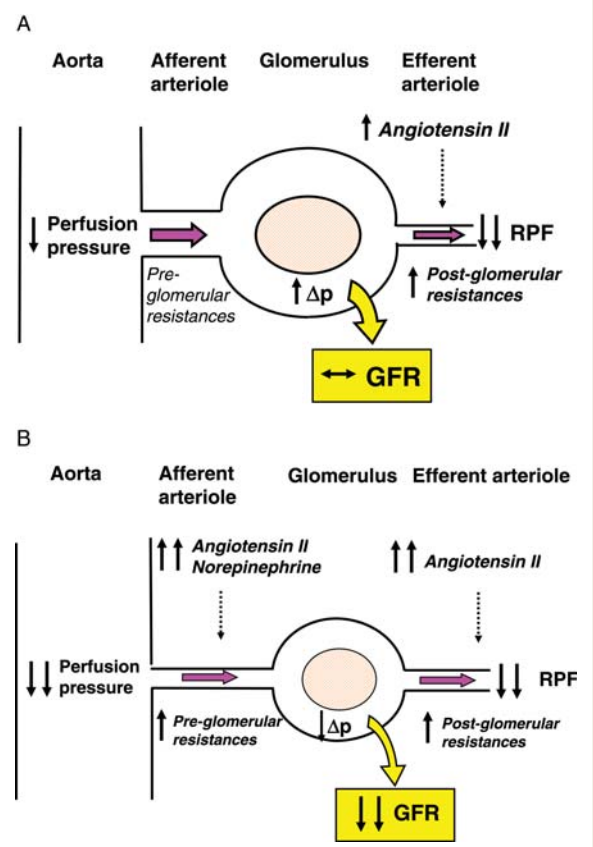

Figure 1 (A) Adaptative mechanisms to renal hypoperfusion in compensated heart failure. Activation of the renin–angiotensin system induces a predominant vasoconstriction of the efferent arteriole with a secondary increase in post-glomerular resistances. Increased post-glomerular resistances increase the intracapillary hydraulic pressure despite decreased kidney perfusion secondary to decreased systemic blood pressure. Thus, the percentage or the renal plasma flow that is ultrafiltered through the glomerular barrier (filtration fraction) increases, which allows maintainenance of the GFR despite decreased kidney perfusion. (B) Pre-renal kidney failure in decompensated heart failure. In decompensated heart failure, activation of the neurohormonal axis induces a maximized vasoconstriction of the afferent arteriole with a secondary increase in pre-glomerular resistances aimed at sustaining systemic blood pressure and redistributing decreased cardiac output mainly to the brain and heart. Increased pre-glomerular resistances reduce the glomerular perfusion pressure and the intracapillary hydraulic pressure despite increased post-glomerular resistances. The glomerulus is hypoperfused and the glomerular filtration area decreases. Thus, the percentage or the renal plasma flow that is ultrafiltered through the glomerular barrier (filtration fraction) decreases. Decreased plasma flow and filtration fraction both contribute to decreased GFR.

Another reason for concern is that most patients with HF also have decreased GFR to start with.[5] Consistently, Blair *et al.*[1] found that at inclusion > 90% of their patients had some degree of renal insufficiency, defined as an estimated GFR <90 mL/min/1.73 m^2. These data, however, should be treated with caution since prediction formulae underestimate the actual GFR, in particular in subjects with normal or near normal renal function,[6] and their use in the study of Blair *et al.* probably led to an overestimation of the real prevalence of kidney dysfunction. In this setting, the GFR may be reduced because of kidney hypoperfusion or renal co-morbidities, or both. Since kidney hypoperfusion is a marker of severe cardiac dysfunction and renal co-morbidities may accelerate the progression of cardiovascular disease,[7] not surprisingly, in patients with HF, renal dysfunction is associated with poor outcomes and appears to be an even stronger predictor of mortality than left ventricular ejection fraction or New York Heart Association functional class.[5] Thus, among patients with HF, those with concomitant renal insufficiency are the patients in most urgent need of effective treatment.

Despite the above background, however, in the study by Blair and co-workers,[1] patients with more severe renal dysfunction were less likely than those with a normal GFR to be taking an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin receptor blocker, or an aldosterone antagonist at baseline. This is not unexpected since prescription rates for ACE inhibitors—as well as β-blockers, statins, and antiplatelet agents—in patients with HF have been consistently reported to be inversely related to renal function, findings that most probably reflect concern about possible side effects of these medications in patients with more severe renal insufficiency. In particular, cardiologists and even nephrologists do not start or even withdraw ACE inhibitors in patients with acute decompensated HF for fear of worsening serum creatinine. Serum creatinine increases associated with ACE inhibitor therapy, however, do not indicate changes in a patient's clinical conditions that might portend worse outcomes, but simply reflect the inhibition of adaptative mechanisms, namely post-glomerular vasoconstriction, aimed to sustain glomerular hydraulic pressure and ultrafiltration despite decreased kidney perfusion. This effect almost invariably translates into worsening kidney function when the mean arterial pressure decreases to < 70–80 mmHg, that is the threshold of kidney autoregulation below which kidney perfusion becomes directly pressure dependent.[3] This explains why in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) serum creatinine increased by 10–15% over the first 2 weeks of enalapril treatment and why this change was largely driven by serum creatinine increases observed in patients with mean blood pressure reduction below 75 mmHg. After this initial increase, however, changes in serum creatinine over time in patients on enalapril were similar to those observed in controls and most probably reflected the natural progression of the underlying renal disease in this population.[8] Thus, early changes in serum creatinine levels during ACE inhibitor therapy reflect haemodynamic phenomena that do not translate into accelerated renal function loss in the long term, and that, based on observations in other clinical settings, might even be renoprotective.[9] On the other hand, ACE inhibitors have effects on the vascular tree that, in addition to directly improving long-term cardiac outcomes, may increase cardiac output and ameliorate arterial underfilling and kidney perfusion and dysfunction. Moreover, they promote natriuresis and diuresis by attenuating proximal tubular sodium and water reabsorption, and by suppressing aldosterone and vasopressin secretion,[4] changes that may further contribute to improving the

