

ActRIIa ILGRSETQEC LFFNANWEKD RTNQTVGVEPC YGDKDKRRHC FATWKNISGS
ActRIIb GRGEAETREC IYNNANWELE RTNQSGLERC EGEQDKRLHC YASWRNSSGT
IEIVKQGCWL DDINCYDRTD CVEKKDSPEV YFCCCEGNMC NEKFSYFPPEM
IELVKKGCWL DDENCYDRQE CVATEENPQV YFCCCEGNFC NERFTHLPEA
EVTQPTSNPV TPKPP SEQIDNO:2
GGPEVTEPP PTAPT SEQIDNO:31

FIG. 1

human	ILGRSETQEC	IFFNANWEKD	RTNQTVGVEPC	YGDKDKRRHC	FATWKNIISGS
sheep	ILGRSETQEC	IFYNANWERD	RTNRRTGVES	YGDKDKRRHC	FATWKNIISGS
mole	ILGRSETQEC	IFFNANWERD	RTNQTVGVEPC	YGDKDKRRHC	FATWKNIISGS
mouse	ILGRSETQEC	IFFNANWERD	RTNQTVGVEPC	YGDKDKRRHC	FATWKNIISGS
chicken	ILGRSETQEC	IYYNANWEKD	KTNRSGIEPC	YGDKDKRRHC	FATWKNIISGS
cow	ILGRSETQEC	IFYNANWERD	RTNRRTGVES	YGDKDKRRHC	FATWKNIISGS
owl	ILGRSETQEC	IYYNANWEKD	KTNRSGIEPC	YGDKDKRRHC	FATWKNIISGS
bat	ILGRSETQEC	IFYNANWERD	KTNRRTGVEL	YGDKDKRRHC	FATWKNIISGS
human	IEIVKQGGCWL	DDINCYDRTD	CVEKKDSPEV	YFCCCEGNMC	NEKFSYFPPEM
sheep	IEIVKQGGCWL	DDINCYDRTD	CIEKKDSPEV	YFCCCEGNMC	NERFSYFPPEM
mole	IEIVKQGGCWL	DDINCYDRTD	CIEKKDSPEV	YFCCCEGNMC	NEKFSYFPPEM
mouse	IEIVKQGGCWL	DDINCYDRTD	CIEKKDSPEV	YFCCCEGNMC	NEKFSYFPPEM
chicken	IEIVKQGGCWL	DDINCYDRND	CIEKKDSPEV	YFCCCEGNMC	NERFFYFPPEM
cow	IEIVKQGGCWL	DDINCYDRTD	CIEKKDSPEV	YFCCCEGNMC	NERFSYFPPEM
owl	IEIVKQGGCWL	DDINCYDRND	CIEKKDSPEV	YFCCCEGNMC	NERFFYFPPEM
bat	IEIVKQGGCWL	DDINCYDRTD	CIEKKDSPEV	YFCCCEGNMC	NERFSYFPPEM
human	EVTQPTSNPV	TPKPP	SEQ ID NO: 6		
sheep	EVTQPTSNPV	TPKPP	SEQ ID NO: 7		
mole	EVTQPTSNPV	TPKAP	SEQ ID NO: 8		
mouse	EVTQPTSNPV	TPKPP	SEQ ID NO: 9		
chicken	EVTQPTSNPV	TPKPP	SEQ ID NO: 10		
cow	EVTQPTSNPV	TPKPP	SEQ ID NO: 36		
owl	EVTQPTSNPV	TPKPP	SEQ ID NO: 37		
bat	EVTQPTSNPV	TPKPP	SEQ ID NO: 38		

FIG. 2

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IgG1  -----THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKF  53
IgG4  ---ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQF  57
IgG2  -----VECPFCPPAVAG--PSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQF  51
IgG3  EPKSCDTPPPCPRCAPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQF  60

      **      .  *  *****;*****;

IgG1  NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT  113
IgG4  NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT  117
IgG2  NWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKT  111
IgG3  KWYVDGVEVHNAKTKPREEQYNSTFRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT  120

;*****;***;*****;*****;*****;*****;*****;*****;*****;

IgG1  ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT  173
IgG4  ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT  177
IgG2  ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT  171
IgG3  ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTT  180

***;*****;*****;*****;*****;*****;*****;*****;

IgG1  PVLDSGDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK  225  (SEQ ID NO: 32)
IgG4  PVLDSGDGSFFLYSRLTVDKSRWQEGNVFCSSVMHEALHNHYTQKSLSLSLCK  229  (SEQ ID NO: 35)
IgG2  PMLDSGDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK  223  (SEQ ID NO: 33)
IgG3  PMLDSGDGSFFLYSKLTVDKSRWQQGNIFSCSSVMHEALHNRTQKSLSLSPGK  232  (SEQ ID NO: 34)

