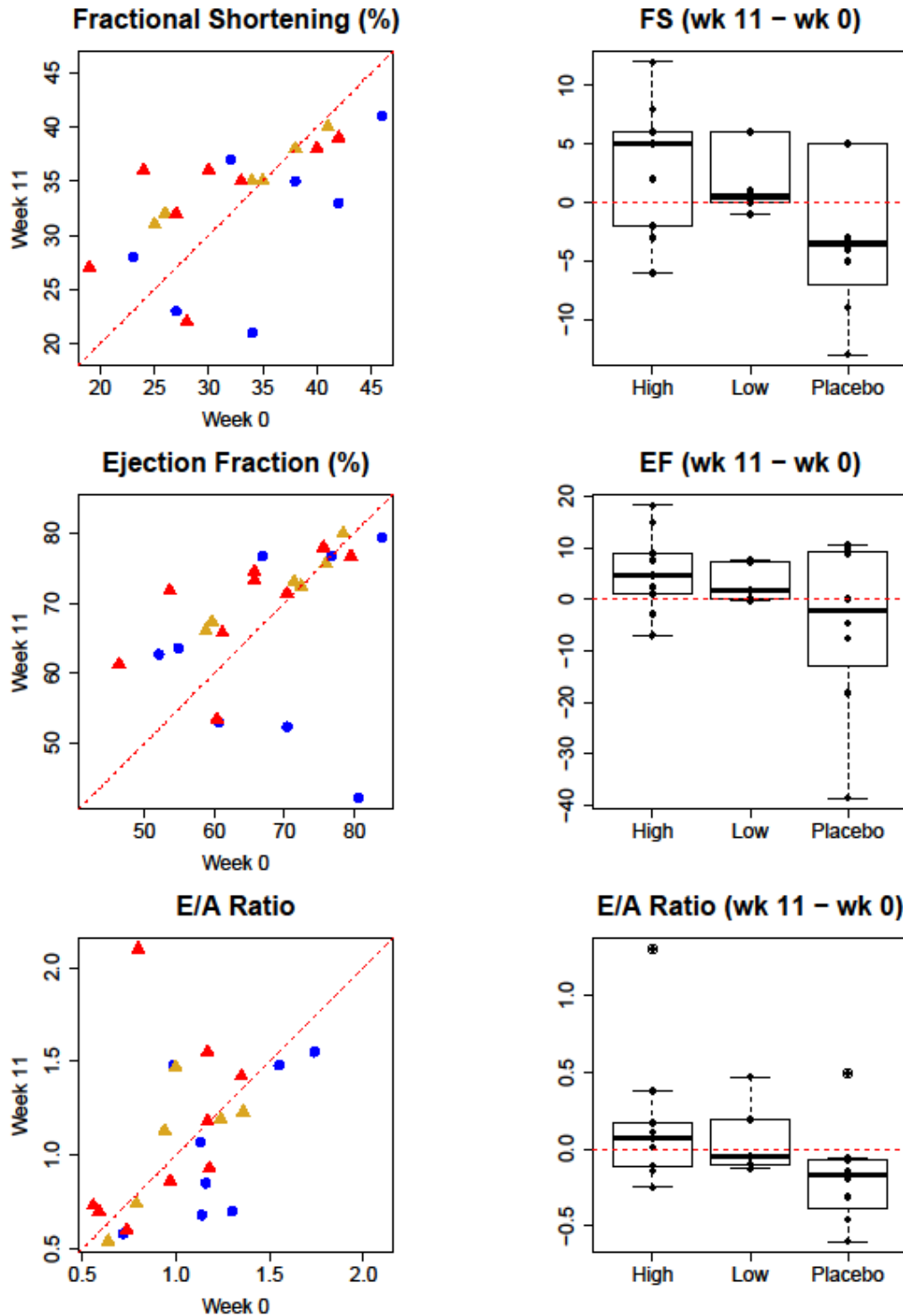
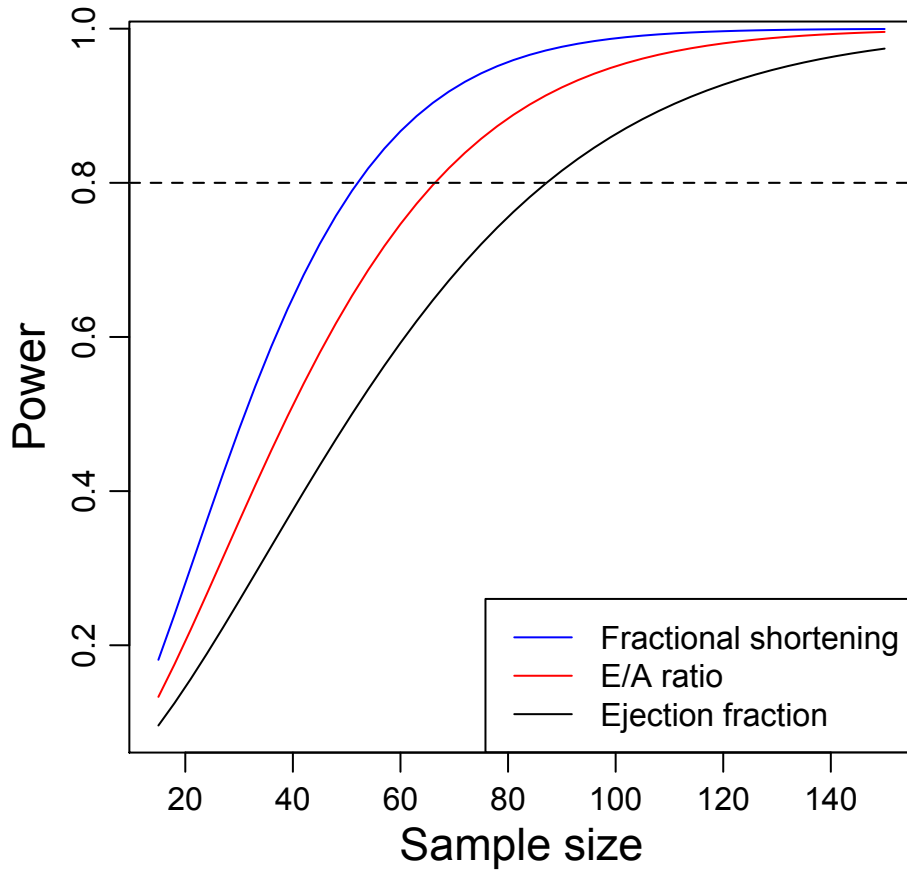


**Supplemental Figure 1. Differences in Fractional Shortening (FS), Ejection Fraction (EF) and E/A Ratio in high dose (red triangles) and low dose (yellow triangles) rapamycin vs. placebo (blue circles). x-axis = value at baseline; y-axis = value at week 11; dotted red lines: no change.**



**Supplemental Figure 2.** Power model for detecting effects of rapamycin on cardiac parameters. The power model is based on Cohen's D, which is a measure of effect size, here calculated as  $t^2/\text{sqrt}(\text{df})$  from each t-test. For sample size, it is assumed that 1/3 of the dogs receive placebo and 2/3 receive rapamycin.



**Supplemental Table 1. Summary of Hematology and Blood Chemistry for dogs receiving placebo or rapamycin at weeks 0, 3 and 11.** The frequency of measures outside of the reference range was not different for any of the measured parameters between treatment groups and mean value for all parameters remained within normal limits. TP: Total Protein, ALB: Albumin, GLOB: Globulins, ALB/GLOB: Albumin/Globulin Ratio, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, AP: Alkaline Phosphatase, GGT: Gamma-Glutamyl Transpeptidase, BILI: Bilirubin, BUN: Blood Urea Nitrogen, CREA: Creatinine, BUN/CREA: Urea/Creatinine ratio, P: Phosphorus, GLU: Glucose, Ca: Calcium, Mg: Magnesium, Na: Sodium, K: Potassium, Na/K: Sodium/Potassium Ratio, Cl: Chlorine, CHOL: Cholesterol, TRI: Triglycerides, AMY: Amylase, CPK: Creatine Phosphokinase, T4: Thyroxine, T4 Eq: Thyroxine equilibrium, WBC: White Blood Cells, RBC: Red Blood Cells, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Content, LYM: Lymphocytes, PMN: Neutrophilic Granulocytes, PLAT: Platelets, MONO: Monocytes, EOS: Eosinophilic Granulocytes. P values are for unadjusted Wilcoxon two-sided tests comparing the values at weeks 3 and 11 to baseline values. No significant differences were detected after controlling for multiple comparisons (Padj=0.00017).

