Experimental models of cardiorenal syndrome: from basic science to the clinic

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The Kidney Cardiac Link

Classification and Pathophysiology

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References


Figure 2

Heart-kidney interactions

Two important features characterize cardiorenal syndromes: the sequence of organ involvement and the bidirectionality of signaling, leading to a vicious cycle of cardiac and renal dysfunction. Another important aspect is the timeframe in which the derangements occur (chronic or acute). The series of conditions shown here indicate that patients may move among the subtypes of cardiorenal syndromes. Modified from (2).
by 5/6 nephrectomy plus a ligature of the coronary artery a week after surgery. They evaluated endothelium-dependent relaxation to acetylcholine in vitro in small arteries isolated from the extirpated 5/6 nephrectomy. After the MI, the nephrectomized rats gradually developed proteinuria in a range varying from 20 to 50 mg/day at week 16, with a peak of 150 mg protein/100 mg creatinine at 131±7 mg Hg. They found that individual renal endothelial function of the healthy rats predicted the extent of renal damage in terms of proteinuria (r = -0.62, p = 0.008) and focal glomerulosclerosis (r = -0.70, p = 0.003) (18).

Fedulov et al. studied serum levels of TGFβ1 and TNFβ in rats with cardiac fibrosis during chronic renal failure. They performed a unilateral nephrectomy and electrocauterization of 25 percent of the cortex of the remnant kidney. The cardiac collagen correlated with both serum TGFβ1 levels and time from onset of follow-up at two, four, and six months (19). Finally, Wong et al. evaluated whether mild and severe renal failure shortens cardiac telomeres and excessively shortens telomeres after MI in rats subjected to sham, unilateral, or 5/6 nephrectomy to induce no, mild, or severe renal failure, and left coronary artery ligation to induce MI. They concluded that severe renal failure, but not mild renal failure, leads to shortening of cardiac telomeres to a similar extent as found after MI, and that renal failure did not induce excessive telomere shortening after MI (20).

Brymon et al. assessed the systemic inflammatory response (defined as the secr haptoglobin level), local inflammation (through use of monocytes chemotactant protein MCP-1 levels), and the arterial response to phlebilephrine in different stages of renal failure. For this purpose they performed a nephrectomy in rats divided into four groups: control, 5/6 nephrectomy, 3/5 nephrectomy, and 5/6 nephrectomy. The investigators found a lower arterial contraction in the 5/6 nephrectomized group. Systemic inflammation was evident in the heart. However, oxidative stress was found in the kidneys of the groups with no evidence in the advanced stages of renal disease. Local inflammation increased progressively with renal failure.

It is clear that inflammation affects smooth muscle cells of the vessels and plays a key role in the final vascular tone (23). We proposed a rat model in three stages: First we performed a 5/6 nephrectomy in the left kidney; a week later, nephrectomy of the contralateral kidney; and finally, a ligature of the coronary artery to achieve mild MI. Sham controls were used in the same technique as treated rats. It would be interesting to study the cardiac arterial wall with different levels of renal insufficiency and with and without myocardial infarction (22,23).

There are three transgenic models in mice: knockout (KO) apolipoprotein E (APOE-/-) mice with accelerated atherosclerosis in uremia (24), KO mice for the LDL receptor (LDL-/-) (25), and AT1 KO mice (26). In the first two models, APOE-/- and LDL-/-, hyperphosphatemia and vascular calcification was found, and animals with chronic renal disease had a worse prognosis. Those treated with bone morphogenetic protein-7 (BMP-7) in the LDL model improved (25).

The third model of Li et al. assessed the molecular pathway mediated by AT1A in cardiac dysfunction and renal dysfunction. They used wild mice and AT1 KO mice. In both cases they performed a 5/6 nephrectomy. The observed effects in the wild type (hypertrophy, dilatation, fibrosis, and a reduction in the capillary density) were significantly less important in the AT1 KO group. The valsalvar treatment in the wild type mice improved the cardiac function to a level as good as that in the AT1 KO group (26).

Increasing evidence links the kidney and the heart through different humoral stimuli. This has not only been proven at an experimental level, but also in day-to-day clinical practice. A better understanding of this tight relationship and consideration of the kidney and the heart as an axis will allow future development of drugs that can interact in such an axis in an integrated way, thus achieving a more rational therapeuticism of the cardiological and renocardiological conditions that affect thousands of patients worldwide. The goal of these experimental models is to find the underlying mechanism enabling improved protection for both kidneys and heart.

References