*****;*****;*****;*****;*****;*****;*****;*****

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FIG. 3

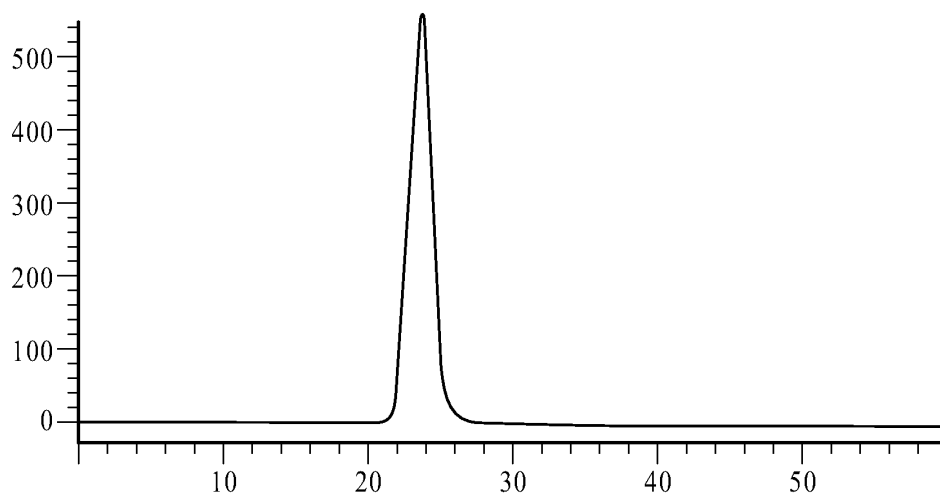


FIG. 4A

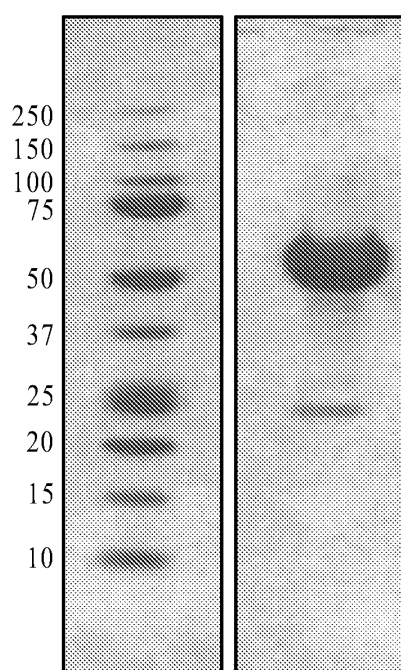


FIG. 4B

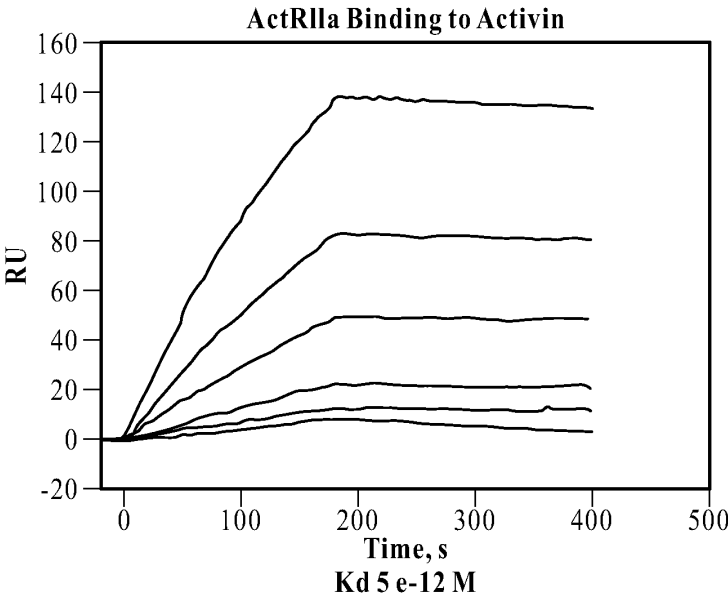


FIG. 5A

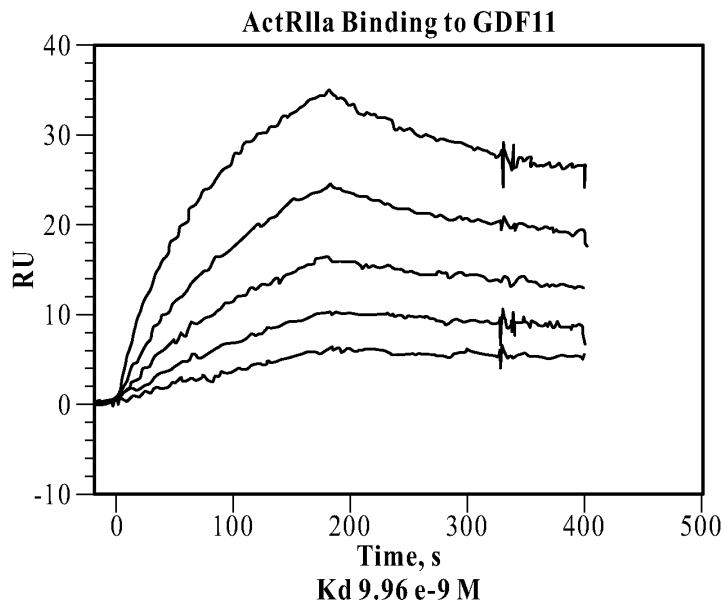


FIG. 5B

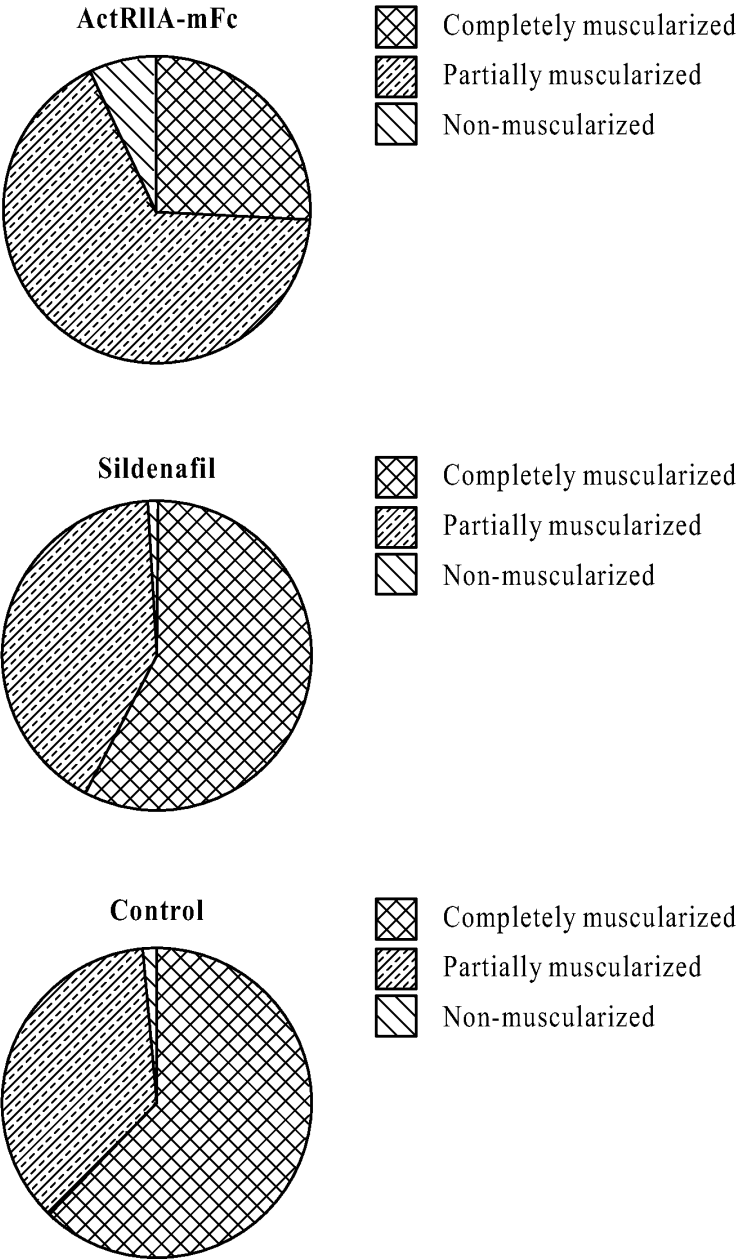


FIG. 6

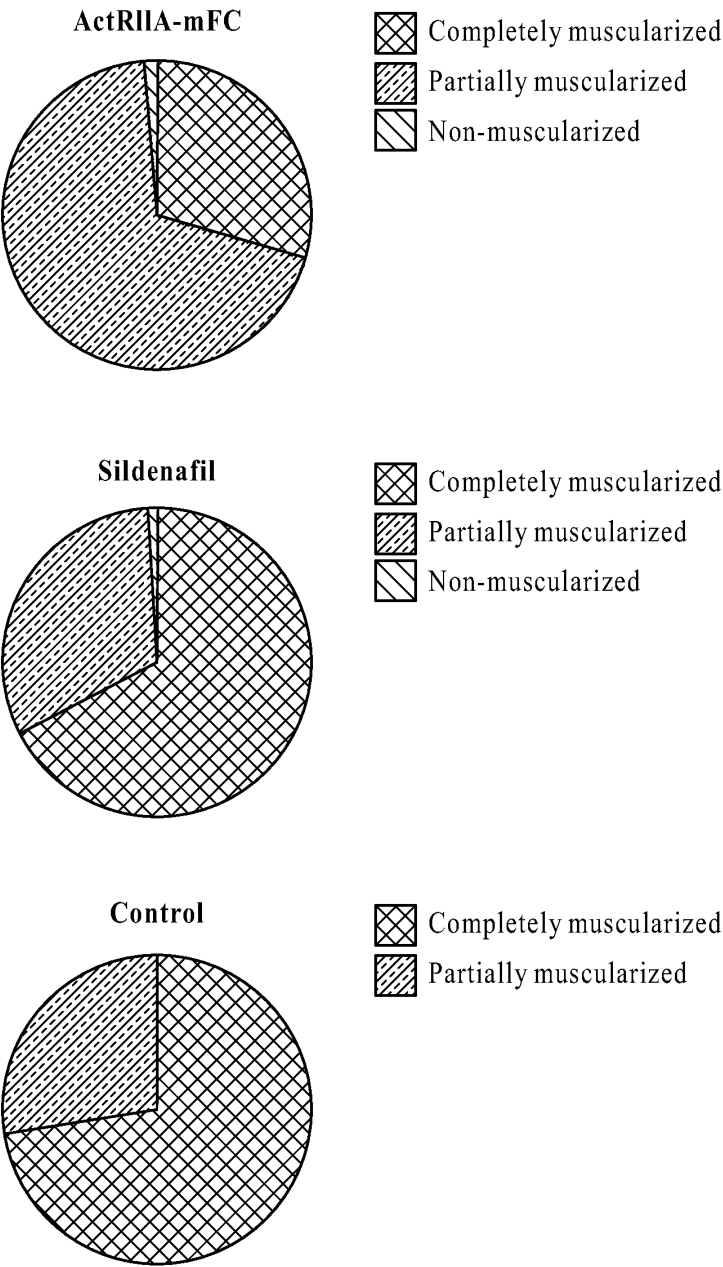


FIG. 7

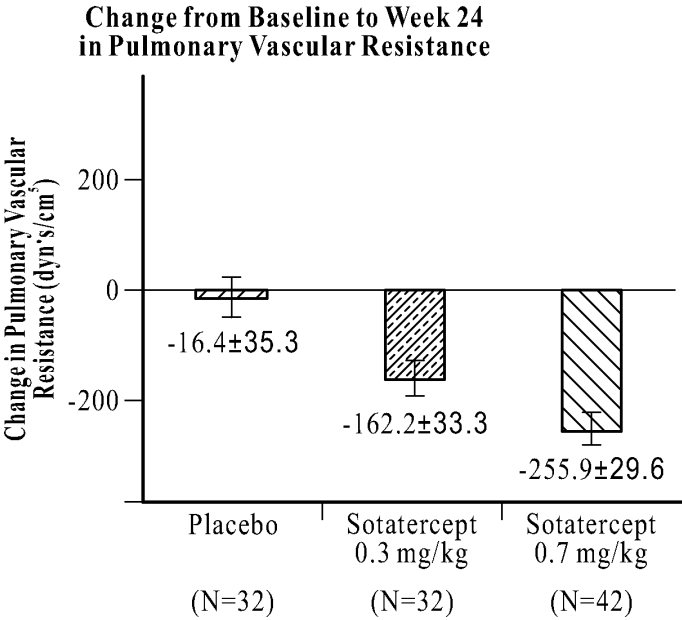


FIG. 8A

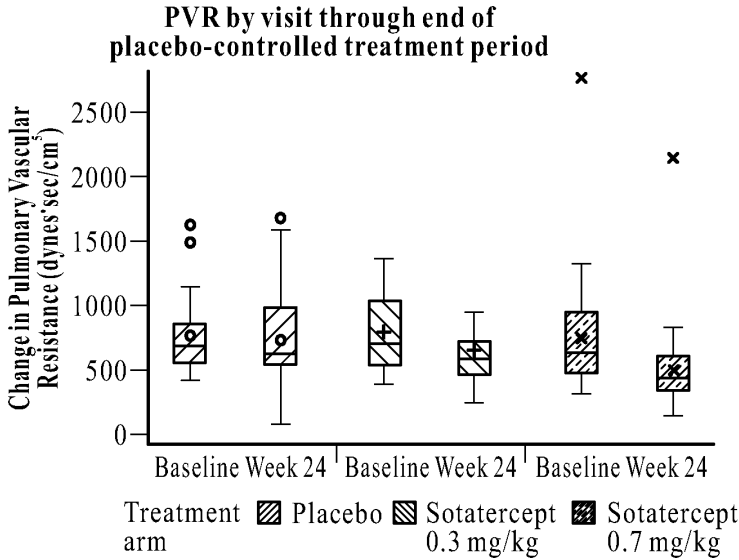


FIG. 8B

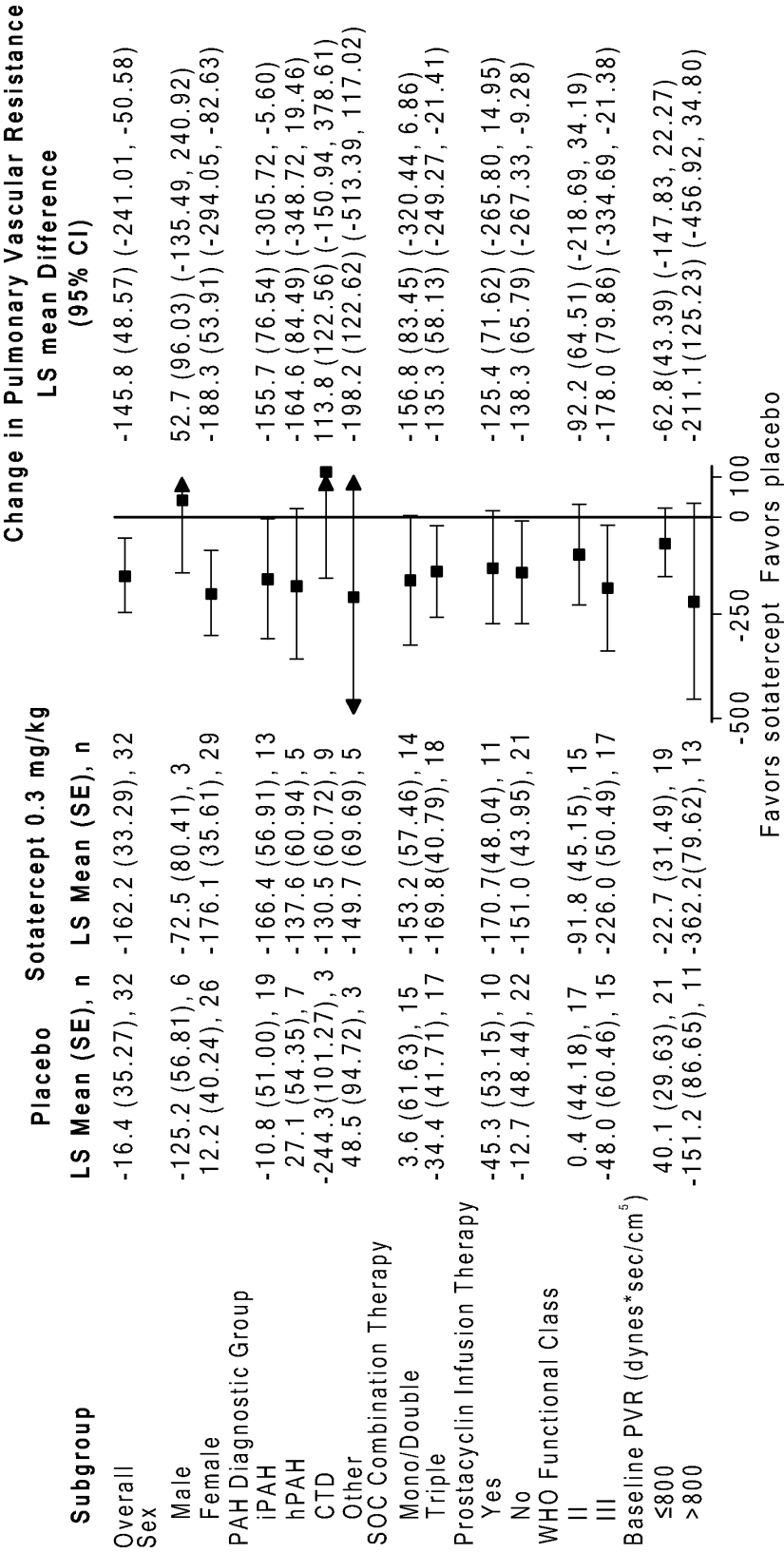


FIG. 8C

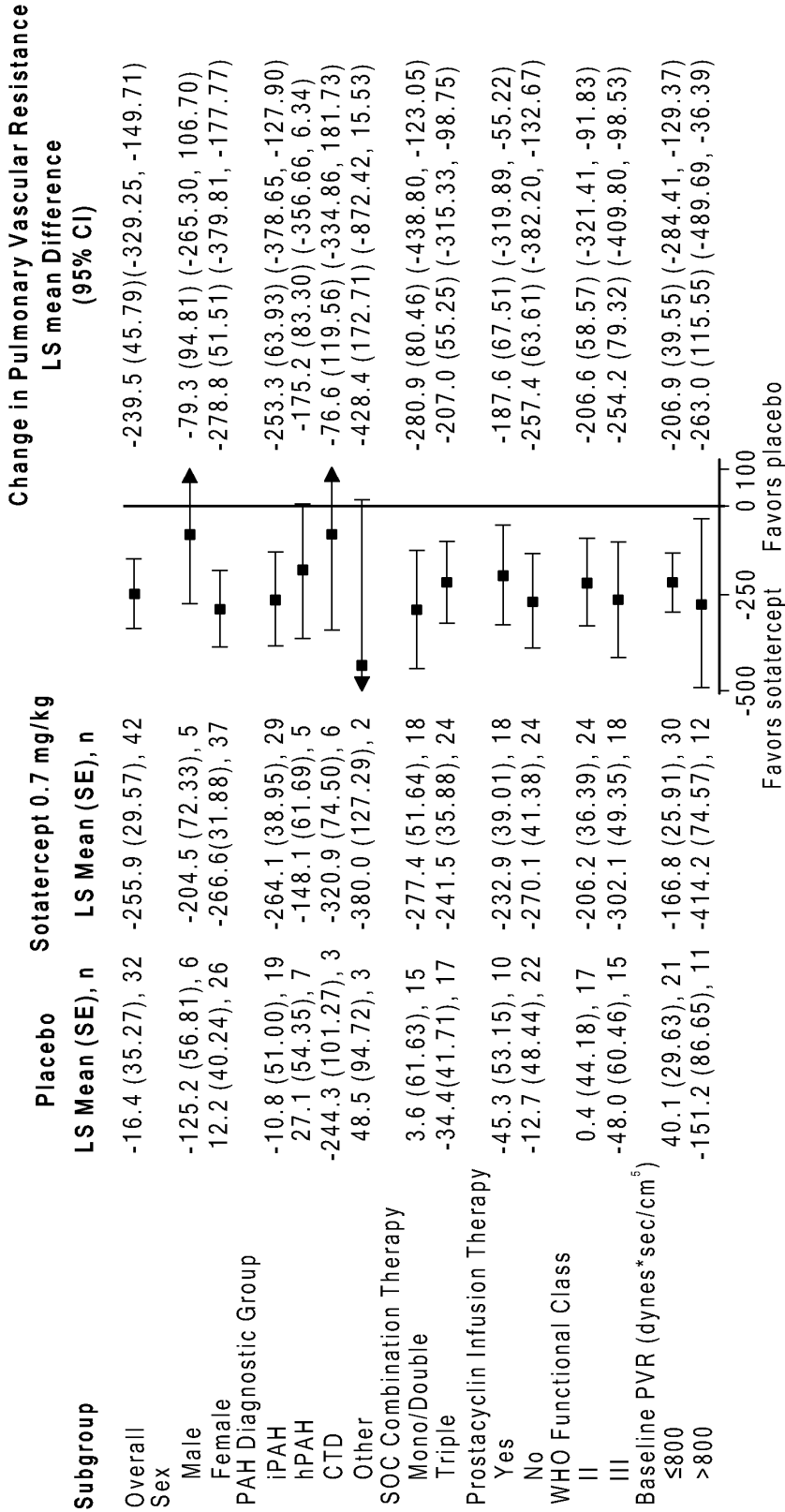


FIG. 8D

End Point	Placebo (N=32)			Sotatercept 0.3 mg/kg (N=32)			Sotatercept 0.7 mg/kg (N=42)			Sotatercept all doses (N=74)		
	LS Mean Change	LS Mean Change	LS Mean Difference (95% CI)	P Value [†]	LS Mean Change	LS Mean Difference (95% CI)	P Value [†]	LS Mean Change	LS Mean Difference (95% CI)	P Value [†]	LS Mean Change	LS Mean Difference (95% CI)
Pulmonary vascular resistance —dyn·s/cm ⁵	-16.4±35.3	-162.2±33.3	-145.8 (-241.0, -50.6)	0.003	-255.9±29.6	-239.5 (-329.3, -149.7)	<0.001	-215.2±22.4	-198.9 (-281.5, -116.3)	<0.001		
mPAP—mmHg	0.5±1.6	-7.8±1.5	-8.3 (-12.7, -4.0)	<0.001	-12.8±1.4	-13.4 (-17.5, -9.3)	<0.001	-10.5±1.1	-11.1 (-14.9, -7.3)	<0.001		
mRAP—mmHg	0.6±0.8	-1.6±0.7	-2.2 (-4.3, -0.2)	0.04	-1.3±0.7	-1.9 (-3.9, 0.1)	0.06	-1.4±0.5	-2.0 (-3.8, -0.3)	0.03		
CO—L/min	0.3±0.2	0.1±0.2	-0.2 (-0.8, 0.3)	0.38	0.1±0.2	-0.2 (-0.8, 0.3)	0.34	0.1±0.1	-0.2 (-0.7, 0.2)	0.29		
CI—L/min/m ²	0.2±0.1	0.1±0.1	-0.1 (-0.4, 0.2)	0.49	0.1±0.1	-0.1 (-0.4, 0.2)	0.42	0.1±0.1	-0.1 (-0.4, 0.2)	0.39		
mPAWP—mmHg	0.2±0.7	-0.8±0.7	-1.0 (-2.8, 0.9)	0.31	0.3±0.6	0.1 (-1.7, 1.9)	0.88	-0.2±0.5	-0.4 (-2.0, 1.2)	0.65		