Parameter	Reference Range		Placebo					
	Low	High	Week 0		Week 3		Week 11	
			Mean	SE	Mean	SE	Mean	SE
TP	5.00	7.40	6.06	0.09	6.08	0.17	6.33	0.16
ALB	2.70	4.40	3.51	0.09	3.48	0.06	3.45	0.09
GLOB	1.60	3.60	2.55	0.13	2.60	0.18	2.88	0.20
ALB/GLOB	0.80	2.00	1.43	0.11	1.41	0.14	1.24	0.09
AST	15.00	66.00	24.50	1.97	25.88	1.22	25.75	1.93
ALT	12.00	118.00	38.50	10.59	39.75	9.29	41.88	9.16
AP	5.00	131.00	22.50	3.54	24.50	4.39	29.63	6.25
GGT	1.00	12.00	5.50	1.27	7.63	1.29	4.63	1.32
BILI	0.10	0.30	0.15	0.02	0.14	0.02	0.14	0.02
BUN	6.00	31.00	17.13	1.41	15.63	1.57	17.75	1.50
CREA	0.50	1.60	1.16	0.07	1.14	0.07	1.15	0.03
BUN/CREA	4.00	27.00	14.88	1.20	13.75	1.18	15.50	1.18
P	2.50	6.00	3.34	0.20	3.60	0.22	3.38	0.27
GLU	70.00	138.00	105.88	3.16	95.50	2.63	101.13	3.00
Ca	8.90	11.40	9.89	0.06	9.78	0.08	9.85	0.08
Mg	1.50	2.50	1.71	0.04	1.71	0.06	1.66	0.04
Na	139.00	154.00	147.13	0.72	148.25	0.56	147.88	0.67
K	3.60	5.50	4.51	0.12	4.41	0.12	4.46	0.13
Na/K	27.00	38.00	32.63	0.96	33.75	0.88	33.38	1.10
Cl	102.00	120.00	114.25	1.18	114.25	1.01	114.25	0.75
CHOL	92.00	324.00	233.13	25.20	231.25	23.97	234.00	22.57
TRI	29.00	291.00	110.25	26.87	100.88	22.61	113.75	26.41
AMY	290.00	1125.00	510.75	71.95	489.63	55.42	528.50	59.17
CPK	59.00	895.00	102.75	16.23	110.25	10.04	164.13	33.76
T4	0.80	3.50	1.79	0.22	1.74	0.14	1.74	0.23
T4 Eq	8.00	40.00	17.38	1.98	16.75	1.91	16.01	1.16
WBC	4.00E+03	1.55E+04	7.24E+03	2.83E+02	8.10E+03	4.54E+02	7.74E+03	6.17E+02
RBC	4.80E+06	9.30E+06	7.14E+06	2.61E+05	7.05E+06	2.65E+05	7.15E+06	2.63E+05
HGB	12.10	20.30	17.14	0.30	16.70	0.44	17.24	0.35
HCT	36.00	60.00	50.63	0.92	49.88	1.52	50.50	1.04
MCV	58.00	79.00	71.00	1.40	70.88	1.36	71.25	1.50
MCH	19.00	28.00	24.18	0.51	23.81	0.49	24.23	0.44
MCHC	30.00	38.00	34.13	0.30	33.63	0.32	34.00	0.27
LYM	1.70E+05	4.00E+05	1.37E+03	3.50E+02	2.13E+03	2.00E+02	1.86E+03	1.81E+02
PMN	2.06E+03	1.06E+04	4.74E+03	2.46E+02	5.11E+03	4.01E+02	5.01E+03	5.51E+02
PLAT	6.90E+02	4.50E+03	2.48E+05	1.90E+04	2.63E+05	2.50E+04	2.56E+05	2.70E+04
MONO	0.00	840.00	235.13	74.07	367.63	42.74	388.38	39.12
EOS	0.00	1200.00	255.13	76.94	503.75	79.05	483.38	81.14

