The Uremic Myocardium and Ischemic Tolerance: A World of Difference

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Uremia is associated with an increased prevalence of ischemic heart disease. Already at the start of dialysis the prevalence of coronary artery disease is 38%\(^1\). The frequency of myocardial infarction in renal patients is high and the outcome is poor\(^2\). Despite significant improvement of therapeutic modalities unadjusted 2-year mortality for dialysis patients after acute MI has not changed over the past decades, remaining around approx. 73%\(^2,3\). It is of particular note that the risk of cardiac events is 20-fold higher in young adults starting dialysis in the first 2 decades of life compared to an age-matched background population\(^4\).

The reasons for the poor outcome are manifold: underdiagnosis due to atypical presentations (e.g. fewer transmural infarctions), therapeutic nihilism due to the burden of disease and the consequences of uremic cardiomyopathy itself\(^3\).

Experimental uremic cardiomyopathy leads to reduced ischemic tolerance and consecutively larger MI size\(^5,6\). The latter was independent of confounders such as hypertension, anemia, sympathetic overactivity and hypervolemia\(^5\). These findings are at least in part the consequence of morphologic changes in uremic myocardial tissue. The number of cardiomyocytes is decreased presumably as a result of apoptosis. Furthermore, the cardiomyocyte diameter and cardiomyocyte area are increased\(^7\), whereas the growth of capillaries does not keep pace, so that oxygen diffusion distance is critically extended. Another explanation for reduced ischemic tolerance is the increased oxygen demand of the uremic cardiomyocyte and a disturbed metabolic compensation during hypoxia. Raine et al. found instability of creatine phosphate and increased degradation of ATP to adenosine under low-flow conditions in hearts of uremic rats\(^8\). Furthermore, in uremia the insulin-mediated glucose uptake by the heart is diminished due to uremia-specific insulin resistance syndrome\(^6\). The latter is a
common feature of chronic renal failure and is observed even in patients with only mild degrees of renal dysfunction\(^9\).

Uremia itself makes an important contribution to cardiac remodeling after acute MI. Previous studies have shown that cardiac dilatation and LV dysfunction occur in 74.9% of dialysis patients after acute MI\(^1\). In these patients (who survived acute MI) the 1-year mortality is 45.9%, the 2-year mortality 63.6% and the 5-year mortality no less than 87.5% (10).

In experimental uremia after acute MI there is a progressive loss of LV function as estimated by echocardiography\(^11\). It is of particular note that a relatively small MI size (approx. 8 percent of LV mass) is associated with a serious loss of ventricular function in uremic rats early after MI with further deterioration of LV function over time\(^11\). The underlying mechanisms which lead to such a disastrous loss of cardiac function after MI are still under investigation. In uremic cardiomyopathy the total number of cardiomyocytes is decreased – not only without MI but particularly after ischemic damage\(^7,11\). Immediate after myocardial ischemia the amount and onset of interstitial fibrosis is enhanced\(^11\), possibly as the result of upregulation of the cardiotonic steroid marinobufagenin in uremia\(^12\).

Given the poor outcome of uremic patients after acute MI, the reduced ischemic tolerance of the uremic myocardium and the adverse functional consequences of even small infarct sizes the clinical implication is to limit the area of total necrosis in the uremic myocardium after acute ischemia at our best.

Thus far there are two published trials to reduce MI size in experimental uremia\(^6,13\). The infarcted area in uremic myocardium can be significantly reduced by a glucose/insulin infusion to override both the insulin resistance syndrome and the diminished cardiac glucose uptake\(^6\). Another strategy – with even more impressive results – is presented in this issue of Circulation.
by Byrne and colleagues. They have systematically tested ischemic pre-conditioning, remote ischemic conditioning and ischemic post-conditioning in two different models of uremic animals with acute MI. It is well known that these strategies lead to significant reduction of infarct size in experimental models, but also in the clinical scenario postconditioning as well as remote ischemic conditioning appear to reduce infarct size. Similarly to previous studies increased infarct size was present in uremic animals while the area at risk was similar to non-uremic controls. However, it is very remarkable that ischemic pre-conditioning, post-conditioning as well as remote conditioning protocols not only are operative in renal disease but are even more effective and powerful in uremic animals leading to significant greater reduction in myocardial infarction size than in non-uremic controls.

Comparing both publications concerning strategies to decrease MI size in uremia all approved therapeutic modalities reveal a fascinating common pattern. In general, the intracellular signaling mechanisms for cytoprotection and ischemic tolerance seem to be intact in the uremic cardiomyocyte. The basal signal transduction may be altered by uremic toxins but it is still possible to activate essential rescue pathways such as the RISK or the SAFE pathway as well as the IRS-regulated signal pathways and the GLUT 4-mediated uptake of energetic substrates.

As a consequence, the uremic myocardium seems to profit in particular from cytoprotective procedures, more than the myocardium not affected by an uremic milieu. The work of Byrne and colleagues highlights this concept and their impressive results should encourage us to develop easy-to-establish protocols for renal patients with acute MI, to decrease infarct size and to improve the poor prognosis. The specific merit of the paper of Byrne and colleagues is to remember us that the uremic myocardium reacts totally different from myocardium not exposed
to uremic toxins. Therefore, it is worth to revisit former studies investigating protective strategies for the ischemic myocardium and to challenge the results concerning renal function.

Taken from all recent experimental studies\textsuperscript{5, 6, 13} there are two promising strategies to improve ischemic tolerance of the uremic myocardium in the clinical practice so far:

1. \textit{Conditioning strategies}. Clinical studies to determine whether remote ischemic conditioning - e.g. using brief limb ischemia - is capable of reducing myocardial injury in renal patients presenting with acute MI are easy to establish. Furthermore, pharmacological agents which have been demonstrated in experimental studies to reduce myocardial infarct size when administered at the point of myocardial reperfusion (pharmacological postconditioning), such as adenosine, GLP-1, or atrial natriuretic peptide should be tested specifically in renal patients.

2. \textit{GIK therapy}. As a complementary approach clinical trials should be set up to investigate the value of administration of glucose-insulin-potassium infusions in renal patients with acute MI to override insulin resistance syndrome.

In conclusion it is time to improve the poor prognosis of renal patients suffering acute MI. Patients with impaired renal function should not be excluded from clinical trials any more. On the contrary, specific studies should be set up for this increasing patient population to improve persistent adverse outcome after acute MI. There are strong hints that they benefit well – and to some extent even more than patients without renal failure - from cardioprotective strategies such as conditioning. It is the difference of the uremic myocardium which we should keep in mind.

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References:


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