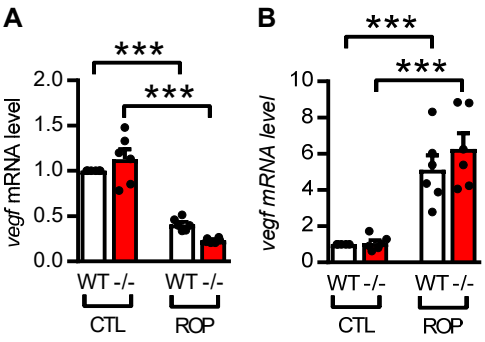
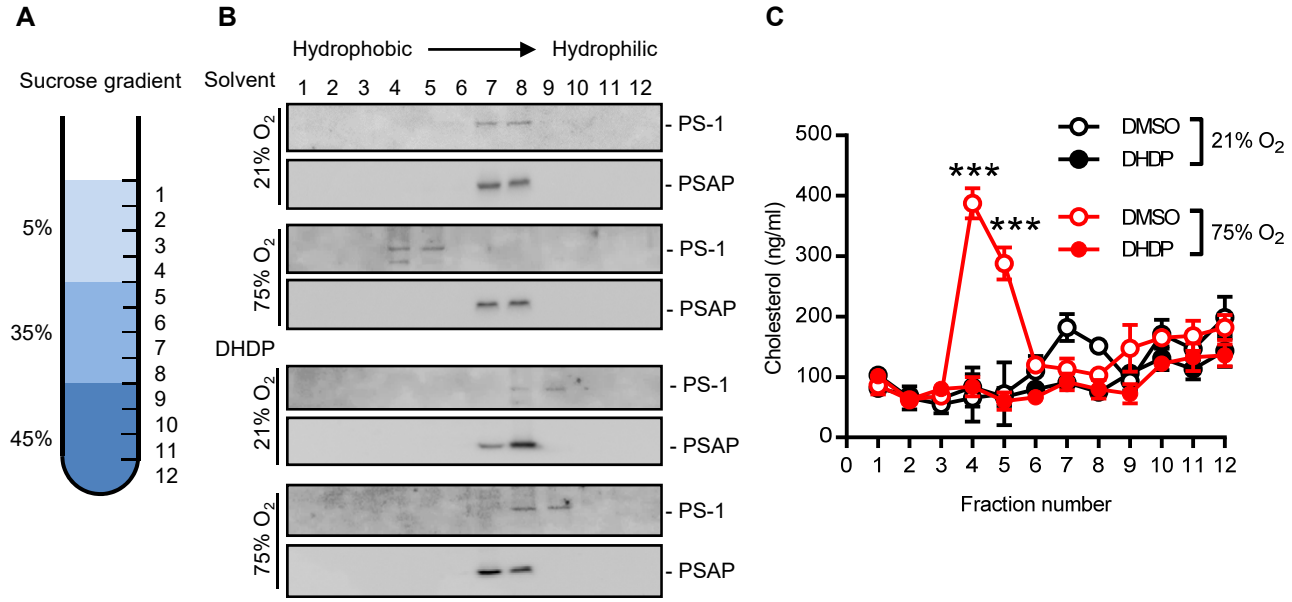
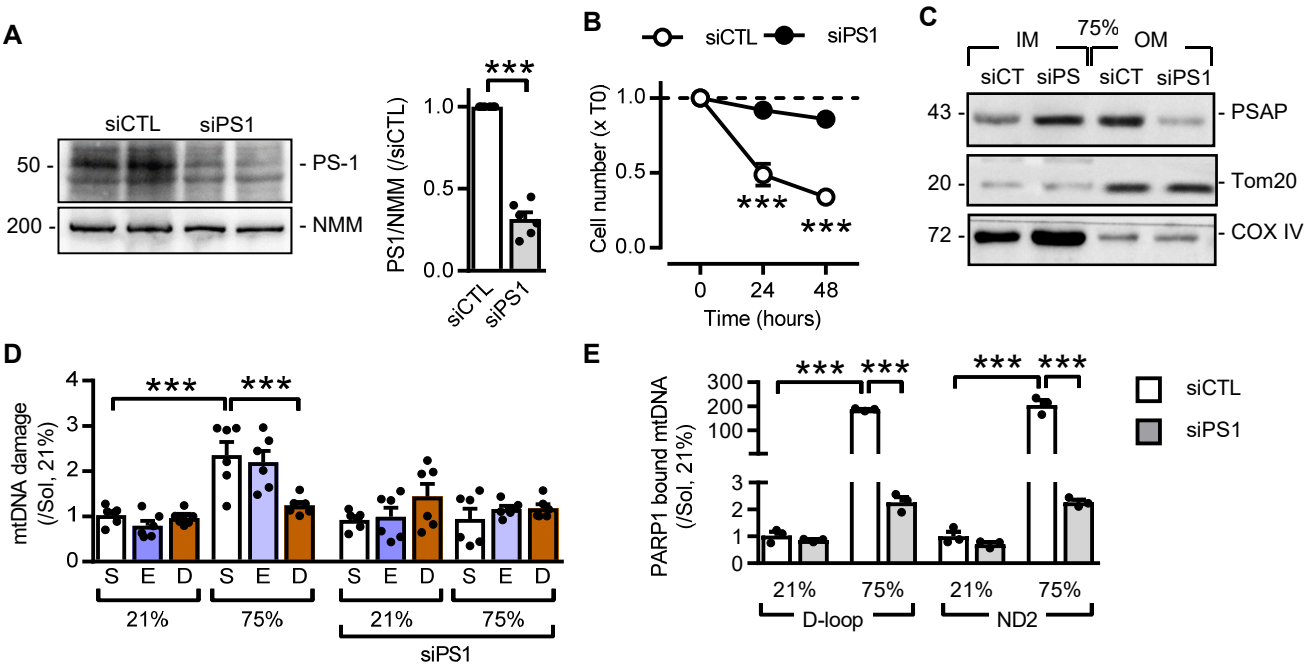


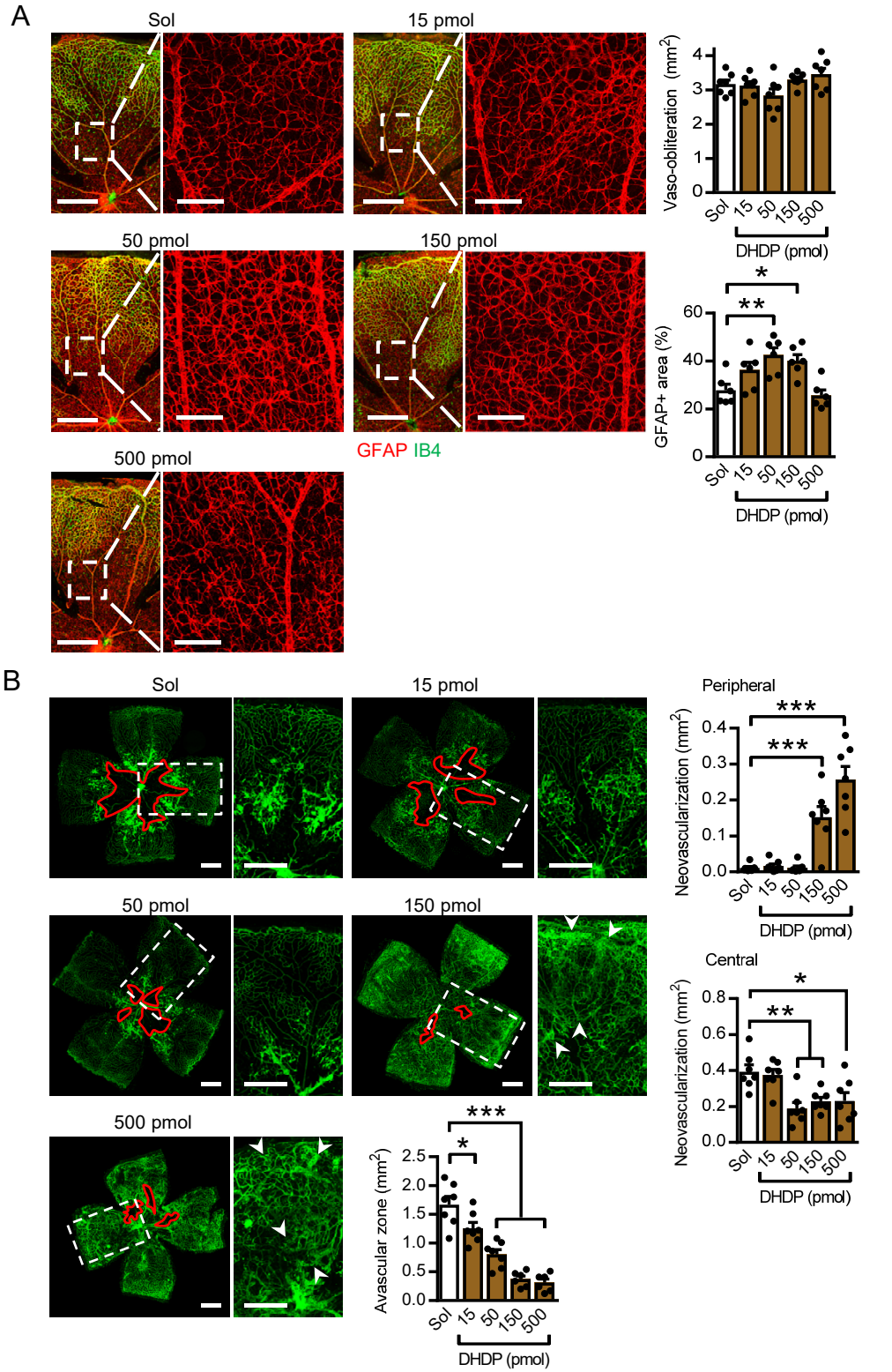
Supplementary Fig. 1. **Retinal VEGF levels in ROP**. Wild-type (WT) and sEH$^{-/-}$ (-/-) mice were subjected to the ROP and retinas were isolated on (**A**) P8 and (**B**) P14. n=6 animals per group (two-way ANOVA & Tukey's multiple comparisons test), ***P<0.001.



