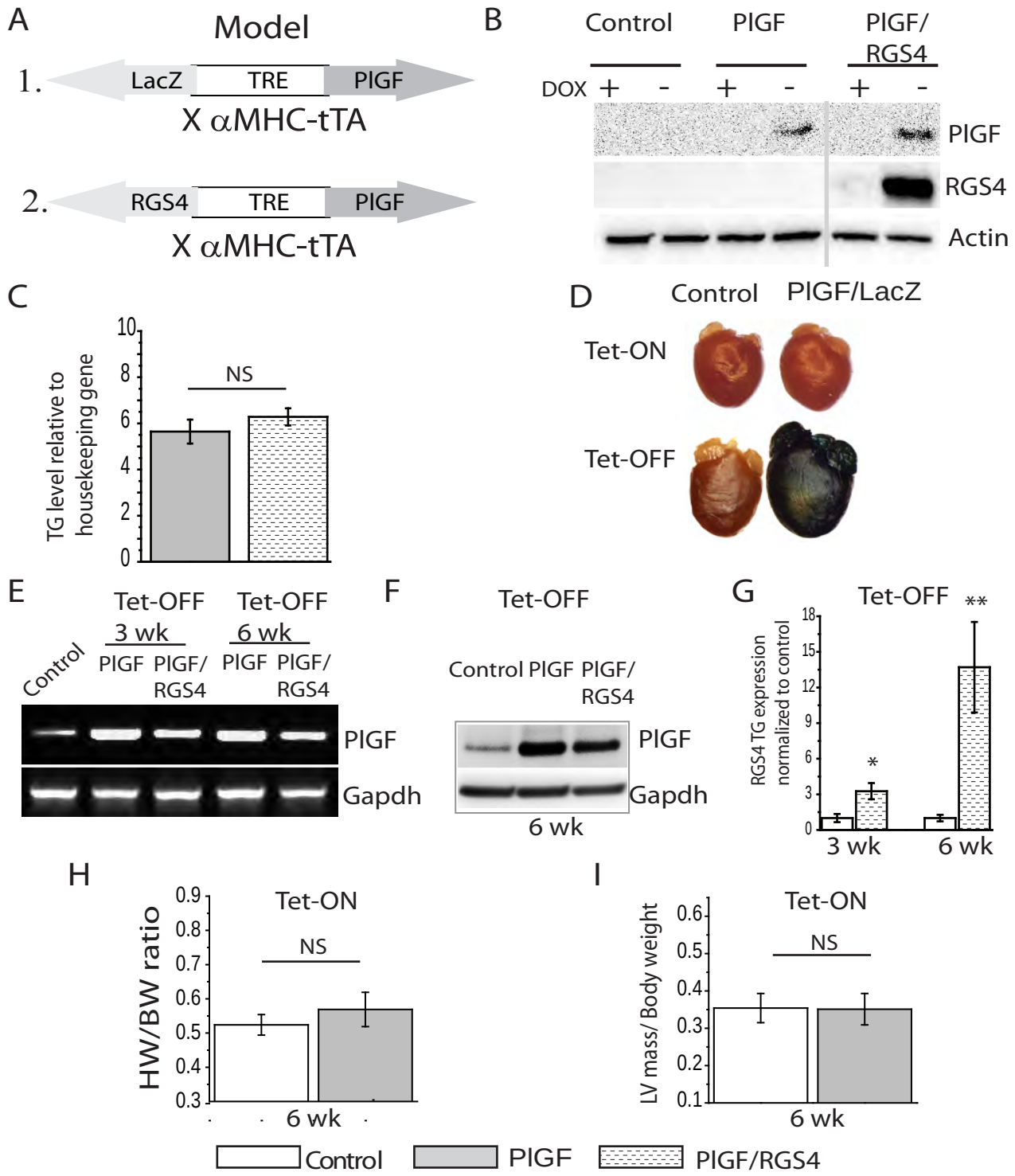
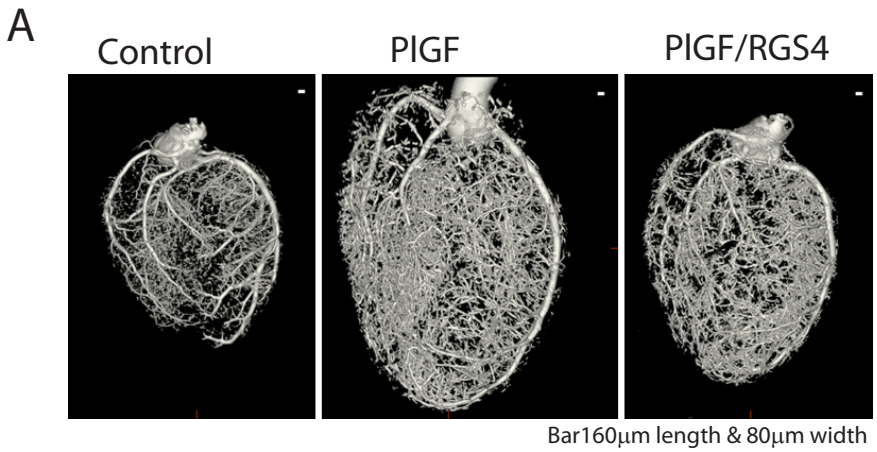
