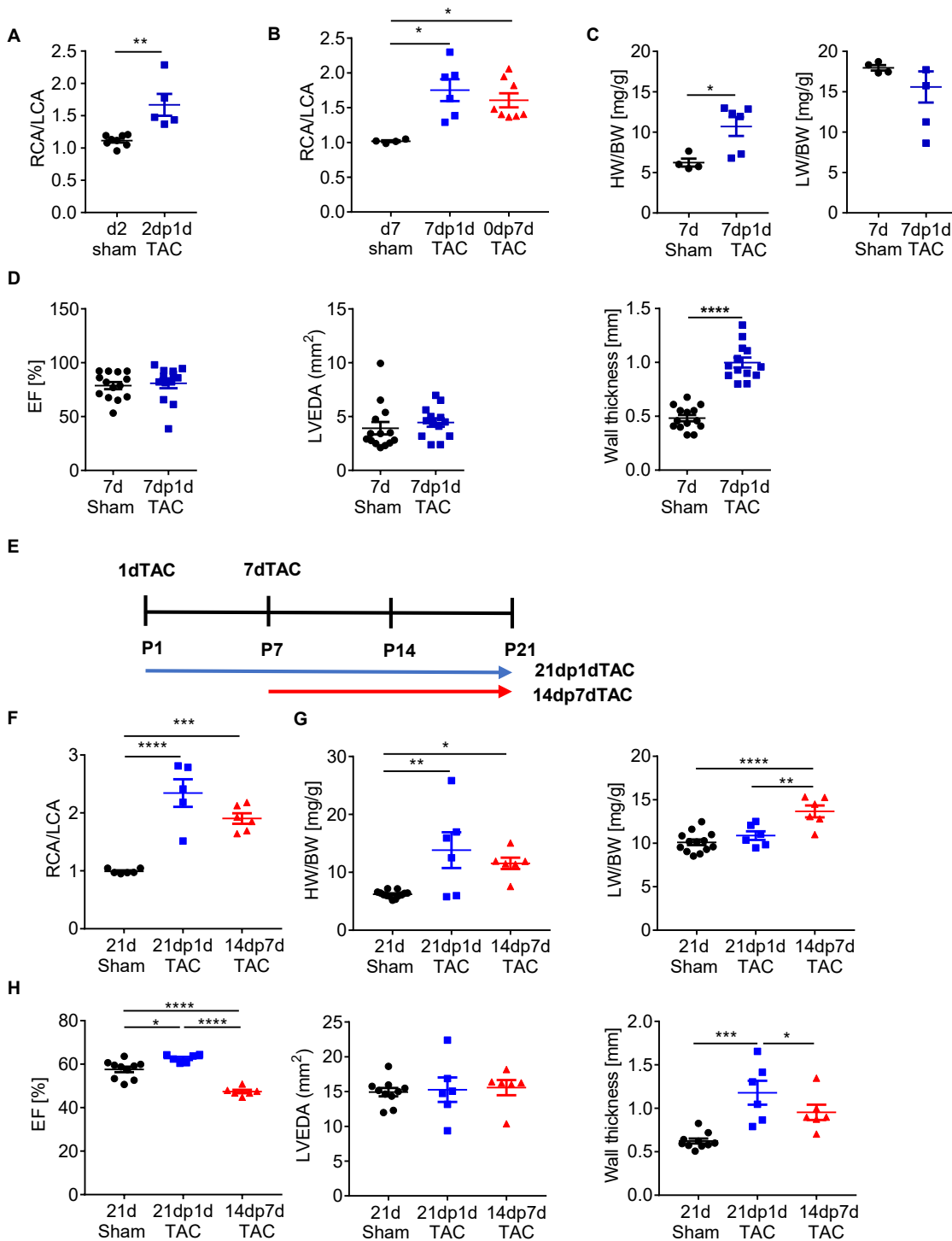
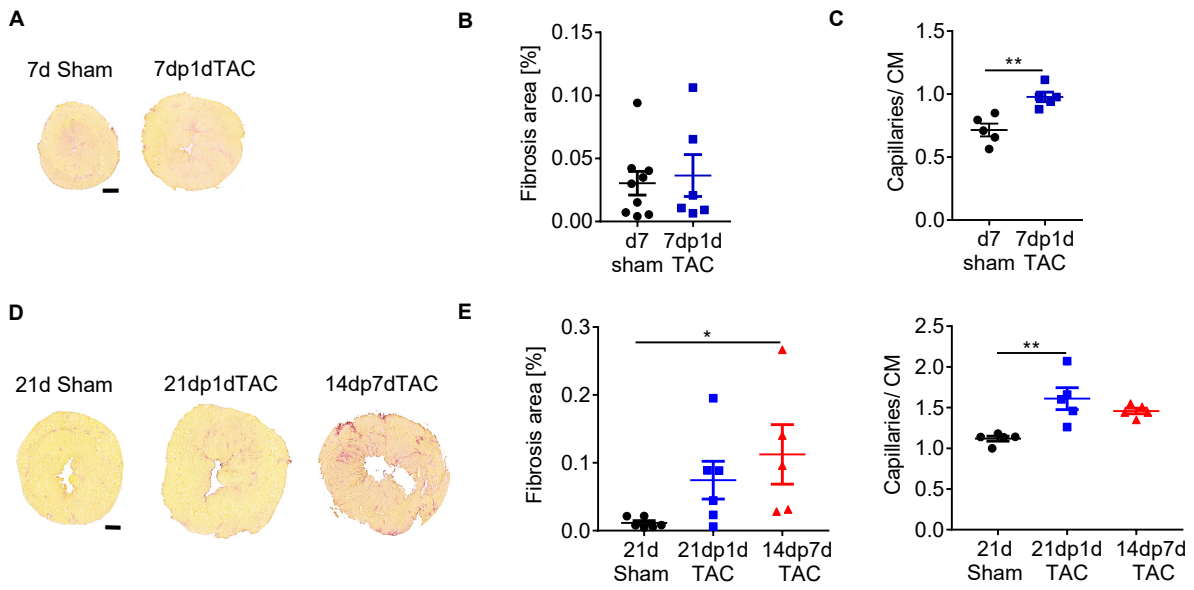


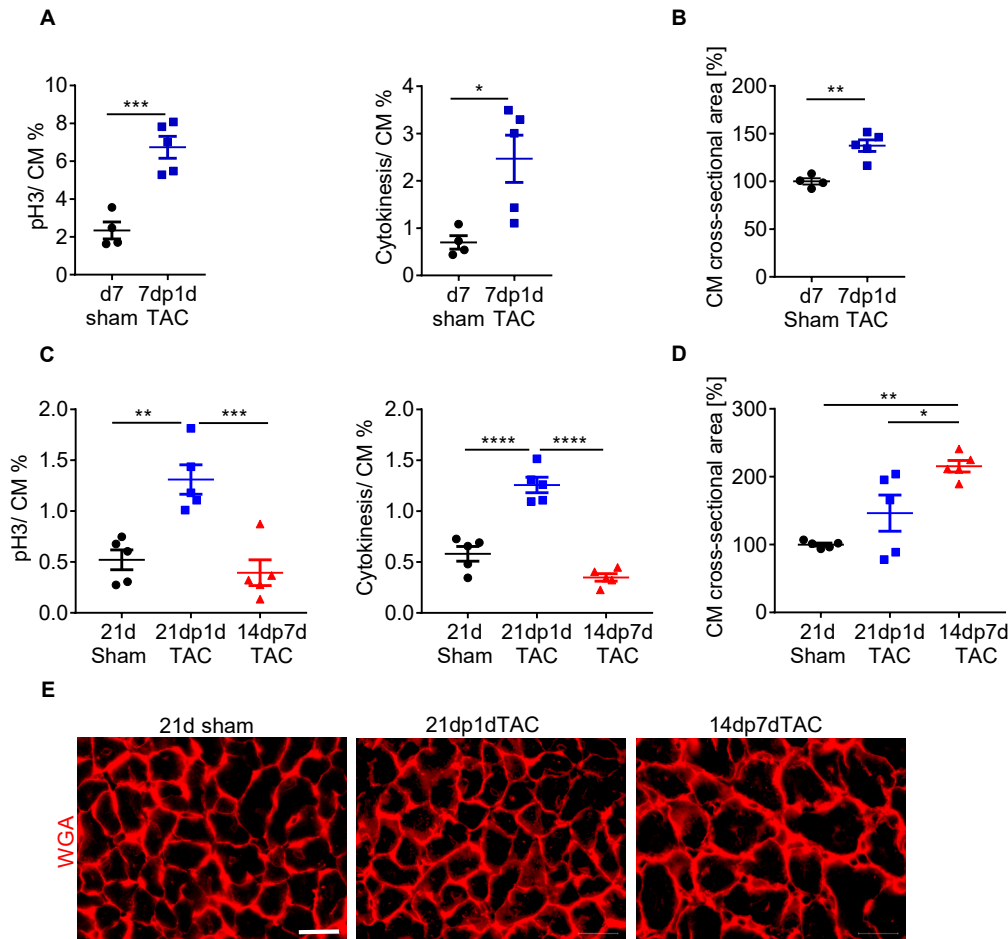
Supplemental Data



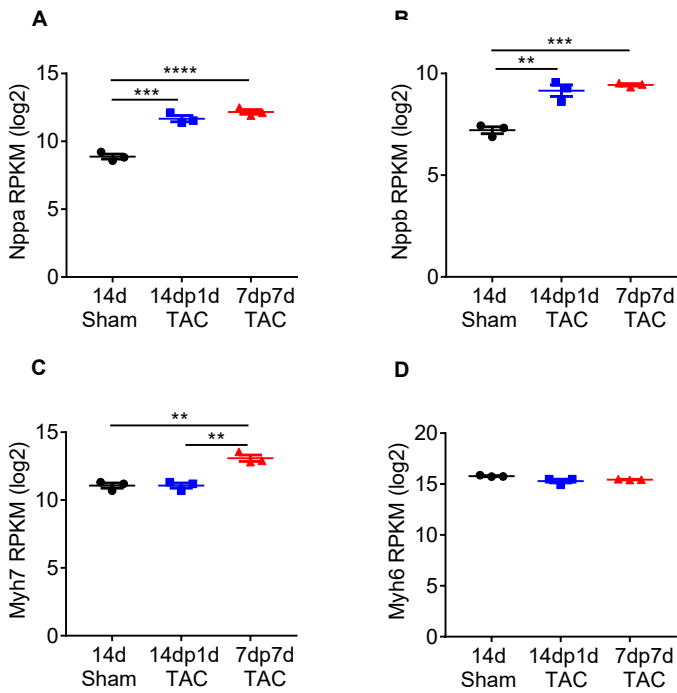
Supplemental Figure 1. Pressure overload in 1-day-old mice does not change the ejection fraction, but increases wall thickness 7 and 21 days after nTAC. (A-B) Flow velocity ratio of the right common carotid artery (RCA) to left common carotid artery (LCA) two and seven days after nTAC in 1-day-old mice and immediately after nTAC in 7-day-old mice as well as in corresponding sham mice; n=8, 2d sham; n=5, 2dp1dTAC; n=4, 7d sham; n=6, 7dp1dTAC and n=8, 0dp7dTAC. ***p*<0.005 and **p*<0.05 (unpaired t test and Kruskal Wallis test/Dunn's multiple comparisons test). (C) Heart weight to body weight ratio (HW/BW) and lung weight to body weight ratio (LW/BW) seven days after nTAC in 1-day-old mice; n=4, 7d sham; n=6, 7dp1dTAC; unpaired t test **p*<0.05 (D) Ejection fraction (EF), left ventricular end-diastolic area (LVEDA) and wall thickness measured by echocardiography seven days after nTAC in 1-day-old mice and sham; n=14, sham 7d; n=13 TAC 7d. Mann-Whitney test and unpaired t test *****p*<0.0001 (E) schematic representation of nTAC induced in 1-day-old mice for 3 weeks and in 7-day-old mice for 2 weeks. (F) RCA/LCA flow velocity ratio 14 days after nTAC in 7-day-old (14dp7dTAC), 21 days after nTAC in 1-day-old mice (21dp1dTAC) and 21d sham; n=6, 21d sham, 14dp7dTAC; n=5, 21dp1dTAC. ****p*<0.001 *****p*<0.0001 (one-way ANOVA/Sidak's multiple comparisons test). (G) HW/BW and LW/BW in 21dp1dTAC, 14dp7dTAC and 21d sham mice; n=13, 21d sham, n=6 21dp1dTAC and 14dp7dTAC. **p*<0.05, ***p*<0.005, *****p*<0.0001 (one-way ANOVA/Sidak's multiple comparisons test). (H) EF, LVEDA and wall thickness measured by echocardiography in 21d sham, 21dp1dTAC and 14dp7dTAC mice; n=10, 21d sham, n=6 21dp1dTAC and 14dp7dTAC. **p*<0.05, ****p*<0.001, *****p*<0.0001 (one-way ANOVA/Sidak's multiple comparisons test).