NT-proBNP—pg/mL	310.4±151.3	-621.1±150.5	-931.5 (1353.2, 509.7)	<0.001	-340±139.4	-651.0 (-1043.3, 258.7)	<0.001	-462.4±101.4	-772.1 (-1125.2, -419.1)	—		
WHO functional class improved	4(12.5)	—	10 (31.3)	0.09	—	7 (16.7)	0.58	—	17 (23.0)	—		

FIG. 9A

from baseline – no. (%)	6-minute walk distance –m									
	Mean Analysis [†]	28.7±9.3	58.1±9.2	29.4 (3.8, 55.0)	0.02	50.1±8.2	21.4 (-2.8, 45.7)	0.08	53.5±6.1	24.9 (3.1, 46.6)
	Median change Estimate	Median change Estimate	Hodges- Lehmann Location Shift (80% CI)	Wilcoxon P value	Median change Estimate	Hodges- Lehmann Location Shift (80% CI)	Wilcoxon P value	Median change Estimate	Hodges- Lehmann Location Shift (80% CI)	Wilcoxon p value
Median Analysis [†]	14.5	54.3			33.6			52.1		–
Clinical worsening										
	Placebo (N=32)	Sotatercept 0.3 mg/kg (N=32)				Sotatercept 0.7 mg/kg (N=42)				Sotatercept all doses (N=74)
Total number of events [§]	3	0				4				4
Total number of subjects with events (%)	2(6.3)	0(0.0)				1(2.4)				1(1.4)

* plus-minus values are least squares means ±SE in the evaluable set with standard multiple imputation for handling missing data. All doses include the 0.1 mg/kg sotatercept group.

† P values were calculated using analysis of covariance of the change from baseline to week 24 compared with placebo using baseline WHO functional class and baseline value covariates.

‡ The Shapiro-wilk normality test was statistically significant (P=0.0157), indicating skewness in the 6-minute walk distance means. As a non-parametric sensitivity analysis, the median analysis was performed using Hodges-Lehmann median location shift with aligned rank Wilcoxon p-value with baseline WHO functional class and baseline value as covariates. Median Change Estimate refers to the average of the median change across imputed datasets in the evaluable set.