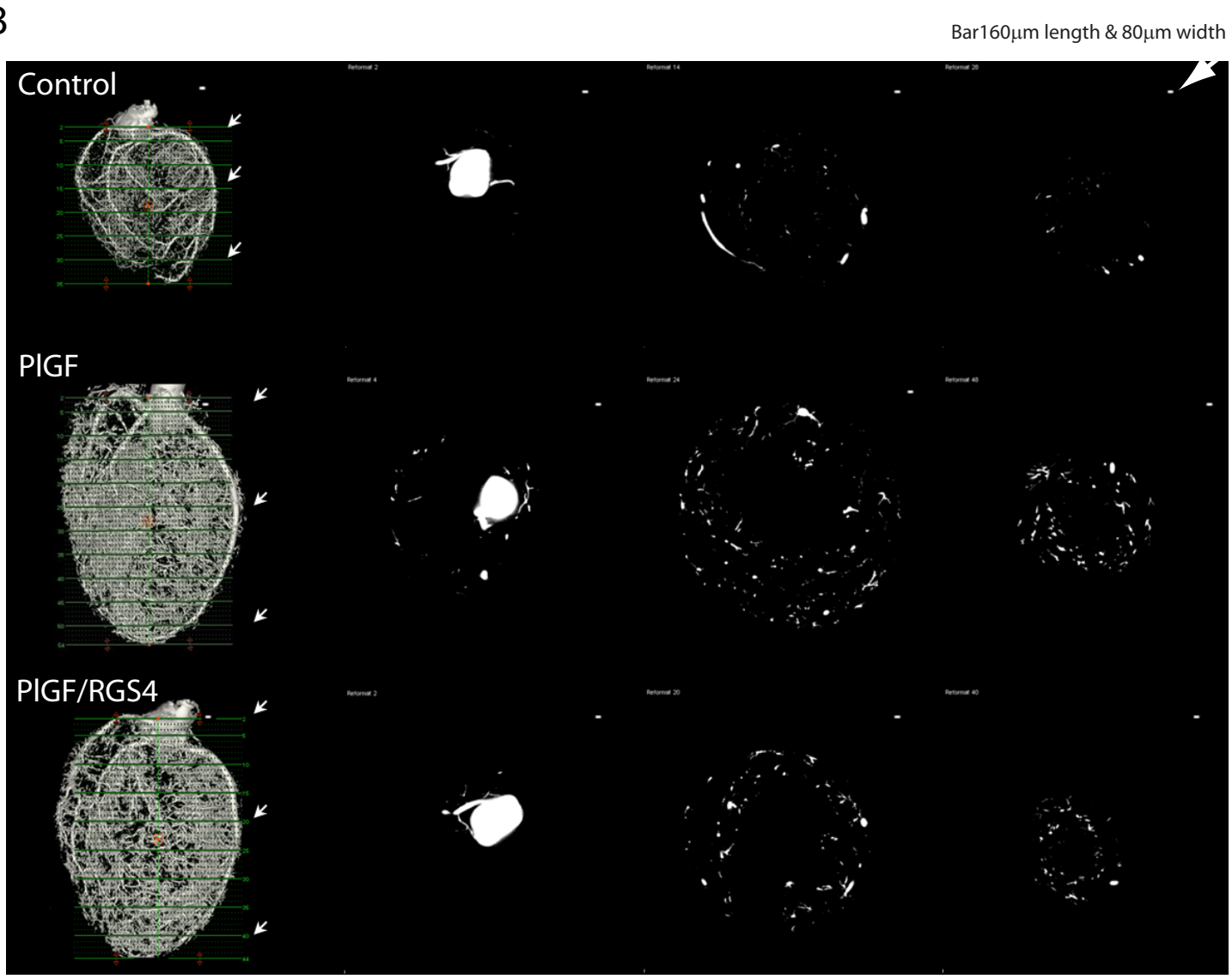
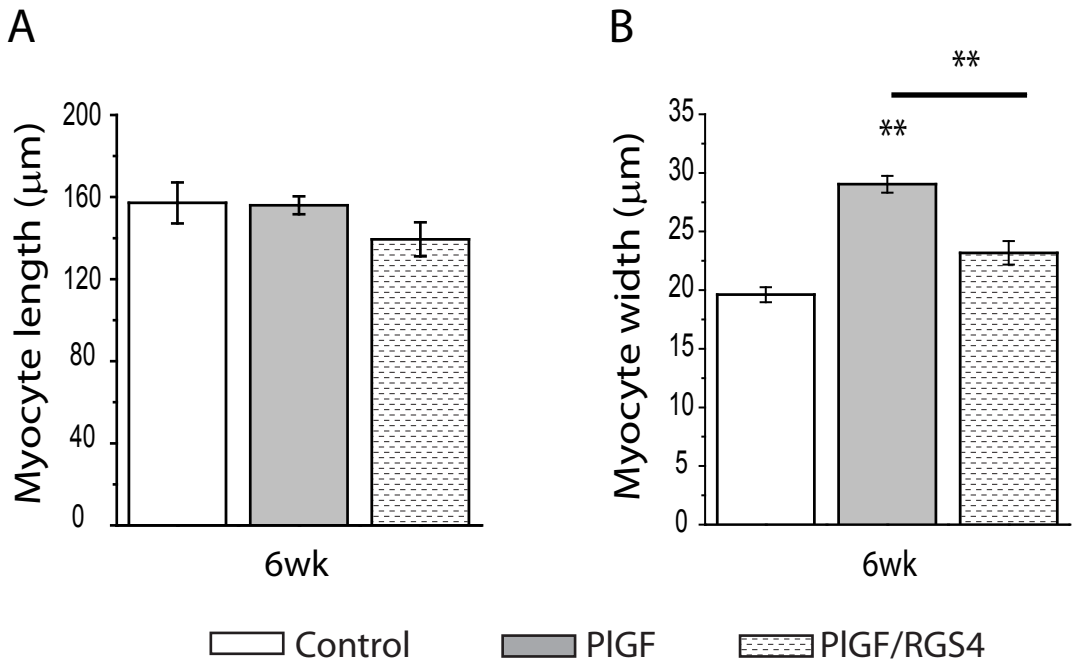


