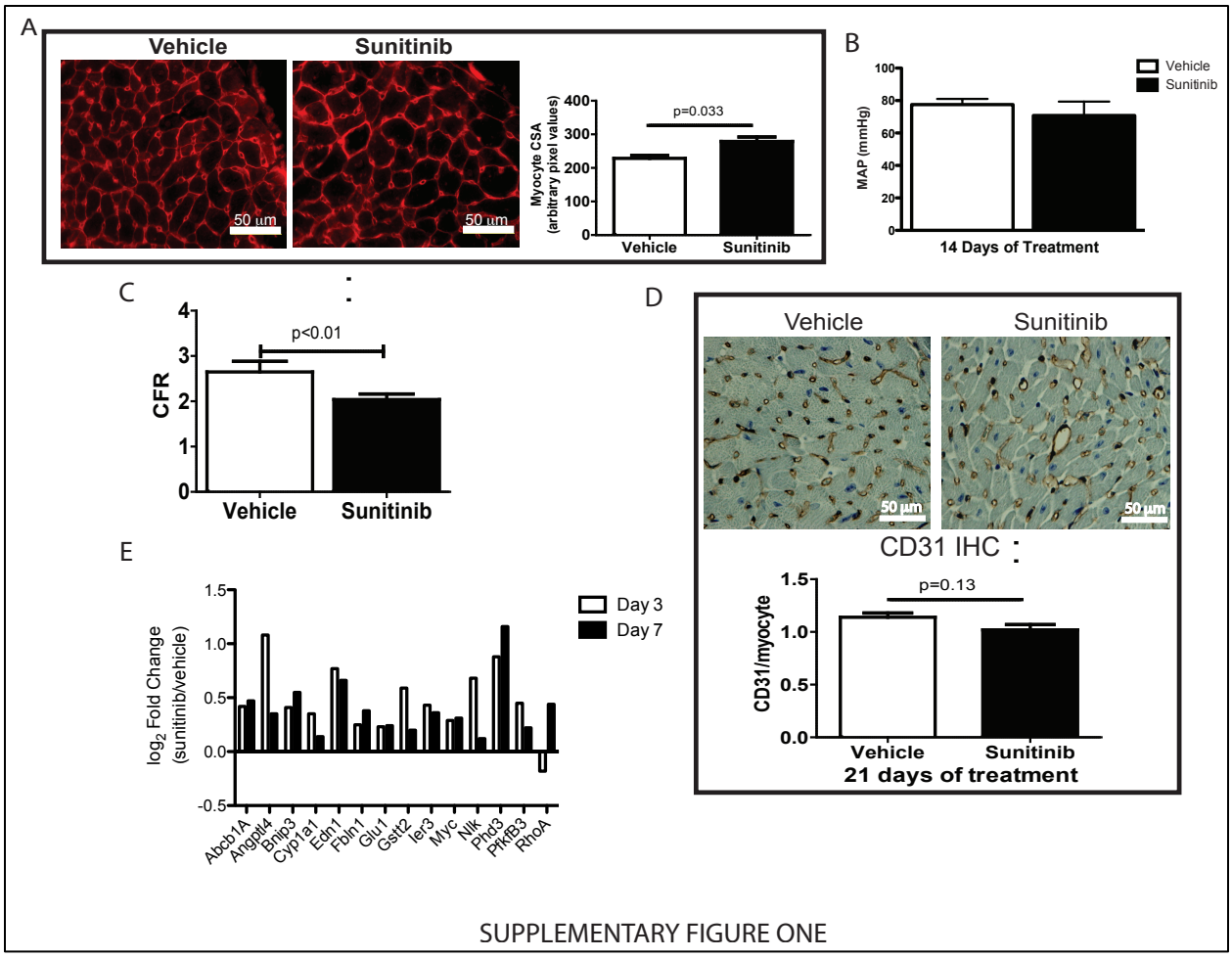
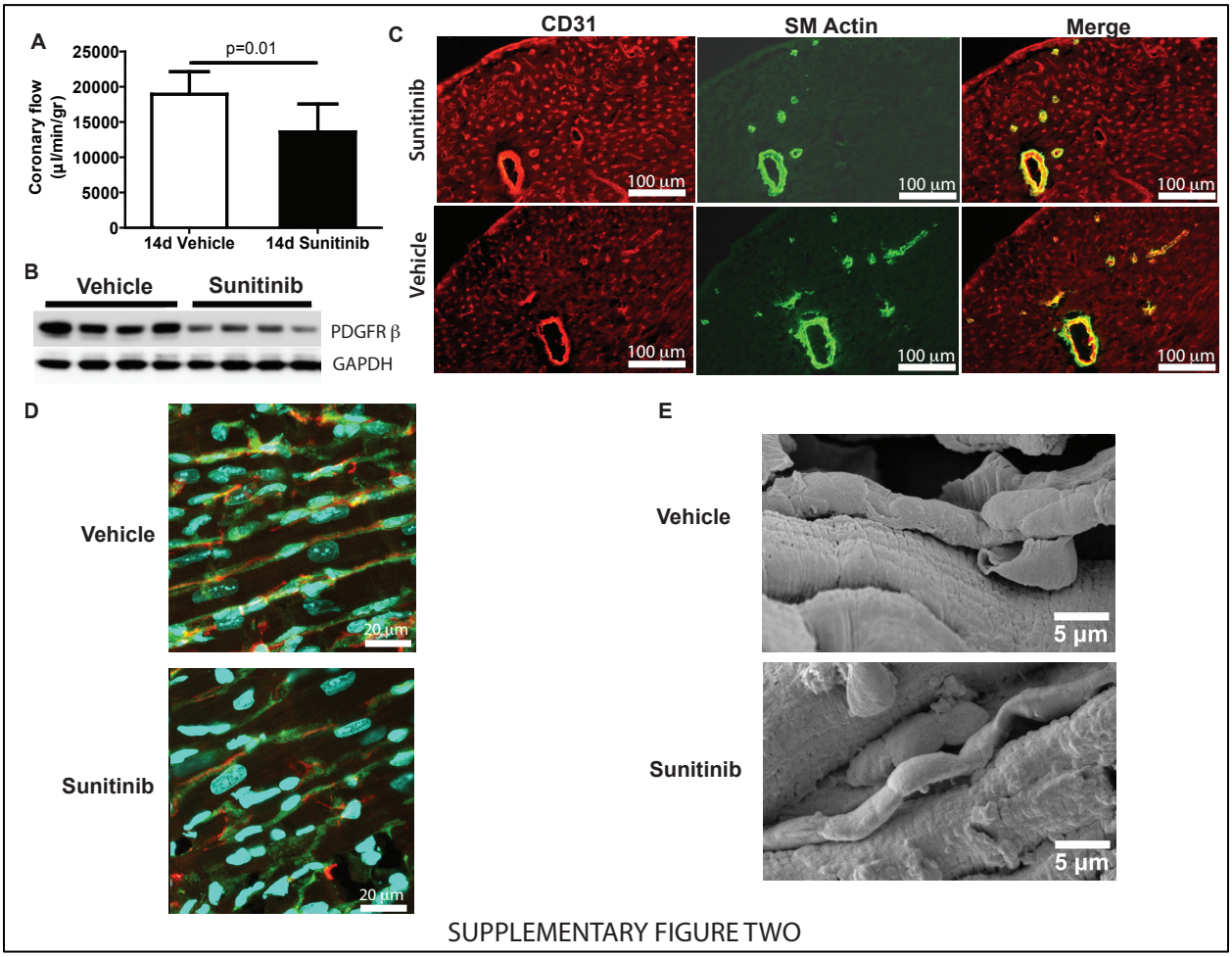
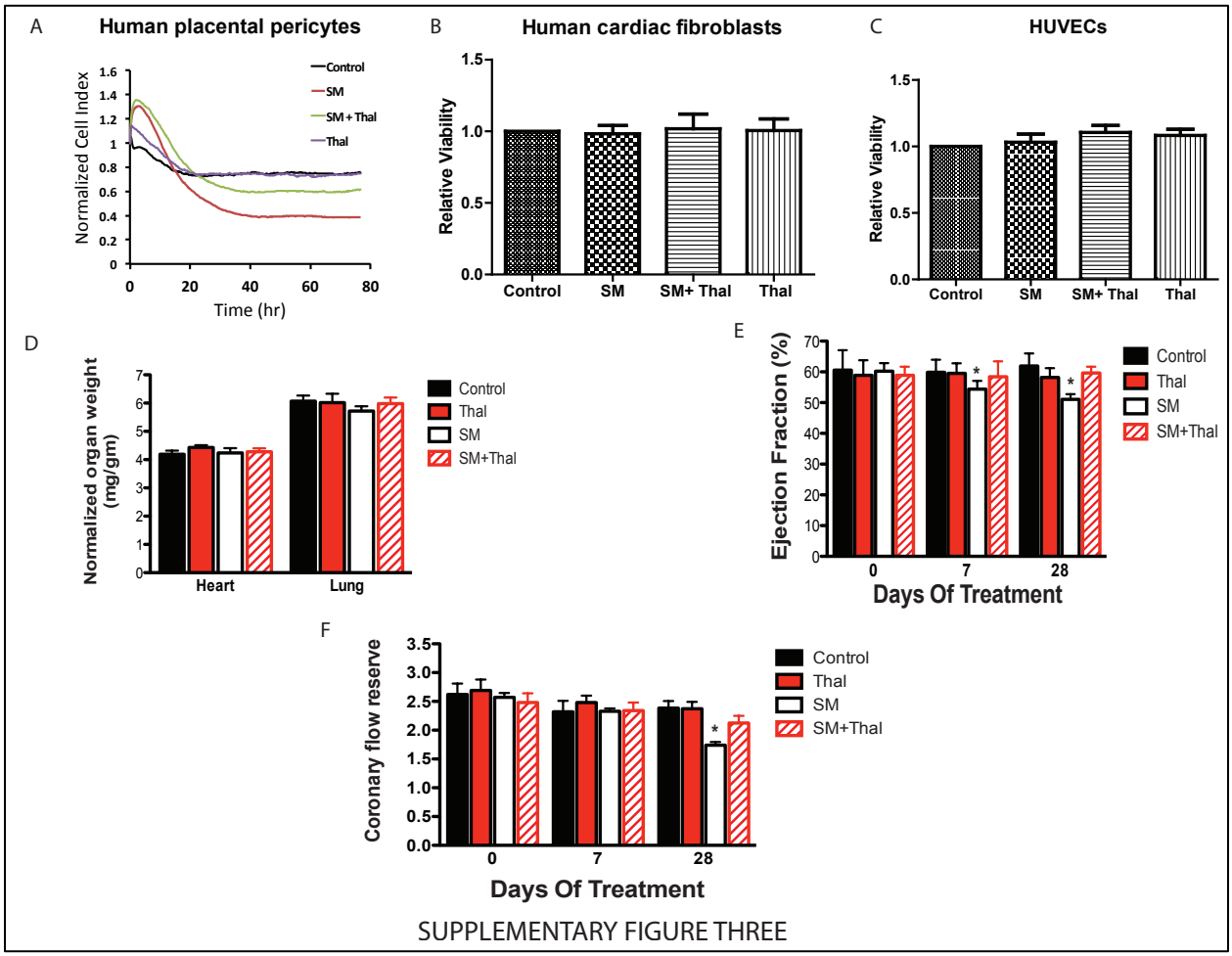


Supplementary Figure 1. Sunitinib treatment induces coronary microvascular dysfunction and cardiac dysfunction. (A) Left: Confocal images of heart sections from mice treated with sunitinib or vehicle for 14 days, stained with lectin-TRITC for visualization of myocyte borders. Right: quantification of average cardiomyocyte cross-sectional area (CSA). Scale bar = 50 μm. (B) Mean arterial pressure (measured by Millar pressure catheter in the ascending aorta) after 14 days of sunitinib (40 mg/kg/d) or vehicle treatment (n=7-8 mice per group). (C) Coronary flow reserves in response to adenosine in mice treated with sunitinib or vehicle for 14 days (n=8-10 mice per group). (D) Top: Representative photomicrographs of immunohistochemical staining for CD31 in cardiac sections from mice treated with sunitinib or vehicle for 21 days. Bottom: Quantification of coronary vessel density in the heart after treatment with sunitinib or vehicle for 21 days (n=4 mice per group). Scale bar = 50 μm. (E) Fold change in cardiac expression of selected genes associated with hypoxia in hearts from sunitinib-treated mice relative to vehicle control. The genes presented are identified using a false discovery rate of 10%. Data derived from Affymetrix microarray platform, n= 4 mice per group.