§ Estimated from Kaplan-Meier.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects

CI: cardiac index; CO: cardiac output; mPAP: mean pulmonary artery pressure; mPAWP: mean pulmonary artery wedge pressure; mRAP: means right atrial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; WHO: World Health Organization

FIG. 9B

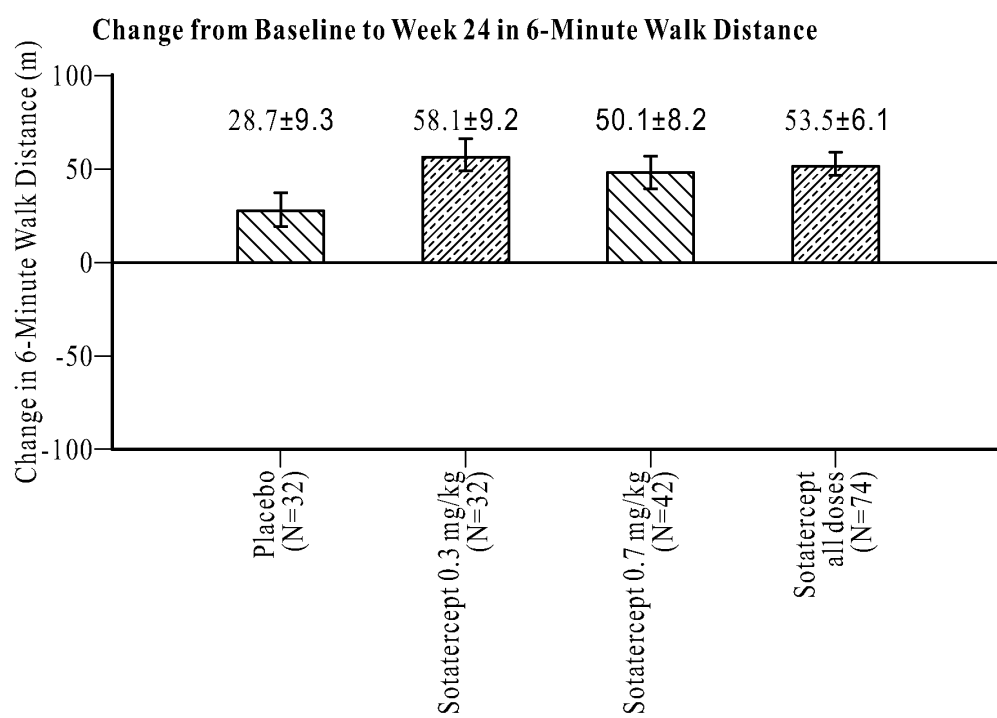


FIG. 10A

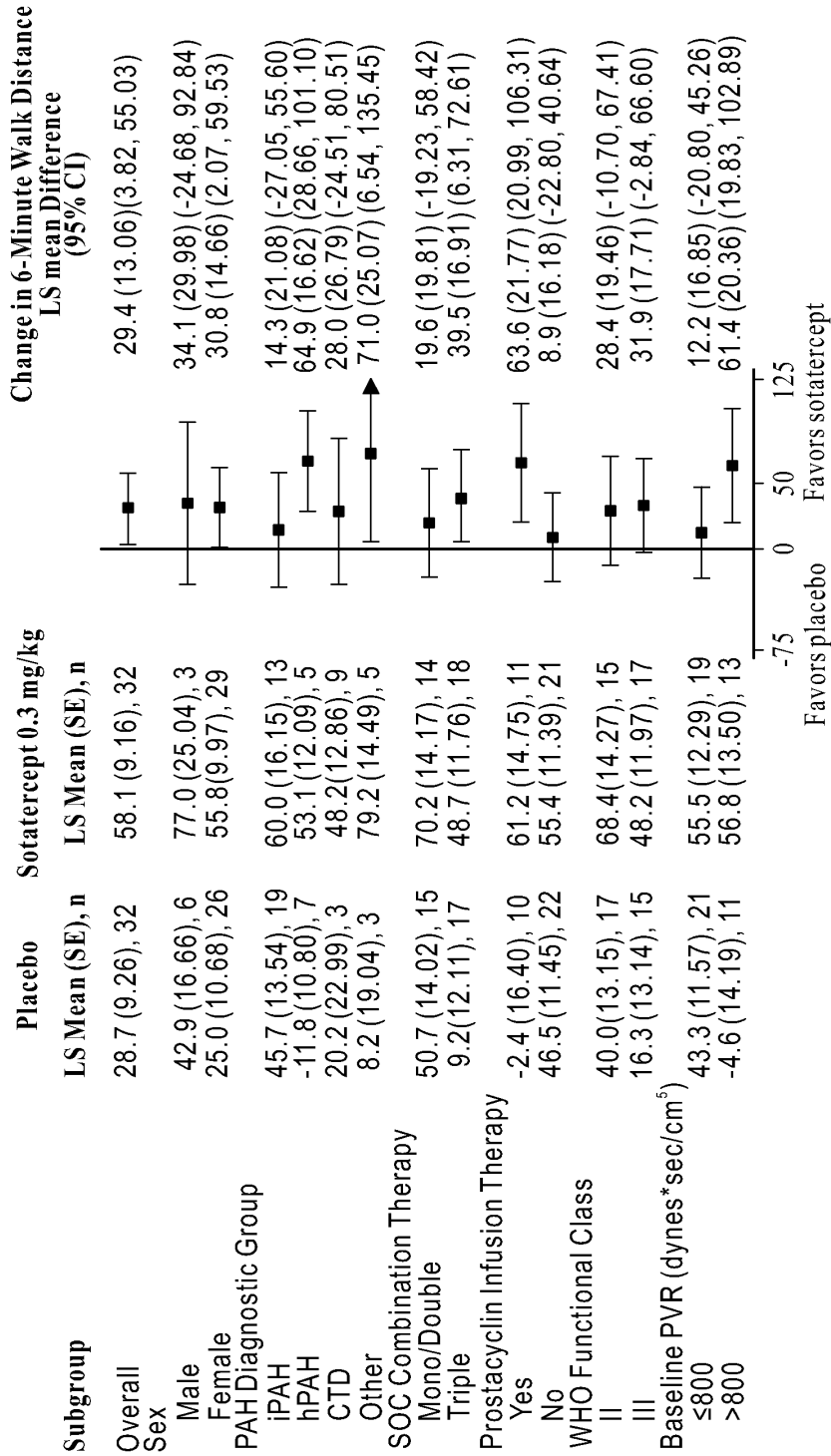


FIG. 10B

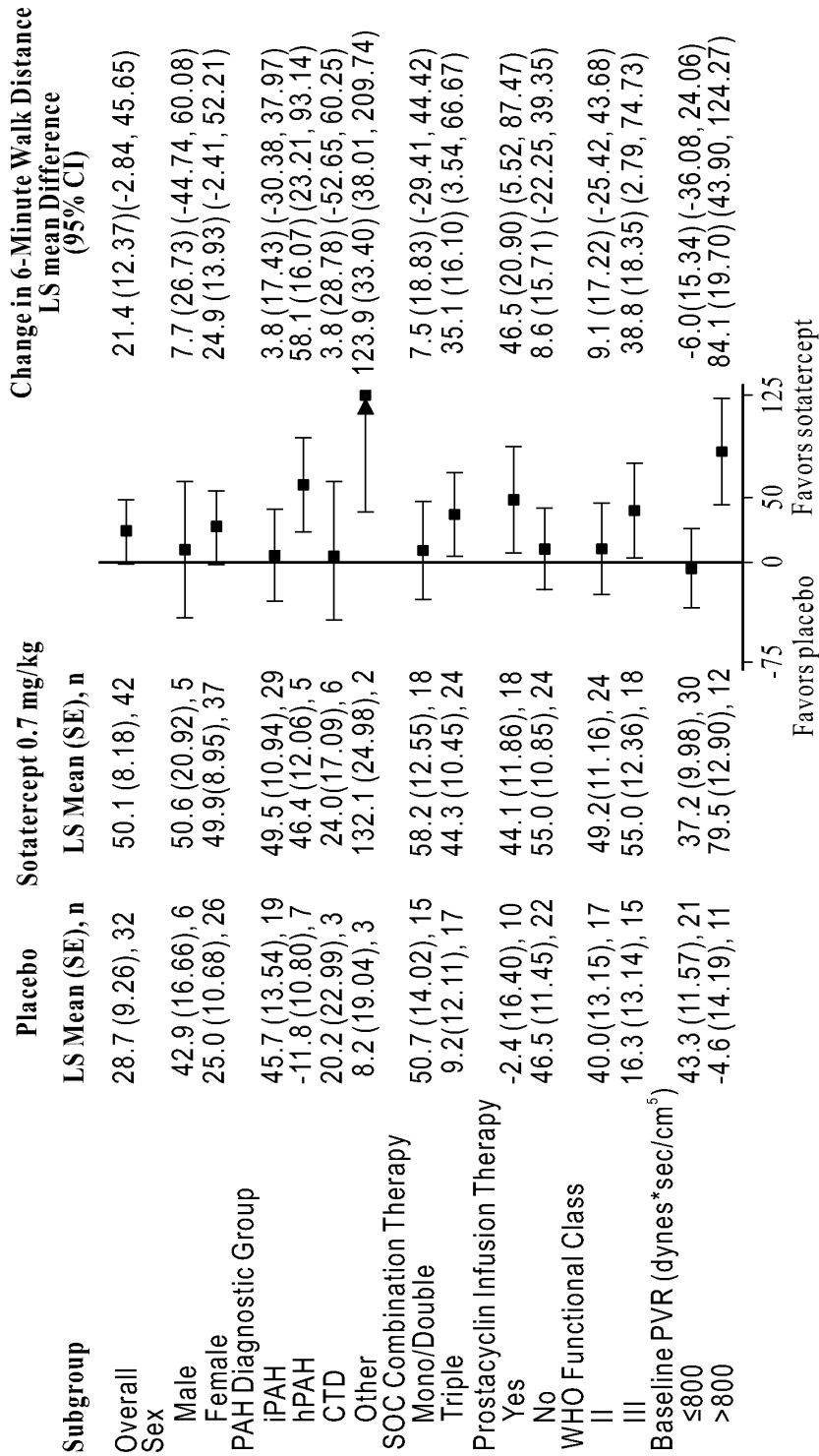


FIG. 10C

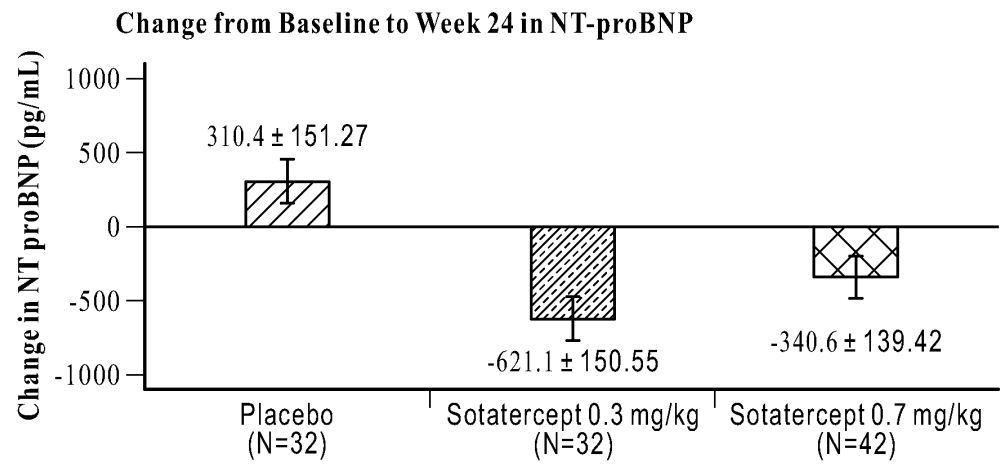


FIG. 11A

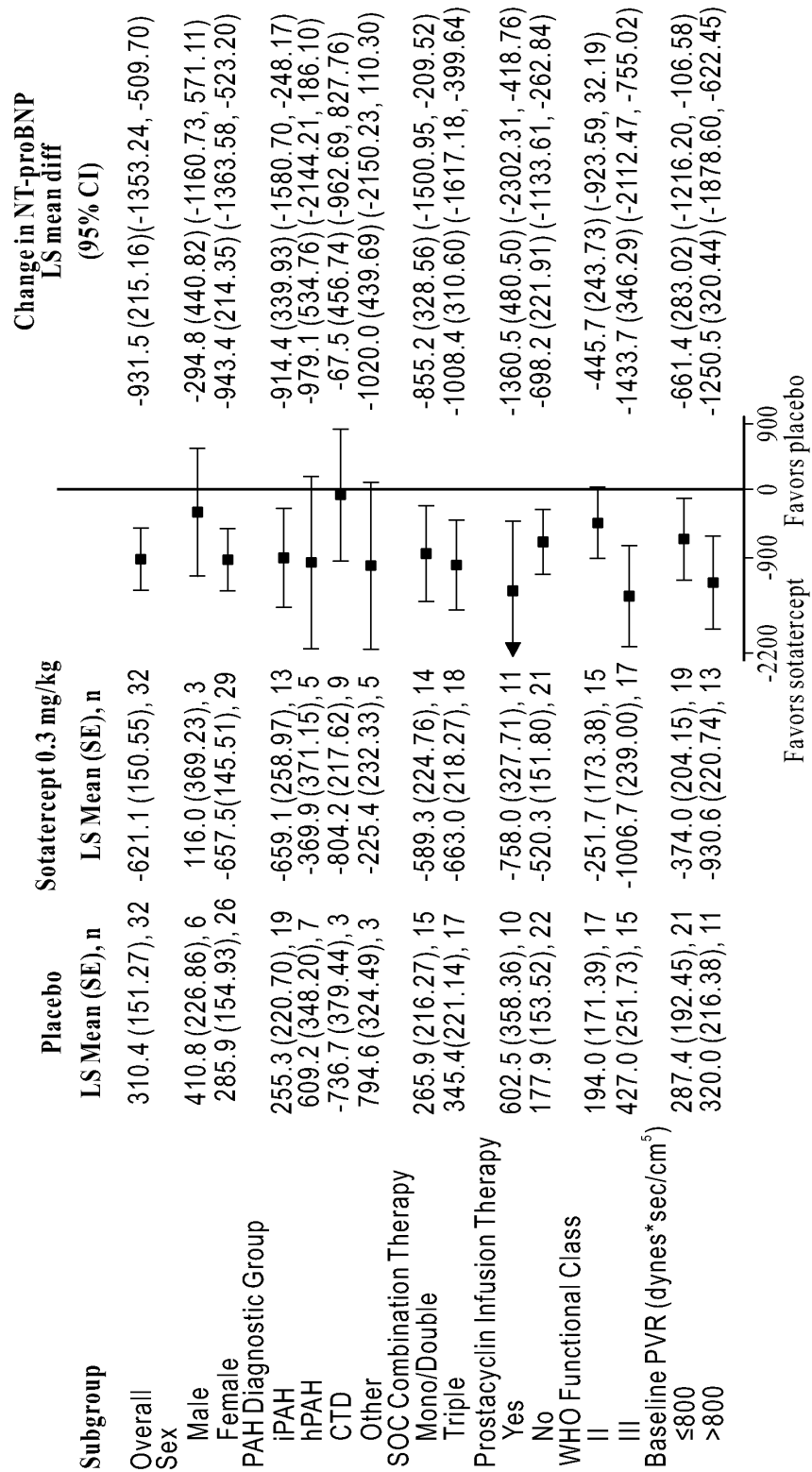