Supplementary Figure 1. PlGF and PlGF/RGS4 inducible mouse models. (A) Design of PlGF/LacZ and PlGF/RGS4 inducible bidirectional tetracycline responsive (TRE-promoter) constructs. (B) TRE-PlGF/LacZ and TRE-PlGF/RGS4 induced expression in MEF/3T3 Tet-OFF cells in the absence of doxycycline (western blot analysis for PlGF and RGS4 expression). (C) PlGF and PlGF/RGS4 transgene level in PlGF and PlGF/RGS4 mice, respectively, as determined by real-time PCR based genotyping (Transnetyx, Inc.); n=50 mice/group. Note similar level of transgene relative to the housekeeping gene indicating a relatively equal transgene copy number for both conditional mouse models. (D) Representative example of PlGF induced mice: upper panel before induction (Tet-ON); lower panel after 6 weeks induction (Tet-OFF). Note homogenous expression of LacZ transgene as demonstrated by X-Gal staining (blue) of the entire heart in Tet-OFF and no staining in Tet-ON. (E) Increased PlGFmRNA expression at 3 and 6 weeks in PlGF and PlGF/RGS4 mice compared with control mice, as determined by RT-PCR. (F) Increased PlGF expression at 6 weeks in PlGF and PlGF/RGS4 mice (western blot analysis). (G) Increased RGS4 transgene mRNA expression in PlGF/RGS4 mice at 3 and 6 weeks compared with controls, as determined by qPCR; n=6 mice/group. (H) Heart weight/Body weight ratio and (I) LV mass/Body weight ratio in PlGF mice (littermates of PlGF mice induced by doxycycline withdrawal) continuously fed with doxycycline including the 6 weeks stimulation period. n=4 mice/group. NS - not significant; *p<0.05, **p<0.01 vs. control.