Parameter	Reference Range		Pooled Rapamycin					
	Low	High	Week 0		Week 3		Week 11	
			Mean	SE	Mean	SE	Mean	SE
TP	5.00	7.40	6.28	0.09	6.28	0.07	6.42	0.09
ALB	2.70	4.40	3.59	0.06	3.50	0.06	3.53	0.07
GLOB	1.60	3.60	2.68	0.10	2.78	0.08	2.89	0.10
ALB/GLOB	0.80	2.00	1.39	0.08	1.29	0.05	1.26	0.06
AST	15.00	66.00	24.69	1.76	28.13	1.62	33.44	3.02
ALT	12.00	118.00	41.38	4.83	43.25	5.82	38.31	2.87
AP	5.00	131.00	33.56	6.10	33.50	4.36	30.81	4.85
GGT	1.00	12.00	3.31	0.83	4.75	0.91	3.75	0.85
BILI	0.10	0.30	0.15	0.01	0.13	0.01	0.15	0.01
BUN	6.00	31.00	18.56	1.54	17.56	1.62	17.19	1.19
CREA	0.50	1.60	1.12	0.05	1.11	0.07	1.12	0.05
BUN/CREA	4.00	27.00	16.75	1.31	16.19	1.32	15.63	1.03
P	2.50	6.00	3.45	0.17	3.64	0.20	3.41	0.18
GLU	70.00	138.00	101.81	2.08	98.56	1.99	101.00	2.23
Ca	8.90	11.40	10.07	0.08	10.03	0.08	10.03	0.07
Mg	1.50	2.50	1.74	0.03	1.75	0.04	1.73	0.04
Na	139.00	154.00	148.00	0.40	147.25	0.52	147.06	0.37
K	3.60	5.50	4.46	0.06	4.48	0.07	4.38	0.06
Na/K	27.00	38.00	33.19	0.48	32.88	0.55	33.75	0.45
Cl	102.00	120.00	113.88	0.58	113.13	0.87	112.81	0.53
CHOL	92.00	324.00	246.56	17.66	272.25	20.80	259.38	19.89
TRI	29.00	291.00	122.25	11.97	132.19	23.37	137.31	27.45
AMY	290.00	1125.00	444.88	34.96	513.56	39.31	508.50	36.15
CPK	59.00	895.00	107.19	14.45	138.25	29.21	140.87	30.82
T4	0.80	3.50	1.72	0.09	1.64	0.09	1.64	0.10
T4 Eq	8.00	40.00	15.33	1.24	16.48	1.98	16.49	1.34
WBC	4.00E+03	1.55E+04	6.85E+03	4.56E+02	7.76E+03	7.39E+02	7.46E+03	4.63E+02
RBC	4.80E+06	9.30E+06	7.02E+06	1.50E+05	7.09E+06	1.53E+05	7.14E+06	1.81E+05
HGB	12.10	20.30	16.96	0.39	17.08	0.36	17.08	0.42
HCT	36.00	60.00	50.38	1.06	50.44	0.94	50.06	1.12
MCV	58.00	79.00	71.81	0.97	71.06	1.00	70.25	0.81
MCH	19.00	28.00	24.19	0.40	24.13	0.39	23.99	0.40
MCHC	30.00	38.00	33.81	0.23	34.00	0.18	34.06	0.25
LYM	1.70E+05	4.00E+05	1.37E+03	8.84E+01	1.49E+03	1.06E+02	1.36E+03	1.02E+02
PMN	2.06E+03	1.06E+04	4.79E+03	3.54E+02	5.62E+03	5.73E+02	5.41E+03	3.55E+02
PLAT	6.90E+02	4.50E+03	2.34E+05	1.73E+04	2.45E+05	1.96E+04	2.61E+05	1.82E+04
MONO	0.00	840.00	335.06	53.56	340.25	52.42	393.94	61.96
EOS	0.00	1200.00	354.75	44.19	308.13	67.41	303.75	39.78

