Markers of reactive oxygen species (ROS) increase in most of the common diseases encountered in the second half of life but the roles of individual ROS, and therefore the selection of a suitable therapeutic target, remain unclear. ROS normally mediate or reinforce renal afferent arteriolar contractions with increased blood pressure (myogenic response), thereby protecting the kidney from hypertensive damage (barotrauma). It was therefore surprising to find impaired or absent myogenic contractions and loss of renal autoregulation in mice with the high salt/reduced renal mass model of chronic kidney disease despite extreme elevations of renal and afferent arteriolar ROS. Equally perplexing was the finding that prevention of oxidative stress in these mice by long term administration of a redox cycling nitroxide preserved myogenic responses and protected the kidneys despite unchanged BP. This lecture will describe our studies that have investigated this conundrum.