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EDITORIAL

Revisiting the cardio-renal hypothesis: the pivotal role of the kidney in congestive heart failure

Matthias Dupont, Kevin Shrestha, and W.H. Wilson Tang*

Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH, USA

This editorial refers to 'Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: The NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial' by A.S. Maisel *et al.*, published in this issue on pages 846–851.

Our conceptual understanding of heart failure over the past century evolves over two common themes. First, the ability to demonstrate the existence of a pathogenic process by a measurement or a physiological finding allows the formulation of a testable hypothesis. Second, the ability to alter the natural history through treatment approaches that target such a process provides validation of the concept. Long before we had bedside haemodynamic and imaging techniques, 'congestive failure' was considered to be a heterogeneous condition but largely attributed to the failure of the kidneys to receive adequate blood flow (the so-called 'cardio-renal hypothesis').[1] Diuretic therapy was the primary approach, and continues to be highly effective at relieving signs and symptoms. With the development of tools to measure intra-cardiac pressures and estimate cardiac efficiencies with calculated output values or increasingly sophisticated imaging techniques, the cardio-centric views placed the word 'heart' into congestive heart failure ('cardio-circulatory hypothesis').[2] This led to the widespread adoption of 'ejection fraction' as an important criterion for determining an underlying impairment in cardiac function, and put forward the promise of vasodilators and inotropic drugs to facilitate circulatory efficiency in the 1970s to 1980s. Next, advances in laboratory measurements recognized high levels of hormonal activation occurring in the setting of congestion and cardiac insufficiency ('neurohormonal hypothesis'). It has led to the development of drugs that counteract both the major regulatory homeostatic hormones (renin-angiotensin−aldosterone and adrenergic systems), and the conduct of large-scale clinical trials to demonstrate their abilities to reduce adverse outcomes beyond haemodynamic improvement in the 1980s and 1990s. Better understanding of how to avert arrhythmogenic death and the ability to visualize electrical and mechanical dyssynchrony catalyzed technological development in device therapy with implantable defibrillators and cardiac resynchronization therapy in the 2000s. Today, patients with heart failure survive longer but with more co-morbid conditions, and yet their recurrent admissions to the hospital with congestion remain the single largest challenge to healthcare providers and to societal costs. The cardio-renal interaction has regained attention in recent years because common aetiologies of heart failure and kidney disease cannot fully explain the co-occurrence of these pathologies.[3] During decongestive treatment of acute decompensated heart failure, this interaction is even more complex and poorly understood. The often-encountered scenario is worsening of renal function during diuretic treatment (conveniently defined as a $\geq$0.3 mg/dL rise in serum creatinine),[4,5] forcing clinicians to hold off on diuretics while the patient is incompletely decongested. However, the presence of significant congestion itself is more predictive of the development of worsening renal function than impaired cardiac output,[6,7] even though in some cases the treatment to relieve congestion may result in improving (or at the least neutral) outcomes despite a rise in serum creatinine.[8–10] Clearly, our bedside insights into the adequacy of the failing heart and/or kidneys to maintain euvolaemia and relieve congestion remain far from precise, and treatment strategies are yet to alter the natural history of the condition.

In this issue, Maisel *et al.*[11] present their findings from a prospective, multi-centre study looking at the prognostic value of a novel biomarker, neutrophil gelatinase-associated lipocalin (NGAL), alone and in combination with B-type natriuretic peptide (BNP) in 186 patients with acute on chronic heart failure confirmed by the presence of an elevated BNP (>100 pg/mL). The investigators report higher plasma levels of NGAL and BNP in patients with events (30-day re-hospitalization or all-cause mortality) compared to patients with no events. They also display an array of statistical findings in an attempt to show that NGAL provides incremental value to standard prognostic measures, despite their acknowledgement of a relatively small event rate (16% or 29 deaths) with short follow-up. The lack of comprehensive description of patient characteristics, their serial changes of plasma NGAL, and treatment regimens over the course of hospitalization precluded more detailed understanding of how to best utilize this biomarker at

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* Corresponding author. 9500 Euclid Avenue, Desk J3-4, Cleveland, OH 44195, Tel: +216 444 2121, Fax: +216 445 6165, Email: tangw@ccf.org

the bedside. These hypothesis-generating results imply the potential value of measuring plasma NGAL beyond standard cardio-renal measurements, even though the prognostic value of circulating NGAL is largely confirmatory to previously reported findings in the literature.[12–14]

