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%. The frequency of myocardial infarction in renal patients is high and the outcome is poor. Despite significant improvement of therapeutic modalities, the unadjusted 2-year mortality for dialysis patients after acute myocardial infarction (MI) has not changed over the past decades, remaining ~73%. 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 in comparison with an age-matched background population.

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

Experimental uremic cardiomyopathy leads to reduced ischemic tolerance and consecutively larger MI size. The latter was independent of confounders such as hypertension, anemia, sympathetic overactivity, and hypervolemia. These findings are, at least in part, the consequence of morphological 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, 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. Furthermore, in uremia, the insulin-mediated glucose uptake by the heart is diminished because of uremia-specific insulin resistance syndrome. The latter is a common feature of chronic renal failure and is observed even in patients with only mild degrees of renal dysfunction.

Uremia itself makes an important contribution to cardiac remodeling after acute MI. Previous studies have shown that cardiac dilatation and left ventricular dysfunction occur in 74.9% of dialysis patients after acute MI. In these patients (who survived acute MI), the 1-year mortality is 45.9%, the 2-year mortality is 63.6%, and the 5-year mortality is no less than 87.5%. In experimental uremia after acute MI there is a progressive loss of left ventricular function as estimated by echocardiography. It is of particular note that a relatively small MI size (~8% of left ventricular mass) is associated with a serious loss of ventricular function in uremic rats early after MI with further deterioration of left ventricular function over time. The underlying mechanisms that 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 also after ischemic damage. Immediately after myocardial ischemia, the amount and onset of interstitial fibrosis is enhanced, possibly as the result of upregulation of the cardiotoxic steroid marinobufagenin in uremia.

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 2 published trials to reduce MI size in experimental uremia. 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. Another strategy, with even more impressive results, is presented in this issue of Circulation by Byrne and colleagues. They have systematically tested ischemic preconditioning, remote ischemic conditioning, and ischemic postconditioning in 2 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 in the clinical scenario, postconditioning and remote ischemic conditioning, as well, appear to reduce infarct size. Similarly to previous studies, increased infarct size was present in uremic animals, whereas the area at risk was similar to nonuremic controls. However, it is remarkable that ischemic preconditioning, postconditioning, and remote conditioning protocols, as well, not only are operative in renal disease, but also are even more effective and powerful in uremic animals, leading to significantly greater reduction in MI size than in nonuremic controls.

In 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 reperfusion injury salvage kinase or the survivor activating factor enhancement pathway, and the insulin receptor substrate-regulated signal pathways and the glucose transporter type 4-mediated uptake of energetic substrates, as well. 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 article of Byrne and colleagues is to remind us that the uremic myocardium reacts totally differently from myocardium not exposed to uremic toxins. Therefore, it is worthwhile 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, there are 2 promising strategies to improve ischemic tolerance of the uremic myocardium in the clinical practice so far.

1. Conditioning strategies. Clinical studies to determine whether remote ischemic conditioning (eg, use of brief limb ischemia) is capable of reducing myocardial injury in renal patients presenting with acute MI, to decrease infarct size, and to improve the poor prognosis. The specific merit of the article of Byrne and colleagues is to remind us that the uremic myocardium reacts totally differently from myocardium not exposed to uremic toxins. Therefore, it is worthwhile to revisit former studies investigating protective strategies for the ischemic myocardium and to challenge the results concerning renal function.

In conclusion, it is time to improve the poor prognosis of renal patients experiencing 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 ad-

verse 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 that we should keep in mind.

Disclosures

None.

References


Key Words: Editorials ■ ischemic tolerance ■ myocardial infarction ■ renal insufficiency
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Circulation. 2012;125:1215-1216; originally published online February 8, 2012;
doi: 10.1161/CIRCULATIONAHA.112.093047
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/125/10/1215

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