Parameter	Reference Range		Low Rapamycin					
	Low	High	Week 0		Week 3		Week 11	
			Mean	SE	Mean	SE	Mean	SE
TP	5.00	7.40	6.16	0.17	6.42	0.15	6.48	0.14
ALB	2.70	4.40	3.64	0.11	3.52	0.12	3.58	0.15
GLOB	1.60	3.60	2.52	0.24	2.90	0.18	2.90	0.20
ALB/GLOB	0.80	2.00	1.54	0.21	1.22	0.10	1.30	0.14
AST	15.00	66.00	19.00	0.84	23.60	1.96	28.40	2.58
ALT	12.00	118.00	28.00	4.09	46.80	18.03	29.00	2.47
AP	5.00	131.00	20.60	4.53	28.00	5.09	24.60	5.45
GGT	1.00	12.00	2.00	0.77	6.60	1.29	4.40	1.89
BILI	0.10	0.30	0.14	0.02	0.14	0.02	0.12	0.02
BUN	6.00	31.00	22.80	2.67	21.00	3.39	19.60	2.89
CREA	0.50	1.60	1.12	0.06	1.14	0.19	1.00	0.08
BUN/CREA	4.00	27.00	20.20	2.06	18.40	1.54	19.40	2.16
P	2.50	6.00	3.86	0.35	3.74	0.40	3.54	0.33
GLU	70.00	138.00	98.20	2.33	101.60	4.25	94.80	1.98
Ca	8.90	11.40	10.36	0.15	10.18	0.21	10.14	0.19
Mg	1.50	2.50	1.76	0.05	1.78	0.10	1.78	0.06
Na	139.00	154.00	147.60	0.51	148.60	1.29	147.80	0.73
K	3.60	5.50	4.52	0.16	4.54	0.14	4.56	0.09
Na/K	27.00	38.00	32.80	1.07	32.80	1.28	32.60	0.75
Cl	102.00	120.00	113.40	1.29	114.60	1.57	114.20	1.16
CHOL	92.00	324.00	273.20	39.21	289.40	42.65	272.80	35.90
TRI	29.00	291.00	110.80	23.28	105.60	7.35	175.00	68.41
AMY	290.00	1125.00	507.40	83.46	490.80	67.05	476.00	68.47
CPK	59.00	895.00	76.00	8.70	97.20	11.67	106.20	14.47
T4	0.80	3.50	1.66	0.13	1.50	0.15	1.76	0.19
T4 Eq	8.00	40.00	13.40	0.97	13.26	0.78	15.10	0.81
WBC	4.00E+03	1.55E+04	6.84E+03	8.99E+02	7.58E+03	1.16E+03	7.48E+03	1.17E+03
RBC	4.80E+06	9.30E+06	7.02E+06	3.71E+05	7.04E+06	4.25E+05	7.02E+06	3.92E+05
HGB	12.10	20.30	16.82	0.63	16.90	0.74	16.84	0.63
HCT	36.00	60.00	50.00	1.90	50.60	1.94	49.20	1.93
MCV	58.00	79.00	71.20	1.74	72.20	2.13	69.60	1.66
MCH	19.00	28.00	24.04	0.60	24.14	0.83	24.00	0.67
MCHC	30.00	38.00	33.80	0.20	33.60	0.24	34.20	0.20
LYM	1.70E+05	4.00E+05	1.24E+03	1.90E+02	1.29E+03	2.09E+02	1.28E+03	2.08E+02
PMN	2.06E+03	1.06E+04	5.01E+03	6.90E+02	5.75E+03	9.17E+02	5.60E+03	9.24E+02
PLAT	6.90E+02	4.50E+03	2.54E+05	4.28E+04	3.03E+05	4.56E+04	2.86E+05	3.05E+04
MONO	0.00	840.00	321.20	57.51	343.60	59.82	340.80	59.60
EOS	0.00	1200.00	267.40	78.47	192.60	58.32	261.00	65.87