In order to appreciate the implications of the findings, we need to better understand exactly what is being measured and what can be interpreted from the observations. NGAL is a 25 kDa glycoprotein of the lipocalin superfamily that reflects tubular injury or necrosis.[15] It is normally expressed and secreted in low amounts by several cell types including neutrophils, cardiomyocytes, and epithelial cells in colon, lung, and kidney. It has the ability to bind and deplete siderophores[16] (small iron-binding molecules synthesized by bacteria) that can interfere with bacterial iron uptake, thus providing bacteriostatic effects. Furthermore, NGAL has a presumed role as a growth and differentiation factor in several cell types (which explains its increase in cancer[17,18]), and local NGAL expression can be markedly increased after injury to certain epithelial cell types (such as in the setting of urinary tract infection[19]). Hence, there is a possibility that NGAL levels may reflect even beyond acute renal tubular injury. Nevertheless, in experimental hypoxic or nephrotoxic kidney injury models, NGAL appears to be one of the most up-regulated genes, leading to increased downstream production of urinary and/or circulating NGAL.[20] Since the rise in NGAL concentrations is evident hours after the insult, NGAL overcomes the classic limitation of creatinine as an early marker of renal dysfunction.[15] NGAL has shown to be an excellent predictor of acute kidney injury in typical acute tubular necrosis situations such as contrast nephropathy, post-cardiopulmonary bypass, and in the setting of intensive care units.[21–23] In contrast, urinary NGAL levels were only modestly elevated in the setting of pre-renal azotaemia (despite higher than normal controls).[23] However, most studies on NGAL in cardiac patients have been cross-sectional in design, and longitudinal studies have focused on those with relatively normal kidney function at baseline. What is not known is whether raised circulating levels of NGAL can be confounded by conditions beyond acute renal tubular injury that may also contribute to adverse outcomes. Understanding the causes of death or re-hospitalizations in those with elevated NGAL levels will therefore be insightful in drawing any cardio-renal conclusions.

This leads to a more fundamental question: what do we know about the underlying mechanisms leading to renal tubular injury in acute decompensated heart failure, and what role does NGAL play? The ability to respond to decongestive therapy means achieving natriuresis and diuresis, which requires an intact renal tubular function in addition to normal glomerular filtration. Loop diuretics need to be excreted in the renal tubular lumen by the proximal tubular cells and subsequently block activity of the Na^+–K^+–$2Cl^-$ co-transporter in the thick ascending limb. We know that worsening renal function during treatment of acute decompensated heart failure is often considered a 'pre-renal' phenomenon, reflecting intravascular volume depletion secondary to overzealous diuretic use or insufficient renal blood flow causing impaired glomerular filtration. This may occur as a consequence of either decreased excretion of diuretics at the level of the renal tubular lumen, or by adaptive increase in Na^+–K^+–$2Cl^-$ co-transporter activity secondary to oxidative or inflammatory stress,[24] thereby contributing to a vicious cycle of progressive water and salt retention. It is conceivable that renal tubular injury may be an important mechanism that detrimentally affects diuretic and natriuretic properties of decongestive therapy in a subset of patients. However, we do not know what triggers NGAL to rise during heart failure hospitalization, nor if such mechanisms are directly precipitated by pre-renal azotaemia. Also, we have yet to appreciate the frequency of and predictors for developing acute renal tubular injury (rather than detection of a rise in NGAL levels) in acute decompensated heart failure. In other words, much work is needed to explore why NGAL levels are elevated in the setting of acute decompensated heart failure.

While urinary NGAL measurements have been considered to be relatively specific to insult at the level of the renal tubules, studies of circulating (blood) NGAL in patients with chronic heart failure have reported systemic and potential myocardial contributions.[25] Furthermore, plasma levels of NGAL were largely independent of intracardiac filling pressures or cardiac structure and function in the acute decompensated setting, yet plasma NGAL correlated with estimated glomerular filtration rate and cystatin C in the chronic setting.[14] As patients with events (vs. no events) in the GALLANT study demonstrated higher plasma NGAL levels not only at discharge but also at baseline, this begs the question: are plasma NGAL levels reflective of renal tubular injury in response to aggressive decongestive therapy for cardiac insufficiency, or are they indicative of underlying intrinsic renal dysfunction that was present at the onset (or persistent rather than acute renal tubular dysfunction), or even of production from extra-renal sources (such as systemic or myocardial expression)?

The findings of this important biomarker study draw the attention of a whole new generation of clinicians and researchers to the importance of the kidneys in the relief of congestion in heart failure, and the need for understanding why and how plasma NGAL levels increase in the first place. With better measurements of specific renal function such as NGAL, our conceptual understanding of heart failure swings back in full circle to the original 'cardio-renal hypothesis'. Perhaps the only difference is that we may need to start appreciating the possibility that the heart may not necessarily be the primary culprit, and that the availability of functioning kidneys is likely a major determinant in clinical outcomes in the setting of congestive heart failure.

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