cardiac performance in particular in patients with concomitant renal insufficiency. This may explain why ACE inhibitor therapy improved 1-year survival compared with placebo in patients with baseline GFR <60 mL/min/1.73 m^2 at least as effectively as in those with higher GFR.[10]

Altogether, the above data suggest that some increase in serum creatinine levels should be tolerated with the use of ACE inhibitors. Changes in serum creatinine can be limited or prevented by decreasing diuretic therapy to limit systemic hypotension and kidney hypoperfusion. Since almost all ACE inhibitors are fully cleared by the kidneys, these drugs may accumulate in the circulation of patients with renal insufficiency, which may further worsen the kidney function in a vicious circle that may end in anuria and need for renal replacement therapy. Thus, careful dose titration to blood pressure and serum creatinine is mandatory in these patients.

Evidence that cardiac function may improve after renal transplantation in patients with primary kidney disease suggests that chronic renal insufficiency may play a pathogenic role in the progression of HF. Renal insufficiency may contribute to multiple changes in vascular pathobiology that may worsen cardiovascular outcome, such as salt and water retention, hyperactivation of the sympathetic nervous and renin–angiotensin system, endothelial dysfunction, insulin resistance, chronic inflammation, abnormalities in the coagulation/fibrinolytic systems, and abnormal vascular calcification associated with elevated calcium phosphorus product and secondary hyperparathyroidism.[7] Thus, preventing the onset and progression of chronic kidney disease might be instrumental in improving cardiovascular outcomes in patients with HF. ACE inhibitors and angiotensin II receptor antagonists have been consistently found to prevent the onset of nephropathy in subjects with diabetes[11] and to limit the progression of diabetic and non-diabetic chronic nephropathies to end-stage kidney disease.[12,13] In a relevant proportion of cases they may also achieve regression or remission of established kidney disease.[14] Thus, it is conceivable that these medications might also slow the progression of chronic kidney disease in patients with HF, which might translate into significant cardioprotection, independent of the direct effects of these drugs on the heart. In this regard, it is worth mentioning that angiotensin II receptor antagonists have been reported to reduce the incidence of hospitalizations because of worsening HF in type 2 diabetes patients with overt nephropathy,[13] an effect that was even larger in patients with more severe renal insufficiency.[15] Finding that these benefits also extend to patients on chronic dialysis therapy because of end-stage renal disease further reinforces the concept that these medications should be offered to all patients with HF, independent of the presence and severity of renal dysfunction. Due to their well-established life-saving effects, ACE inhibitors should be started as soon as the diagnosis of HF is established and should never be stopped.

Conflict of interest: none declared.

References

1. Blair JEA, Pang PS, Schrier RW, Metra M, Traver B, Cook T, Campia U, Ambrosy A, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Konstam MA, Gheorghiade M. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. *Eur Heart J* 2011;**32**:2563–2572. First published on 23 July 2011. doi:10.1093/eurheartj/ehr238.
2. Merrill AJ. Edema and decreased renal blood flow in patients with chronic congestive heart failure; evidence of forward failure as the primary cause of edema. *J Clin Invest* 1946;**25**:389–400.
3. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. *Drugs* 1990;**39** Suppl 4:10–21; discussion 22–14.
4. Ichikawa I, Pfeffer JM, Pfeffer MA, Hostetter TH, Brenner BM. Role of angiotensin II in the altered renal function of congestive heart failure. *Circ Res* 1984;**55**: 669–675.
5. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation* 2010; **121**:2592–2600.
6. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004;**141**:929–937.
7. McCullough PA. Cardiorenal risk: an important clinical intersection. *Rev Cardiovasc Med* 2002;**3**:71–76.
8. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial). *Am J Cardiol* 1992;**70**:479–487.
9. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986;**77**:1925–1930.
10. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004;**109**:1004–1009.
11. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, Rubis N, Gherardi G, Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini AR, Remuzzi G. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004;**351**:1941–1951.
12. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. *Lancet* 1998;**352**:1252–1256.
13. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–869.
14. Ruggenenti P, Perticucci E, Cravedi P, Gambara V, Costantini M, Sharma SK, Perna A, Remuzzi G. Role of remission clinics in the longitudinal treatment of CKD. *J Am Soc Nephrol* 2008;**19**:1213–1224.
15. Remuzzi G, Ruggenenti P, Perna A, Dimitrov BD, de Zeeuw D, Hille DA, Shahinfar S, Carides GW, Brenner BM. Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results. *J Am Soc Nephrol* 2004;**15**:3117–3125.