FIG. 11B

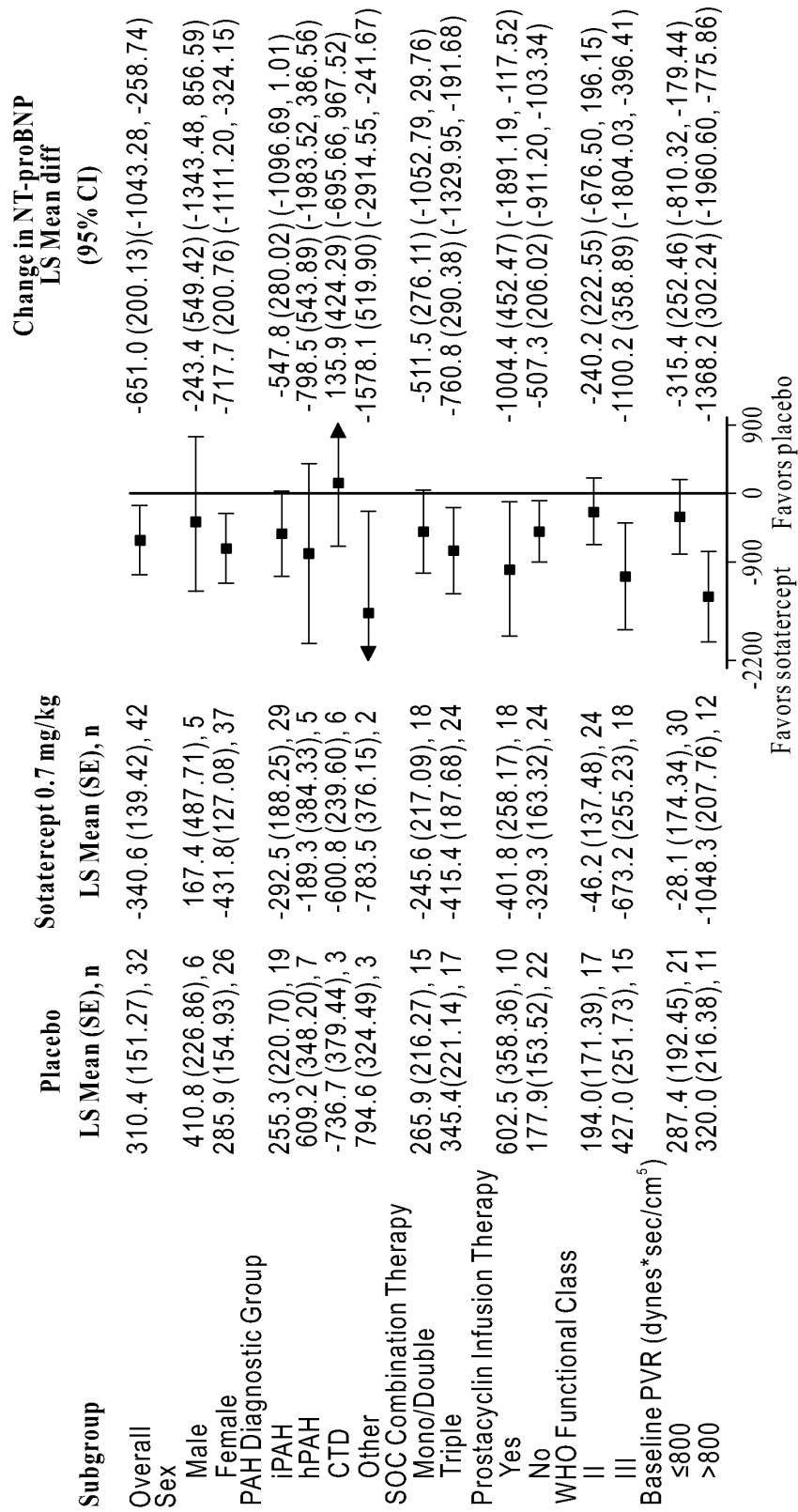


FIG. 11C

Measure	Placebo (N=32)		Sotatercept 0.3 mg/kg (N=32)		Sotatercept 0.7 mg/kg (N=42)		Sotatercept all doses (N=74)	
	LS Baseline	LS Mean Change	LS Baseline	LS Mean Change	LS Baseline	LS Mean Change	LS Baseline	LS Mean Change
				LS Mean Difference (95%CI)		LS Mean Difference (95%CI)		LS Mean Difference (95%CI)
TAPSE (cm)	1.8(0.4)	0.0±0.05	1.8(0.2)	0.0(-0.2, 0.2)	1.8(0.4)	-0.1±0.1 -0.1(-0.2, 0.1)	1.8(0.3)	-0.0± 0.0(-0.2, 0.1)
RVFAC (SE)	25.5 (5.5)	1.9±1.2	28.4(8.1)	5.0±1.1	28.4(10.1)	6.2±1.1	28.5(8.5)	5.5± 0.7 3.7(0.1, 6.4)

