## SIGNIFICANCE STATEMENT

Ischemia-reperfusion injury (IRI) is an important risk factor for progressive renal failure. This study characterized modes of regulated cell death post-IRI over time in tubular and microvascular compartments and their relative importance in renal fibrosis. Using unilateral renal artery clamping in caspase-$3^{-/-}$ mice, we show that caspase-3 is an important regulator of microvascular injury and rarefaction post-IRI. We also report that caspase-3 activation operates as an acute death pathway in tubular epithelial cells. In the long term, however, absence of caspase-3 led to reduced tubular hypoxia, preserved tubular integrity, and reduced renal fibrosis. Collectively, these results highlight the predominant importance of microvascular over epithelial injury in renal fibrosis post-IRI, and identify caspase-3 as a novel regulator of microvascular rarefaction and renal fibrosis.