Stigmata of death: for kidneys and patients

Claudio Ronco¹ and Joseph V. Bonventre²,³,⁴

¹Department of Nephrology, Dialysis, and Transplantation, International Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital, Vicenza, Italy, ²Renal Division and Biomedical Engineering Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA, ³Division of Health Sciences and Technology, Harvard-Massachusetts Institute of Technology, Cambridge, MA, USA and ⁴Harvard Stem Cell Institute, Cambridge, MA, USA

Correspondence and offprint requests to: Claudio Ronco; E-mail: cronco@goldnet.it

The Framingham study [1], which has recently celebrated its 65th anniversary, has brought great insight into the epidemiology and risk factors associated with cardiovascular diseases. Risk factors for cardiovascular disease include not only family history and diabetes, smoking and hypertension but also biochemical abnormalities such as lipid abnormalities, or to be more specific, increased low-density lipoprotein (LDL). In recent years, these observations have been extended to include markers of inflammation. For example, the thrombolyis in myocardial infarction investigators showed that outcomes following statin therapy were determined not only by control of LDL but were also associated with C-reactive protein (CRP) [2]. Control of LDL or CRP alone offered some benefit in terms of subsequent cardiovascular events, but the lowest risk was for patients with both LDL and CRP below target. These markers, LDL and CRP, are bad prognostic signs, stigmata if you will, for patients with cardiovascular disease.

In a large study published in this issue of NDT, Murugan et al. analysed patients from the VA/NIH Acute Renal Failure Trial Network (ATN) study of intensive versus conventional renal support in acute kidney injury (AKI) [3], looking for ‘death stigma’ that would predict the inability of patients to recover from AKI and come off dialysis and/or predict patient non-survival. The authors focused on markers of inflammation and apoptosis in patients with severe AKI on renal replacement therapy (RRT) [4]. What they found was important in demonstrating a strong relationship between inflammation and bad outcomes in patients. What was not surprising was that inflammation was increased on Day 1 in patients that did poorly compared with those that did well. This is consistent with the renal literature on AKI [5, 6], as well as the cardiology [2] and sepsis literature [7]. There were pleotropic changes in the plasma markers which play varying roles in the systemic inflammatory response. Interleukin 8 is a chemokine and has been implicated in the pathogenesis of AKI [8]. It attracts neutrophils, monocytes and macrophages—cells that mediate organ injury but also influence repair. Macrophage migration inhibitory factor also influences the behaviour of monocytes and macrophages, not by attracting them but by getting them to stay once they arrive. Finally, tumour necrosis factor receptor activation triggers cell apoptosis further adding to organ injury. These inflammatory mediators likely work in concert with other mediators to reduce organ recovery and ultimately to reduce the chances for survival. This association between inflammation and adverse outcomes is not only a feature of AKI but also of chronic kidney disease [9].

In AKI, the kidney both contributes to this inflammatory response and is adversely affected by it. Local kidney production and/or circulating effects of cytokines may contribute to endothelial injury, upregulation of adhesion molecules, capillary blood flow compromise and increased vascular permeability which can collectively result in impaired oxygen delivery to the outer medulla [6]. Thus, a positive feedback process ensues with increased tubule cytokine production and further vascular compromise. The damage to the organ that ensues may be severe and the adverse effects may be amplified by some level of chronic disease (low creatinine does not exclude this), and tubule cell senescence. The kidney’s ability to recover may be seriously compromised. Furthermore, the inflammatory mediators produced in the kidney are released into the systemic circulation and can have important effects on distant organs including the lung, brain and heart [10, 11]. This organ crosstalk can certainly contribute to other consequences of renal failure, such as bleeding tendencies and enhanced susceptibility to sepsis, worsening systemic illness with adverse consequences on overall mortality. The fact that the APACHE scores were similar in the comparison groups in the Murugan study does not exclude confounding since the
general scoring systems are not weighted optimally and do not capture all the factors that contribute to adverse outcomes in patients with AKI.

Interestingly, the biomarker profiles observed in this study did not differ by aetiology of AKI and the markers that were independently associated with kidney death (non-recovery) were also associated with non-survival. One possibility is that AKI itself is causing these abnormalities and that failing to recover kidney function is, not surprisingly, in the causal pathway to death. Alternatively, high circulating markers of inflammation may reflect a generalized pathophysiological state in the patient that would predispose to renal non-recovery. AKI is often seen in the setting of multiple organ failure. Brain, liver and lung injury are each independently associated with systemic inflammation and kidney failure [12]. Each organ system can contribute to mortality. Circulating factors in sepsis have been found to alter the function and induce apoptosis in kidney tubule epithelial cells [12]. Use of mechanical ventilation, for example, was greater in those patients in the study who did not recover and who did not survive.

Does this study provide a road map to follow in order to design strategies to alter the natural history for patients with severe AKI? The study raises many questions that have to be answered. Could we use these systemic inflammatory and apoptosis markers to develop therapies analogous to statins for LDL? Is inflammatory cell recruitment, persistence and then apoptosis of cells in the kidney and elsewhere a likely set of mechanisms responsible for organ failure and death? Certainly we have evidence to support these possibilities, but many pieces of the puzzle are still lacking. Most importantly, we should know what effect treatment has on these markers and whether altering the expression of the markers predicts a better outcome. Patients in the ATN study were randomized to high- or low-intensity RRT. Did RRT alter the trajectory of these markers? Did RRT work differently in patients with high levels of these mediators compared with patients with low levels? Blood purification techniques could be optimized to influence these molecules. Rather than our existing strategy of choosing one prescription for everyone, could we adopt a personalized medicine approach where our treatment was tailored to the patient’s inflammatory and apoptotic marker profile?

In summary, the Murugan study [4] clearly shows that in critically ill patients receiving RRT, elevated concentrations of inflammatory and apoptosis biomarkers are stigmata of death for both kidneys and patients. As the authors suggest, future studies should examine whether broad-spectrum immune modulation of inflammatory and apoptosis markers improves outcomes.

(See related article by Murugan et al. Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy. Nephrol Dial Transplant 2014; 29: 1854–1864.)

REFERENCES