

My early studies were the first to demonstrate that superimposition of atherosclerosis on renal artery stenosis, as occurs in human atherosclerotic renovascular disease, amplifies renal injury compared to each insult alone. Using a combination of novel and powerful in vivo and in vitro imaging techniques on a unique swine model of renovascular disease (RVD, induced by renal artery stenosis), these studies demonstrated that co-existence of renal hypoperfusion and atherosclerosis synergistically deteriorates renal function, increased inflammation, and accelerates renal scarring by decreasing extracellular matrix turnover. These pathological events were largely mediated by increased oxidative stress, as my subsequent studies blocking the oxidative stress pathway demonstrated a renoprotective effect of targeted antioxidant interventions.

Chronic RVD in humans is characterized by hypertension, glomerulosclerosis, tubulo-interstitial fibrosis and tubular atrophy, arteriolar hyalinosis and deterioration of renal function. We have developed and characterized a novel swine model of RVD. By implanting a local irritant coil in the main artery, renal artery stenosis develops gradually and mimics the renal injury found in humans. Moreover, we have developed unique physiological imaging techniques using multi-detector computerized tomography (MDCT) to non-invasively measure renal regional volume, total renal blood flow (RBF), glomerular filtration rate (GFR), tubular dynamics, and endothelial function, and micro-CT to study the 3D architecture of the renal microcirculation in situ. These techniques allow us to serially follow the time course of the deterioration of the stenotic kidney with previously unavailable accuracy.

Intra-renal microvascular disease in RVD likely precedes the onset and represents the silent phase of ischemic renal disease, and as the damage of the renal parenchyma progresses, the injury evolves towards a point of no return. The extent of damage of the intra-renal microcirculation may explain why the stenotic kidney does not always restore its function, and sometimes even continues to deteriorate after revascularization in up to 70% of the patients. More recently, I focus my attention on the chronically obstructed kidney to understand the mechanisms that are activated by chronic reduction in blood flow. My studies have shown for the first time that the stenotic kidney has a significant reduction in cortical microvascular density. This reduction in the renal microcirculation contributes to renal functional deterioration and tissue injury in the stenotic kidney, as I have demonstrated that by promoting neovascularization, the chronically obstructed kidney significantly improves. Current efforts in my laboratory are devoted to discovery and development of novel therapeutic strategies to protect the renal microcirculation and recover renal function in RVD and, potentially, other forms of acute and chronic renal disease frequently observed in humans.

The sequence of events and the mechanisms by which renal functional and structural injury in RVD becomes irreversible are unclear. Understanding those mechanisms, identifying markers and using targeted interventions could have important ramifications to identify those patients who will benefit from revascularization and other available treatments for RVD. My goal is to contribute to not only the understanding of the pathophysiology of this disease, but also to determine the feasibility of new treatments to recover the kidney in a manner potentially applicable to humans.