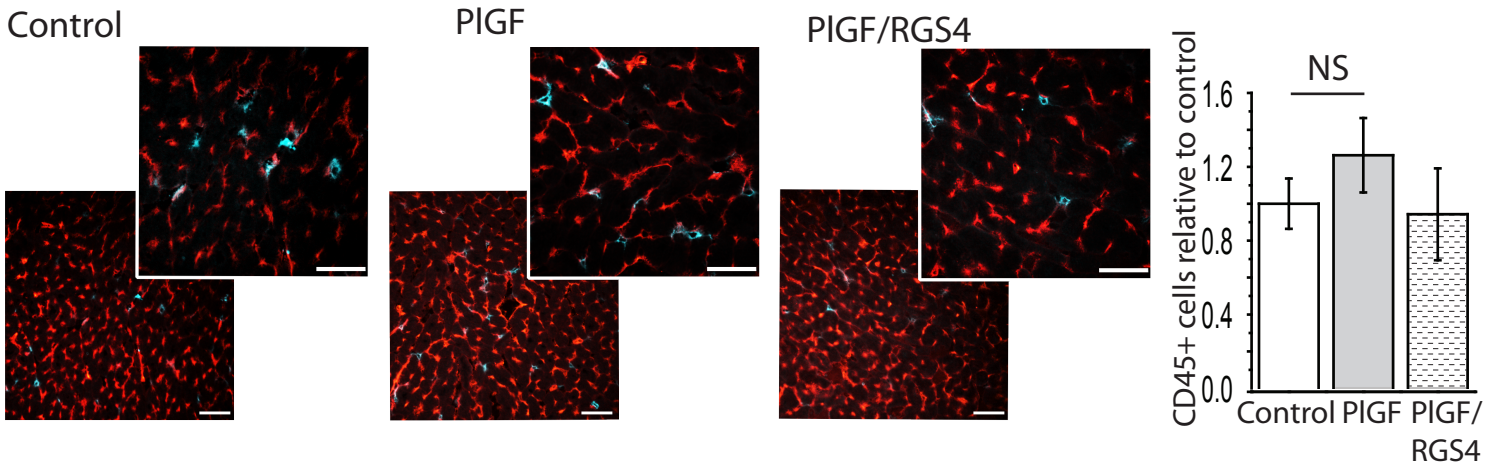




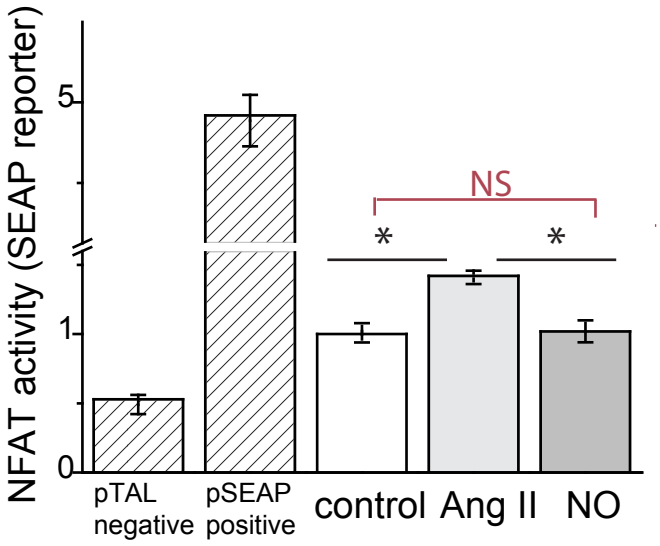
Supplementary Figure 2. Cardiac vasculature assessed by micro-CT. (A) Micro-CT angiograms after 6 weeks of PlGF or PlGF/RGS4 transgene expression compared with control. (B) Homogenous distribution of vascular structures in the myocardium in 2D microCT sections in PlGF and PlGF/RGS4 mice at 6 weeks. Representative images at three comparable levels.