Parameter	Reference Range		High Rapamycin					
	Low	High	Week 0		Week 3		Week 11	
			Mean	SE	Mean	SE	Mean	SE
TP	5.00	7.40	6.38	0.10	6.24	0.08	6.44	0.12
ALB	2.70	4.40	3.59	0.09	3.48	0.07	3.50	0.08
GLOB	1.60	3.60	2.79	0.10	2.76	0.09	2.94	0.12
ALB/GLOB	0.80	2.00	1.31	0.07	1.30	0.06	1.21	0.06
AST	15.00	66.00	27.30	2.35	30.40	2.10	36.60	4.46
ALT	12.00	118.00	43.80	5.27	40.50	3.93	41.80	3.59
AP	5.00	131.00	41.40	8.74	37.90	6.16	35.10	7.10
GGT	1.00	12.00	4.00	1.24	4.20	1.20	3.70	1.01
BILI	0.10	0.30	0.15	0.02	0.12	0.01	0.16	0.02
BUN	6.00	31.00	16.50	1.81	16.00	1.87	15.50	1.00
CREA	0.50	1.60	1.07	0.05	1.04	0.04	1.12	0.03
BUN/CREA	4.00	27.00	15.60	1.58	15.70	1.84	14.00	0.79
P	2.50	6.00	3.28	0.19	3.54	0.25	3.38	0.24
GLU	70.00	138.00	102.70	2.93	97.20	2.40	102.30	2.53
Ca	8.90	11.40	9.96	0.07	9.96	0.09	9.98	0.07
Mg	1.50	2.50	1.73	0.04	1.71	0.05	1.69	0.05
Na	139.00	154.00	148.40	0.54	146.60	0.45	146.80	0.44
K	3.60	5.50	4.47	0.06	4.44	0.08	4.30	0.07
Na/K	27.00	38.00	33.10	0.53	33.00	0.65	34.30	0.56
Cl	102.00	120.00	114.00	0.71	112.40	1.14	112.10	0.55
CHOL	92.00	324.00	233.00	20.74	263.80	26.93	251.40	27.39
TRI	29.00	291.00	122.70	14.96	141.60	37.13	103.50	22.69
AMY	290.00	1125.00	430.10	34.19	544.50	50.61	543.40	43.15
CPK	59.00	895.00	113.80	19.78	151.60	45.54	163.89	50.47
T4	0.80	3.50	1.74	0.13	1.70	0.13	1.57	0.14
T4 Eq	8.00	40.00	16.16	1.79	18.24	3.06	16.51	2.00
WBC	4.00E+03	1.55E+04	7.11E+03	5.44E+02	8.14E+03	1.02E+03	7.79E+03	3.59E+02
RBC	4.80E+06	9.30E+06	7.05E+06	1.69E+05	7.11E+06	1.49E+05	7.18E+06	2.28E+05
HGB	12.10	20.30	17.09	0.56	17.09	0.46	17.11	0.60
HCT	36.00	60.00	50.70	1.46	50.20	1.22	50.30	1.56
MCV	58.00	79.00	72.00	1.33	70.40	1.23	70.40	1.05
MCH	19.00	28.00	24.22	0.58	24.06	0.49	23.93	0.57
MCHC	30.00	38.00	33.80	0.36	34.20	0.25	34.00	0.39
LYM	1.70E+05	4.00E+05	1.47E+03	9.69E+01	1.59E+03	1.31E+02	1.42E+03	1.28E+02
PMN	2.06E+03	1.06E+04	4.87E+03	4.25E+02	5.82E+03	7.75E+02	5.60E+03	2.27E+02
PLAT	6.90E+02	4.50E+03	2.27E+05	1.87E+04	2.24E+05	1.52E+04	2.53E+05	2.46E+04
MONO	0.00	840.00	354.00	81.88	353.40	79.18	439.40	93.08
EOS	0.00	1200.00	408.10	54.72	377.50	99.68	335.00	54.20