FIG. 12

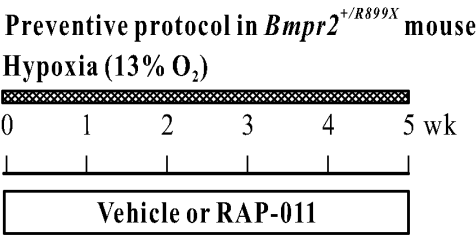


FIG. 13A

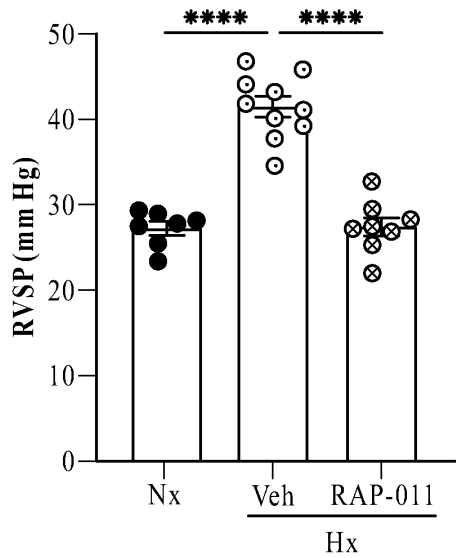


FIG. 13B

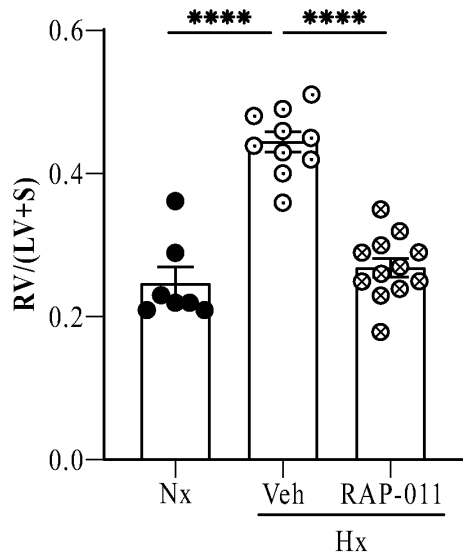


FIG. 13C

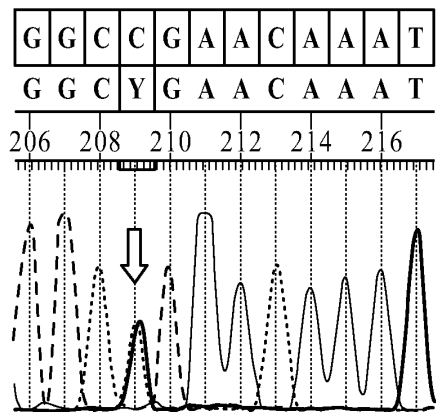


FIG. 13D

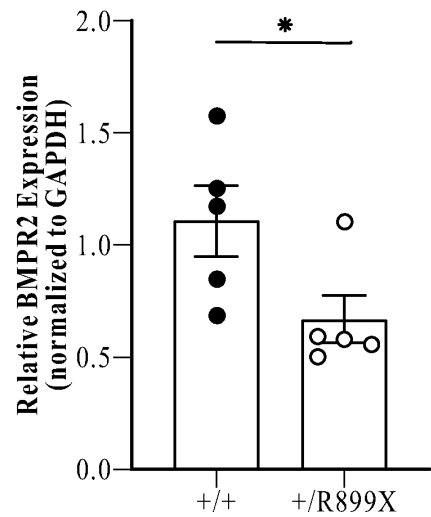


FIG. 13E

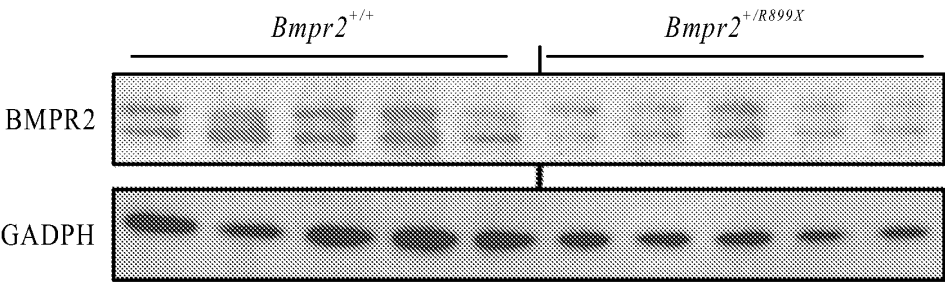


FIG. 13F

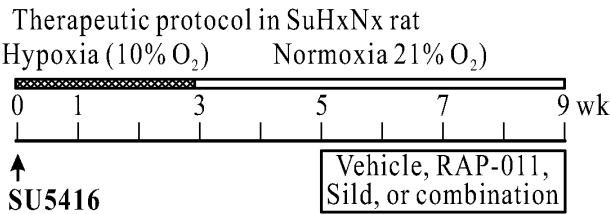


FIG. 14A

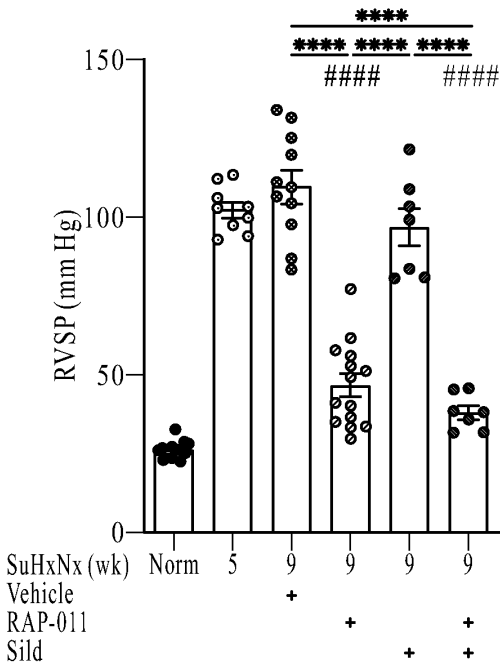


FIG. 14B

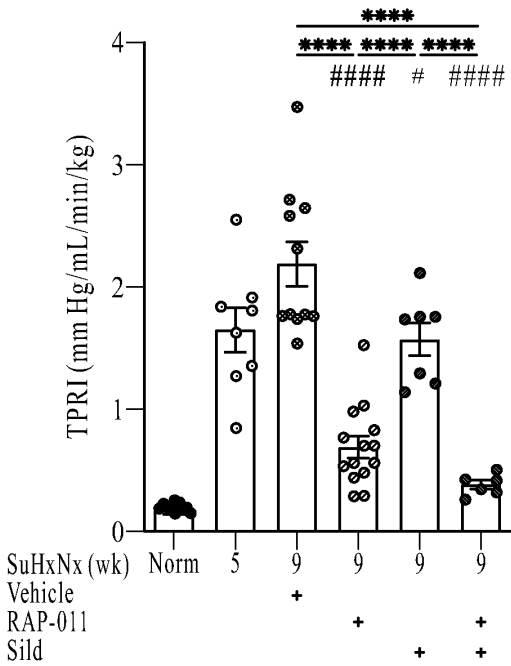


FIG. 14C

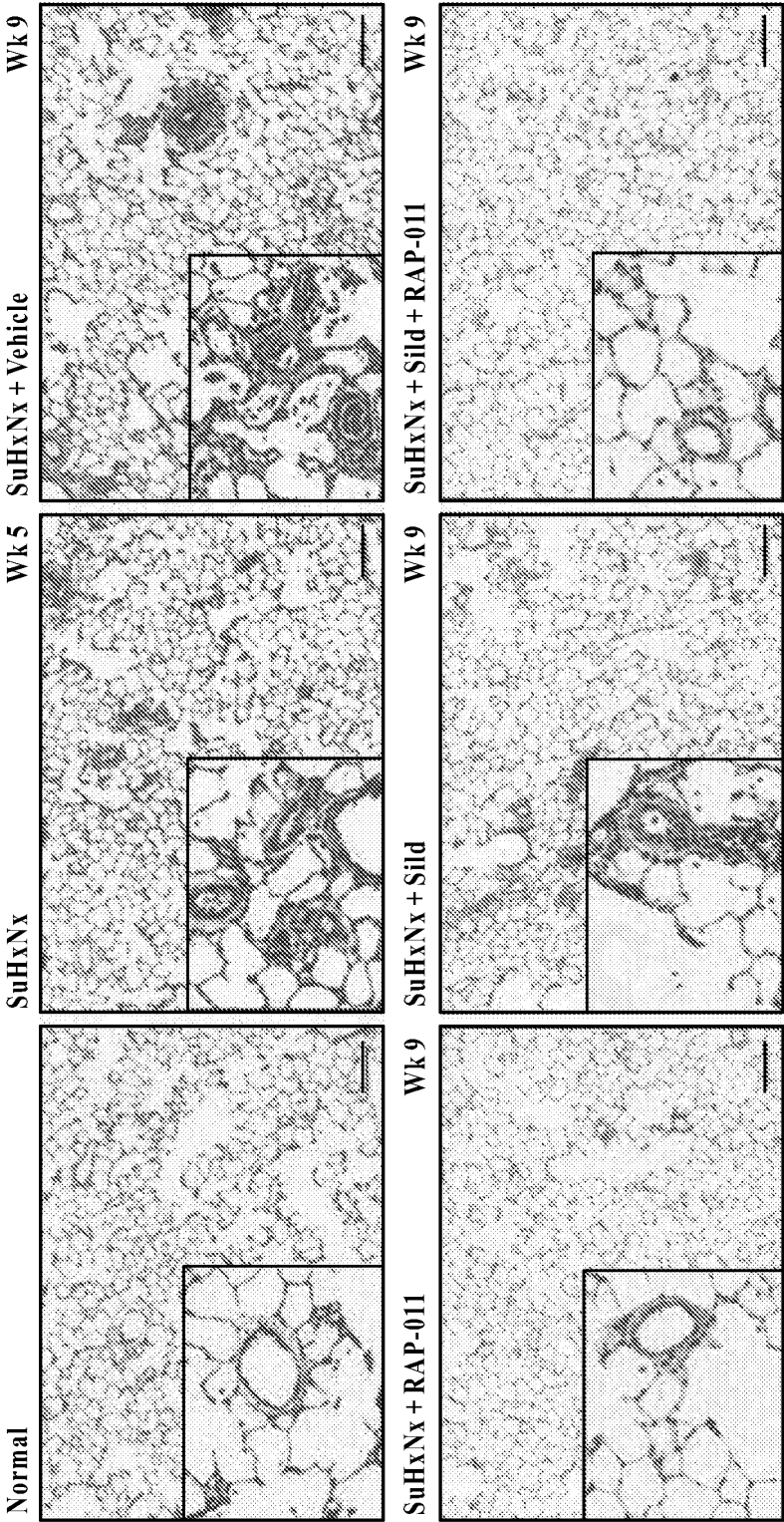
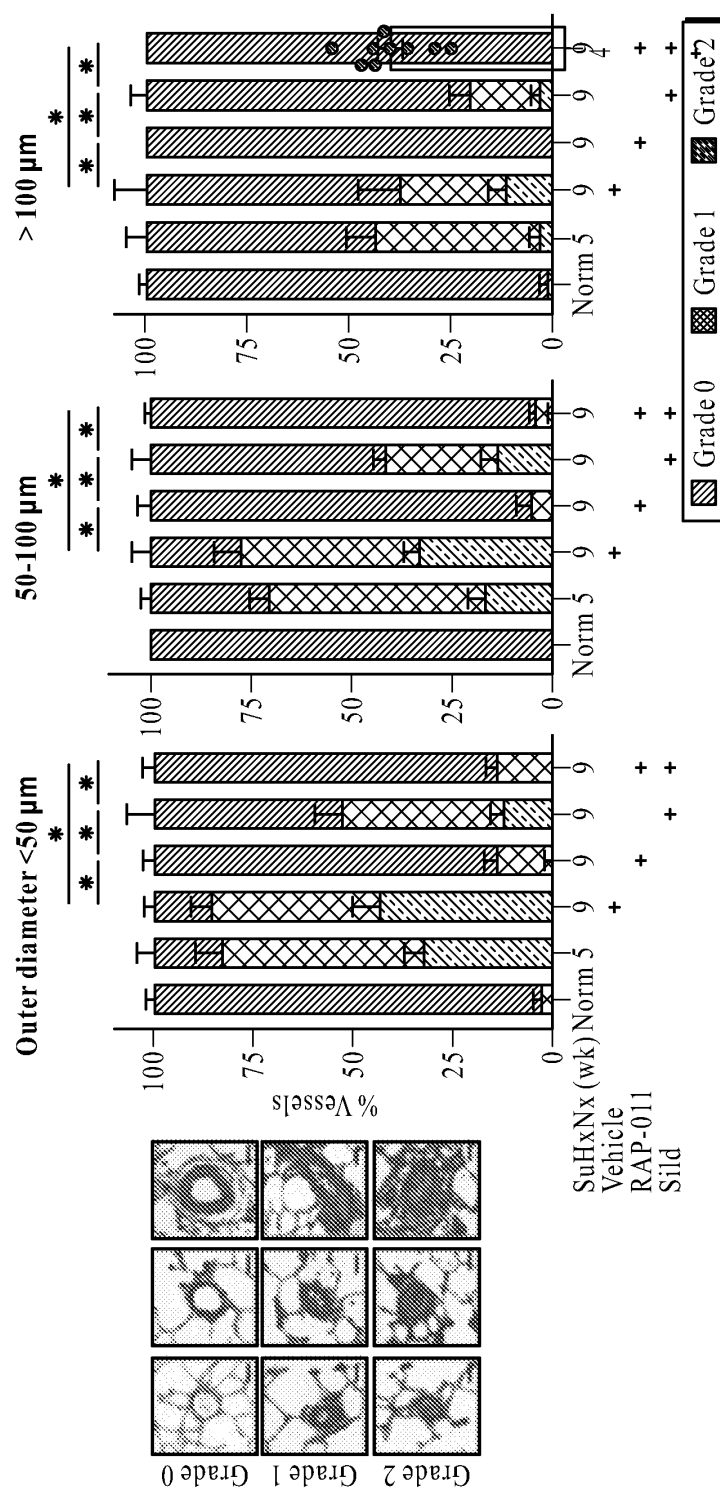