Supplementary Figure 2. Sunitinib causes loss of pericyte coverage in mouse hearts. (A) Total coronary flow in response to acetylcholine in sunitinib or vehicle-treated mice as measured by Langendorff ex-vivo perfusion method. (B) Western blot demonstrating total PDGFRβ and GAPDH protein concentrations in cardiac lysates from mice treated with vehicle or sunitinib for 14 days. (C) Confocal images of heart sections from mice treated with either sunitinib or vehicle control showing staining with anti-CD31 (red) and anti-smooth muscle alpha actin (green). Scale bar = 100 µm. (D) Confocal micrographs from representative long-axis cardiac sections showing staining for CD31 (green) and NG2 (red), from mice treated with sunitinib (bottom panel) or vehicle (top panel) for a total of 14 days. Scale bar = 20 µm. (E) Representative gray-scale scanning electron micrographs of the cardiac microvasculature from mice treated with vehicle or sunitinib for 14 days. Scale bar = 5 µm. (F) Representative confocal micrographs of cardiac sections from hearts of mice treated with sunitinib or vehicle for 14 days, then perfused with 0.9 kDa cadaverine conjugated to Alexa Fluor-555 . (G) Western blot of skeletal muscle lysates from sunitinib-treated or vehicle-treated mice, probed for NG2, PDGFRβ, or GAPDH.



Supplementary Figure 3: Thalidomide blocks sunitinib-induced pericyte cytotoxicity in vitro and cardiac and coronary microvascular dysfunction in vivo. (A) Real time pericyte viability assay in the presence of vehicle, thalidomide (Thal), sunitinib (SM) or sunitinib+thalidomide (SM + Thal) for 3 days. Cell viability relative to vehicle-treated control, measured by MTT assay, in human cardiac fibroblasts (B) or human umbilical vein endothelial cells (HUVEC, C) treated with SM, Thal, or SM + Thal for 24 hours under serum-starved conditions. (D) Organ weight normalized to body weight (mg/gm) in vehicle, Thal, SM, or SM + Thal treated tumor-bearing mice after 28 days (n=6-10 animals per group). (E) Left ventricular ejection fraction in vehicle, Thal, SM or SM + Thal treated tumor-bearing mice at day 0, 7 and 28 (n=6-10 animals per group). (F) Coronary flow reserves in vehicle, Thal, SM or SM + Thal treated tumor-bearing mice at day 0, 7 and 28 (n=6-10 animals per group). * $p < 0.05$.