Supplemental Figure 2. Fourteen days of pressure overload induce fibrosis, but not angiogenesis after nTAC in the non-regenerative phase. (A) Sirius Red staining of heart sections 7 days after nTAC in 1-day-old mice (7dp1dTAC) and sham. Scale bar: 500µm (B) Quantification of fibrosis in heart sections from 7dp1dTAC and sham mice; n=9, 7d sham; n=6, 7dp1dTAC; (unpaired t test and Kruskal Wallis test/Dunn's multiple comparisons test). (C) Quantification of capillary density in 7dp1dTAC and sham mice; n=5, 7d sham and 7dp1dTAC. **p<0.005, unpaired t test (D) Sirius Red staining of heart sections 21 days after nTAC in 1-day-old mice (21dp1dTAC), 14 days after nTAC in 7-day-old mice (14dp7dTAC) and in 21-day-old sham mice. Scale bar: 500µm (E) Quantification of fibrosis in 21dp1dTAC, 14dp7dTAC and 21d sham mice; n= 6, 21d sham and 21dp1dTAC, n=5, 14dp7dTAC. *p< 0.05 (Kruskal Wallis test/Dunn's multiple comparisons test). (F) Quantification of capillary density 21dp1dTAC, 14dp7dTAC and sham; n=5 for each group. **p< 0.005 (Kruskal Wallis test/Dunn's multiple comparisons test).



Supplemental Figure 3. Pressure overload in 1-day-old mice, but not in 7-day-old mice induces cardiomyocyte proliferation and angiogenesis 7 days and 21 days after surgery. (A) Quantification of pH3 positive cardiomyocytes and cardiomyocyte cytokinesis 7 days after nTAC in 1-day-old mice (7dp1dTAC) and 7-day-old sham mice; n=4, 7d sham; n=5 7dp1dTAC. * $p < 0.05$, *** $p < 0.001$ (unpaired t test). (B) Cardiomyocyte cross-sectional area in 7dp1dTAC and sham. n=4, 7d sham; n=5, 7dp1dTAC. ** $p < 0.005$ (unpaired t test). (C) Quantification of pH3 positive cardiomyocytes and cardiomyocyte cytokinesis 21 days after nTAC in 1-day-old mice (21dp1dTAC), 14 days after nTAC in 7-day-old mice (14dp7dTAC) and in sham mice; n=5 for each group. ** $p < 0.005$, *** $p < 0.001$, **** $p < 0.0001$ (one-way ANOVA/Sidak's multiple comparisons test). (D) Cardiomyocyte cross-sectional area in 21dp1dTAC, 14dp7dTAC and sham mice; n=5 for each group. ** $p < 0.005$, * $p < 0.05$ (one-way ANOVA/Sidak's multiple comparisons test). (E) Representative pictures of immunofluorescence staining for WGA of heart sections from 21d sham, 21dp1dTAC and 14dp7dTAC mice, used to quantify the cardiomyocyte cross-sectional area (as show in (D)). Scale bar: 20 μm .



Supplemental Figure 4. Expression of embryonic genes in the RNA-sequencing data set. (A) Expression of *Nppa* in left ventricles of 14d sham, 14dp1dTAC and 7dp7dTAC mice; n=3/group. ***p<0.001, ****p<0.0001 (one-way ANOVA/Sidak's multiple comparisons test). (B) Expression of *Nppb* in left ventricles of 14d sham, 14dp1dTAC and 7dp7dTAC mice; n=3/group. **p<0.005, ***p<0.001 (one-way ANOVA/Sidak's multiple comparisons test). (C) Expression of *Myh7* in left ventricles of 14d sham, 14dp1dTAC and 7dp7dTAC mice; n=3/group. **p<0.005 (one-way ANOVA/Sidak's multiple comparisons test). (D) Expression of *Myh6* in left ventricles of 14d sham, 14dp1dTAC and 7dp7dTAC mice; n=3/group; (Kruskal Wallis test/Dunn's multiple comparisons test).



Supplemental Figure 5. The majority of the upregulated genes in the regenerative nTAC and in each of the different GO classes are direct targets of GATA4. (A-F) Pie chart showing the percentage of the genes related to immune system, proliferation, angiogenesis, neuron, wound healing and muscle contraction that are direct or not direct targets of GATA4. The table on the right side of each pie chart shows GATA4 direct and not direct target genes in each group.