FIG. 14D



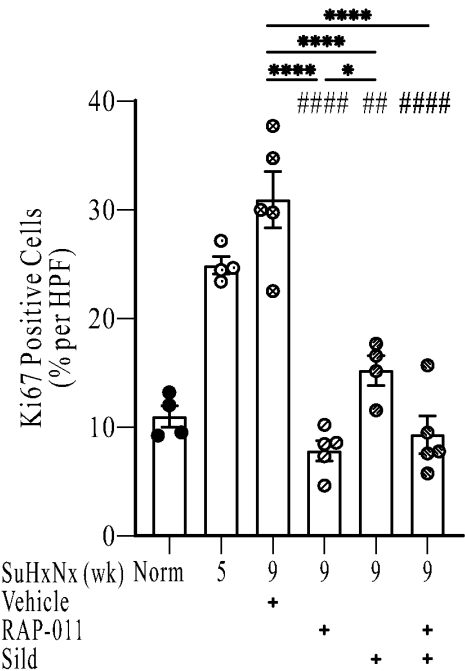


FIG. 15A

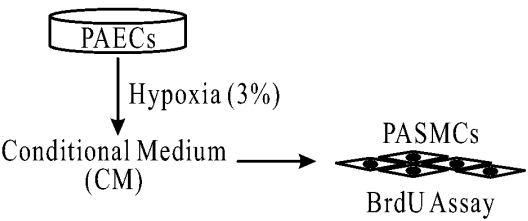


FIG. 15B

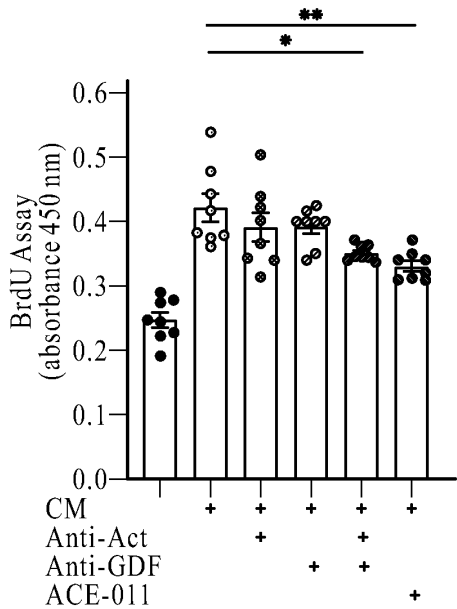


FIG. 15C

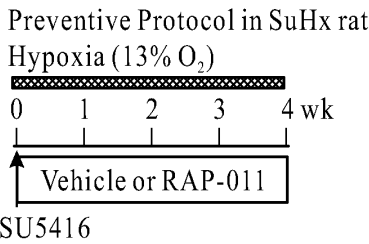


FIG. 15D

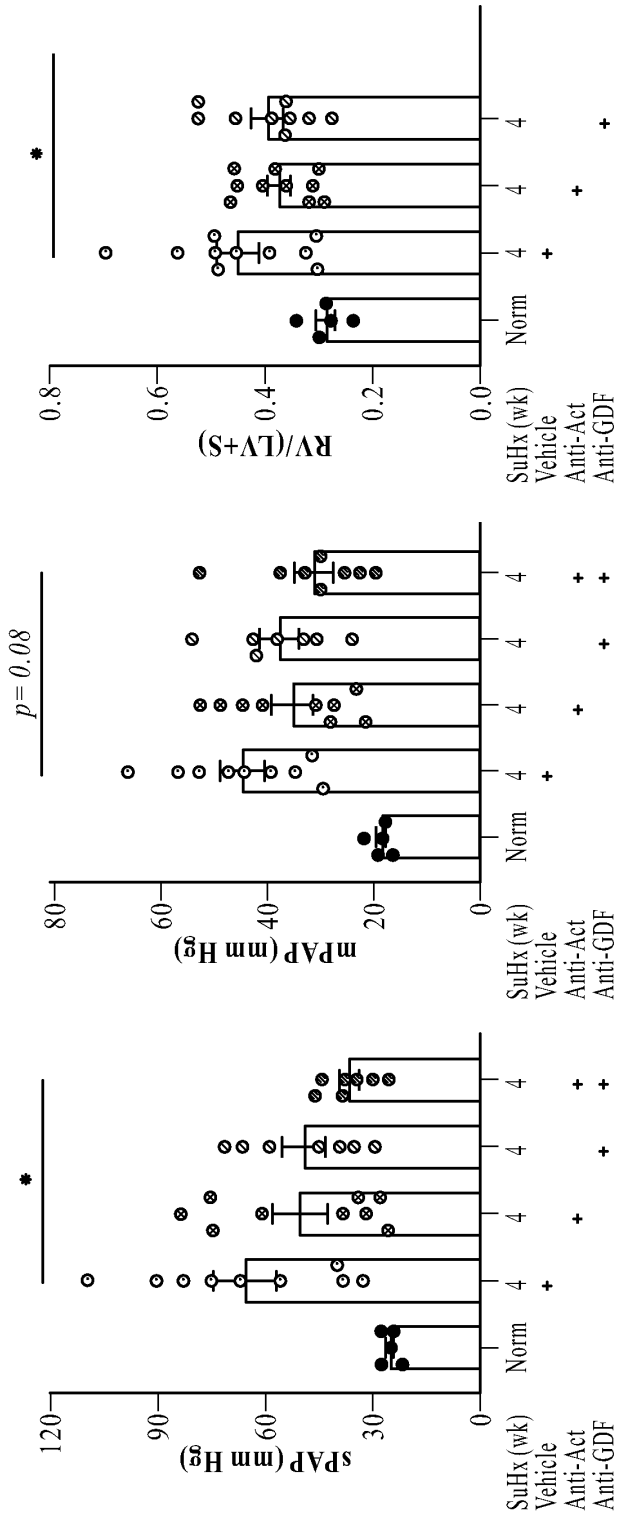


FIG. 15E

FIG. 15F

FIG. 15G

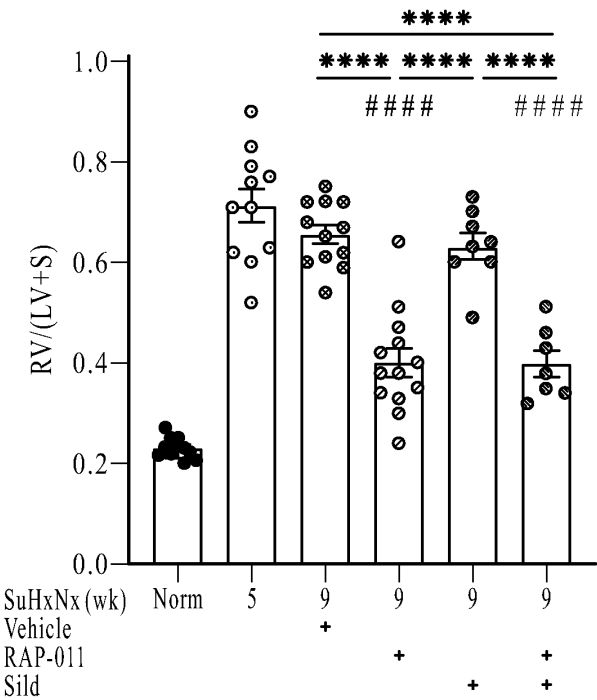


FIG. 16A

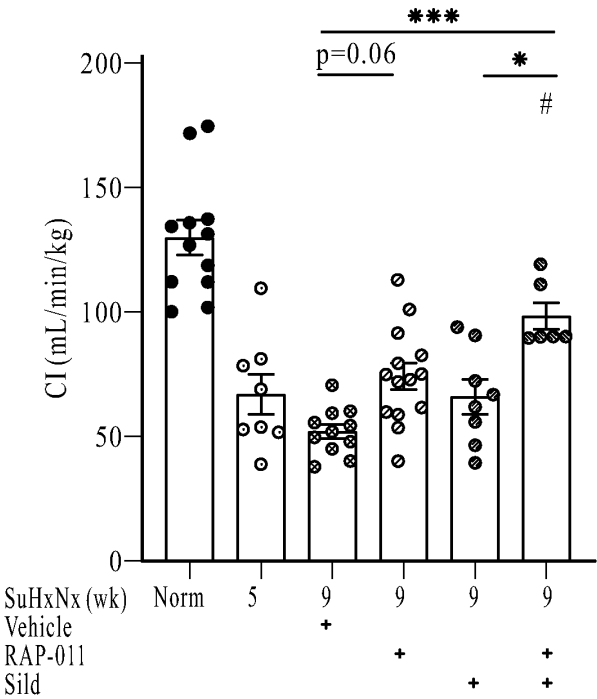


FIG. 16B

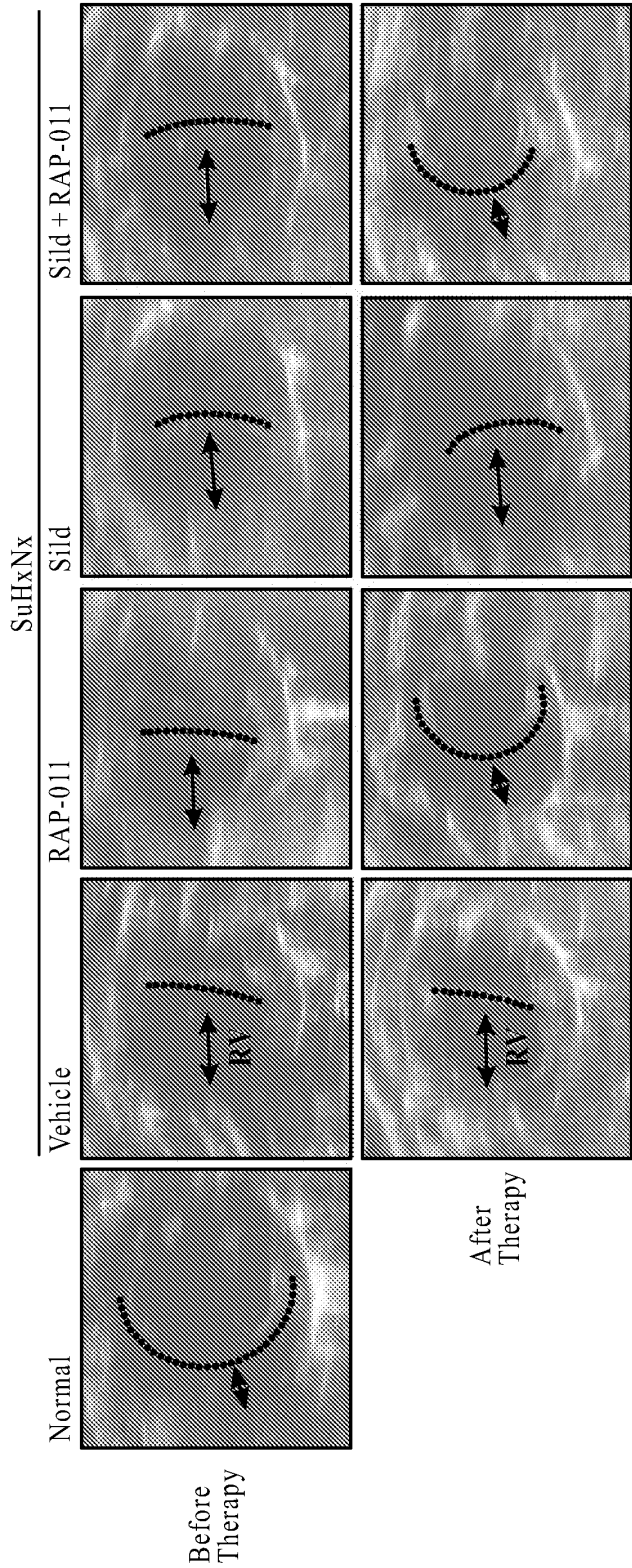


FIG. 16C