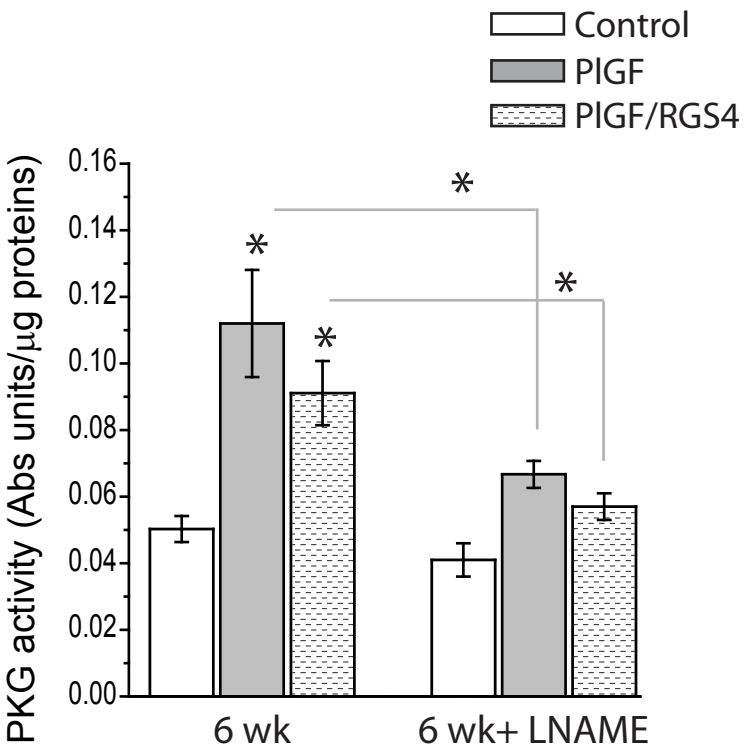
Supplementary Figure 3. Myocyte length (A) and width (B) characteristics in PlGF and PlGF/RGS4 mice at 6 weeks. *Note the increase in myocyte thickness in PlGF mice as compared with PlGF/RGS4 or control mice.* n=80-180 per group; ***p*<0.01 vs. control or as indicated.



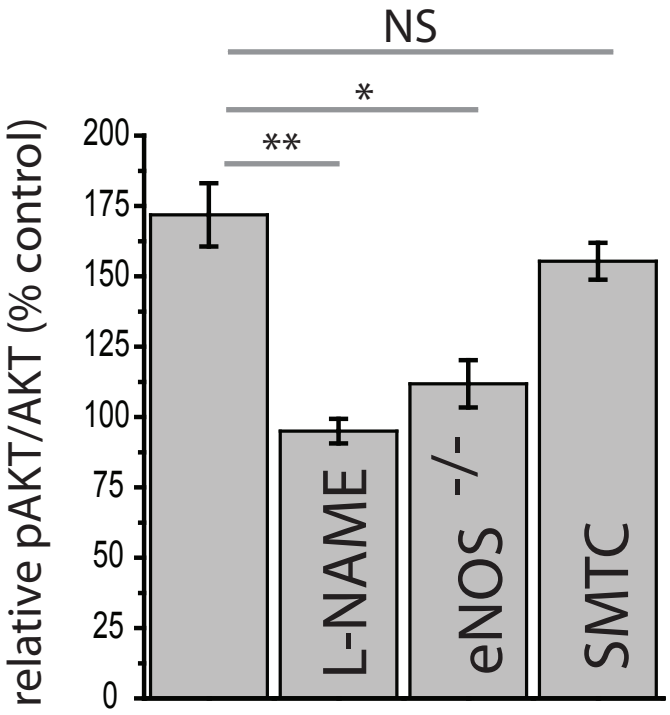
Supplementary Figure 4. CD45^{+} cell recruitment in the heart after 6 weeks of transgene stimulation. Representative immunostaining of LV myocardium with specific antibodies against CD45 and CD31. Bar 50 µm. *Note no recruitment of CD45^{+} cells in the heart in PlGF or PlGF/RGS4 mice at 6 weeks compared with control mice (histogram)*. NS- not significant.



Supplementary Figure 5. NFAT promoter activity determined with SEAP (secreted alkaline phosphatase) reporter in NO-treated versus AngII-treated or untreated cells, after 24 hr. *p<0.05, vs. control or NO-treated cell. NS- not significant.



Supplementary Figure 6. PKG activity in PlGF and PlGF/RGS4 mice at 6 weeks with and without L-NAME treatment. n=6-14 per group; *p<0.05 vs. control or as indicated.



Supplementary Figure 7. The level of Akt phosphorylation at Ser 473 determined as pAkt /Akt ratio in western blots in PlGF mice: untreated, L-NAME-treated, $eNOS^{-/-}$ background and SMTC treated, relative to their appropriate controls. n=4-6 per group. * $p<0.05$, ** $p<0.01$.

Supplementary Table 1. Heart rates for untreated, L-NAME-treated, SMTC-treated and eNOSKO mice. No significant differences were found between groups.

	Heart Rate	
Control	463.4 ± 18.04	n=24
PlGF	495.5 ± 13.25	n=24
L-NAME-treated control	493.7 ± 22.07	n=9
L-NAME-treated PlGF	500.9 ± 20.68	n=8
eNOSKO control	423.7 ± 22.75	n=7
PlGF-eNOSKO	421.8 ± 44.32	n=5
SMTC-treated control	449.2 ± 18.62	n=5
SMTC-treated PlGF	454.4 ± 41.02	n=7