# “Acute renal success”: the value of an unusual perspective

This blog article is about a research paper from long ago that I still refer to every year, because it provides such great material for making second-year medical students, to whom I teach renal physiology, think. It does so because it provokes its readers to shift their perspective on disease and, perhaps, to see opportunities for better treatment.

The kidney is a complicated organ and it does many things, but its main function can be summarized relatively simply: it filters small molecules out of the blood, then it recovers the molecules that are useful to the body and lets the others (waste products, toxins etc.) leave in the urine. The filtration is done by around a million nephrons: long, thin tubes with a blood-filter ('glomerulus') at one end and a connection to the plumbing that leads to the bladder at the other. Filtration is driven physically, by the pressure in the blood, while the processes of resorption along the tubule are driven by very biological, food- and oxygen-consuming, active processes. Like the most reliable machines we build, nephrons monitor their own performance. In particular, a set of specialized cells near the end of the tube (technically, 'the macula densa and juxtaglomerular apparatus', but let's just call them the monitoring station) measure how salty the urine passing through them is. If it is abnormally salty, the monitoring station concludes that flow along the tubule is too fast for salt recovery to have happened properly. Since the speed of flow along the tubule is set by the speed of flow through the filter, and that speed is in turn set by blood pressure, fast flow means that blood pressure is probably too high. The monitoring station therefore commands the blood vessel that brings blood to the filter to constrict, and so reduce pressure at the filter itself. If the urine passing the monitoring station is abnormally low in salt, on the other hand, the opposite conclusion is drawn and a signal is generated to raise blood pressure in the whole body.

Unfortunately for medical students, while the above explanation is basically correct, they have to know a great deal more about details. In addition, they have to learn about the ways in which kidneys can go wrong. One of these, which is every bit as dramatic as it sounds, is 'acute renal failure'. Acute renal failure usually makes itself known when the patient produces very much less urine than normal ('oliguria'): the patient will later suffer from the unpleasant consequences of toxin build up in the blood, because the toxins are no longer being excreted well enough. Acute renal failure can have a variety of causes, including poor blood supply to the kidney and poisoning of the cells of the tubule by, for example, fungal products of drugs.

The strange thing about acute renal failure is that one might naively expect that damaging the cells of the nephron that normally recover things from urine, or starving those cells of oxygen or food, would actually produce more urine. After all, the entry of fluid to the nephron just depends on the simple physics of blood pressure while it is the recovery of things back to the body that depends on complicated biology that will not happen if the tubule cells are not healthy. So why does failure of recovery systems not result in the loss of more urine? The physiologist Brandt-Rehberg, writing in 1929, was probably the first person to work out how failure of the nephron's active physiology results in less, rather than more, urine. If salt recovery processes do not work properly along the tubule, the urine will still be very salty by the time it reaches the monitoring station. The monitoring station will conclude that flow is much be too fast, and will close down the blood vessels feeding the filter, dropping the blood pressure at the filter and slowing entry of fluid into the nephron. Effectively, the monitoring station has commanded filtration pressure to reduce enough not to overwhelm whatever whatever small molecule-resorptive capacity remains. If this happens to all nephrons, the flow rate of urine in the kidney as a whole will be very slow and the oliguria that is the hallmark of acute renal failure will be seen.

In 1976, Klaus Thurau and John Boylan, thinking deeply about this, published an intriguing review article that turned the concept of 'acute renal failure' on its head, and argued that the 'failure' of nephrons is actually a protective mechanism designed to promote regeneration and recovery. They pointed out several features that make it useful. One rests on the fact that the kidney's ability to recover water from urine depends completely on its ability to recover salts and, if nephrons were allowed to carry their normal flow when salt recover was not working properly, neither water nor salts would be recovered and the patient would lose body fluids very quickly. The shutting down of flow along damaged nephrons would prevent this. Yes, it will allow toxins to build up in blood but this is a slow process that will become a problem over days, whereas the loss of body fluids that would happen if flow carried on as normal would kill within just a few hours. Also, in a nephron damaged by toxins, fast urine flow would multiply damage as dying cells from the early part of the nephron (the 'proximal tubule', particularly sensitive to a range of poisons) falling away into the urine space would get stuck in the narrower regions of nephron beyond and start to block the flow: if this happened faster than the processes that clear up cell debris, pressure in the nephron would rise and its cells would be damaged further. An automatic shut-down of flow could be seen as a protective feature to stop dying cells being swept down to and make blockages faster than they can be cleared.

Thurau and Boylan underlined their view that the action of the monitoring station in shutting down

urine flow is protective by entitling their provocative article “acute renal success”: the low urine flow maximizing the chances of repair and the return of a properly working nephron.

This view that oliguria may reflect a protective action has interesting clinical consequences. Normally, inhibition of the signalling system (RAS) that the kidney uses to increase blood pressure in the whole body is considered to increase the risk of acute kidney failure and to make this injury worse by conventional measures. But, as Tim Ellam and Bisher Kawar pointed out in 2011, 'conventional measures' assess severity of acute kidney failure by how seriously urine flow drops. If this drop is actually a measure of protection, i.e. of 'success', what looks like 'worse' may actually be 'better in the long run'. The authors pointed out that, in animal models, inhibition of RAS made the reduction in urine flow worse but was associated with a better final outcome in terms of the extent of renal recovery.

The jury is still out on these issues: they are contentious and that is precisely why I use them in the final stages of teaching, when the students (should) have gained a good grasp of basic renal physiology and are ready to start pondering what it all means. My job as a scientist teaching medical students is not to tell them what to prescribe (nobody without a medical qualification should ever do that!), but to get them to think. Part of this is the thinking they expect to do, about how bodies work, how they fail and how they recover. But some of it is about how the words they use to describe a condition will influence their choice, as doctors of the future, of whether to push with that condition or push against it. That is why I so like the Thurau's and Boylan's idea of 'acute renal success': changing the word changes the perspective, and changing the perspective can, sometimes, change everything.

Jamie Davies
Edinburgh
February 2014

Links:
The Thurau and Boylan paper: http://www.amjmed.com/article/0002-9343(76)90365-X/pdf
The Ellam and Kumar paper: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4421638/