Supplementary Fig. 2. Changes in PS-1 localization induced by hyperoxia in cholesterol enriched domains of intact mitochondria. HEK-239 cells were treated with solvent (0.03% DMSO), 19,20-EDP (3 μM) or 19,20-DHDP (3 μM) and exposed to 21% or 75% O_2 for 24 hours in the presence of an sEH inhibitor. Mitochondria were isolated and processed to sucrose gradient centrifugation. (**A**) Composition of sucrose used in the experiment. (**B**) Distribution of PS-1 and PSAP in the different sucrose fractions after centrifugation; n=3 independent experiments. (**C**) Cholesterol levels in different sucrose fractions after centrifugation; n=3 independent experiments (two-way ANOVA & Tukey's multiple comparisons test). *P<0.05, **P<0.001.



Supplementary Fig. 3. Effect of PS1 downregulation on cell number and mitochondria. Astrocytes from wild-type mice were treated with control oligonucleotides (siCTL) or siRNA directed against PS1 (siPS1) for 36 hours and cultured in the presence of 21% or 75% O_2 up to 48 hours. (**A**) Effectiveness of the siRNA-mediated downregulation of PS1, n=6 independent experiments (Students t-test). (**B**) Astrocyte numbers, n=4 different cell batches (Two way Anova, Tukey). (**C**) Immunoblot showing PSAP localization in the outer (OM) and inner (IM) mitochondrial membrane from astrocytes exposed to 75% O_2 for 24 hours, comparable results were obtained in 4 independent experiments. COX IV and Tom20 were used as markers for the IM and OM, respectively. (**D**) mtDNA damage in astrocytes treated with solvent (S), 19,20-EDP (E; 100 µM) or 19,20-DHDP (D; 100 µM) and either maintained under normoxic (21% O2) or hyperoxic (75% O2) conditions for 24 hours, n=6 independent experiments (Three way Anova, Bonferonni). (**E**) Fold enrichment of the D-Loop and ND-2 domains of mtDNA bound to cleaved PARP1 in astrocytes treated with either control oligonucleotides or siRNA against PS1 and exposed to 21% or 75% O_2 for 24 hours, n=3 independent cell batches, each in duplicate (two-way ANOVA, Tukey's multiple comparisons test). *P<0.05, **P<0.01, ***P<0.001.



Supplementary Fig. 4. Effect of different concentrations of 19,20-DHDP on the vascularization of the wild-type murine retinas. Wild-type mice were treated with a bolus of solvent (Sol, 1% DMSO) or different doses of 19,20-DHDP (15, 50, 150 or 500 pmol) on P7 before moving to hyperoxia. (**A**) Astrocyte scaffold (GFAP) and endothelial cell (Isolectin B4) coverage in retinas isolated on day 8 after 24 hours in hyperoxia. Bars = 500 µm in the whole mounts and 100 µm for the close up images; n=7 animals per group (ANOVA, Bonferroni). (**B**) Vascularization (Isolectin B4) in retinas isolated on day 17 i.e. after 5 days in room air. The red lines highlight the border of avascular region. Arrows indicate abnormal vessel morphology after high dose DHDP treatment. Bars = 500 µm in the whole mounts and 100 µm for the close up images; n=7 animals per group (ANOVA, Bonferroni). *P<0.05, **P<0.01, ***P<0.001.