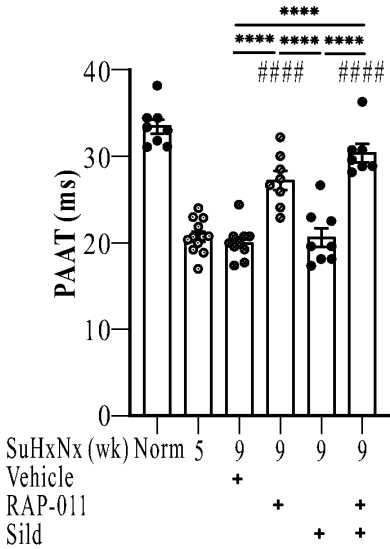


FIG. 16D

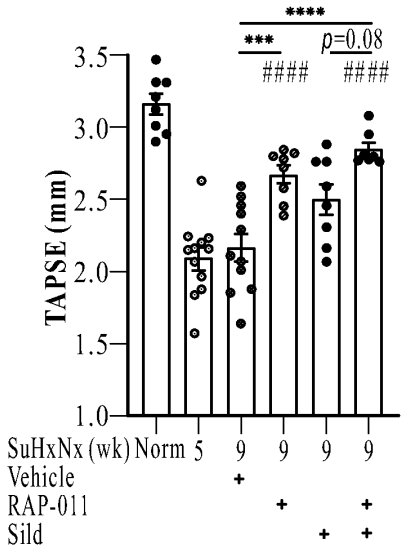


FIG. 16E

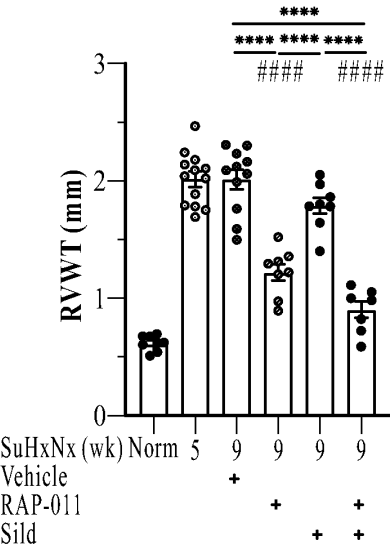


FIG. 16F

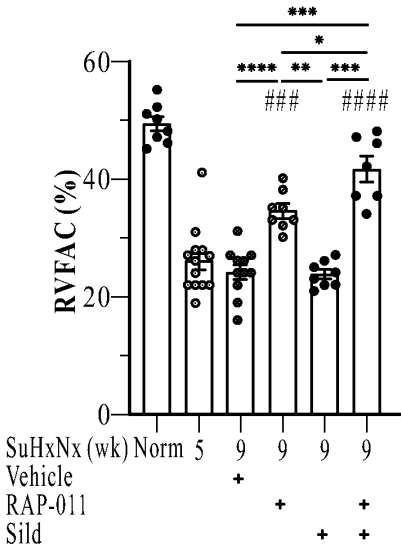


FIG. 16G

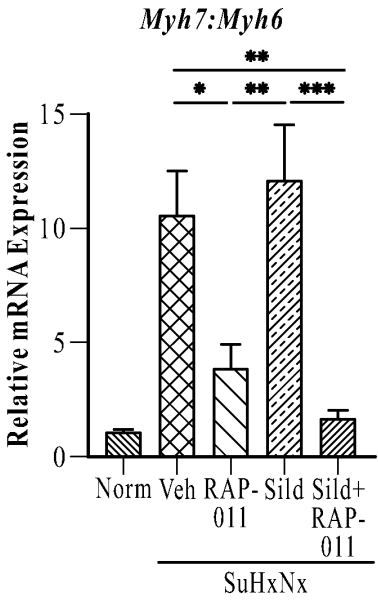


FIG. 16H

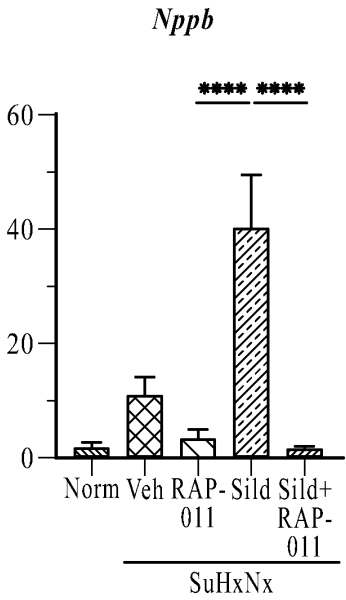


FIG. 16I

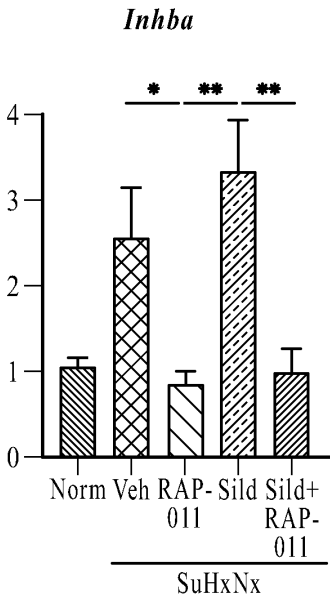


FIG. 16J

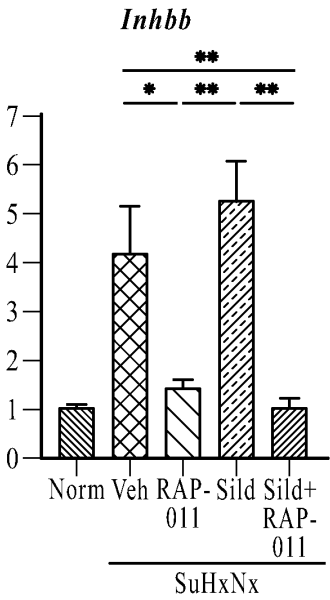


FIG. 16K

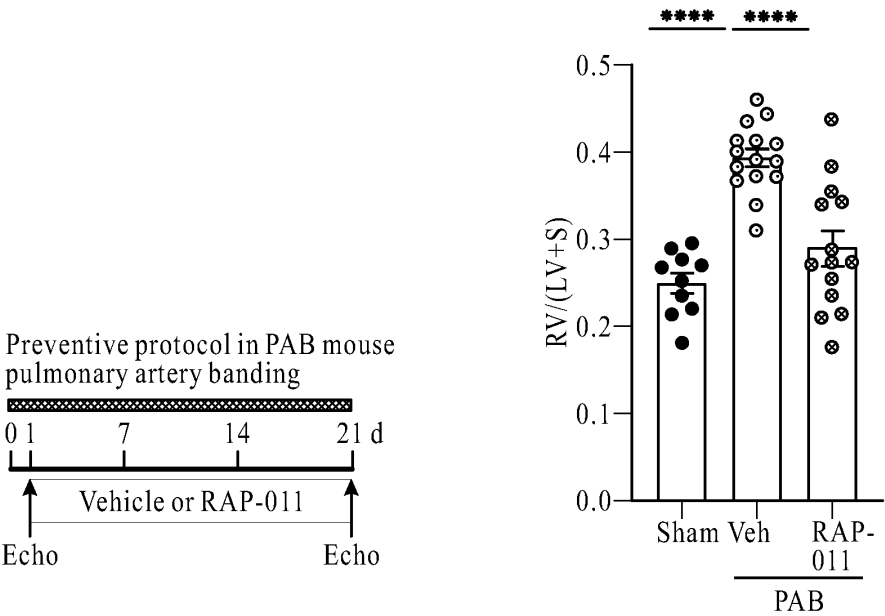


FIG. 17A

FIG. 17B

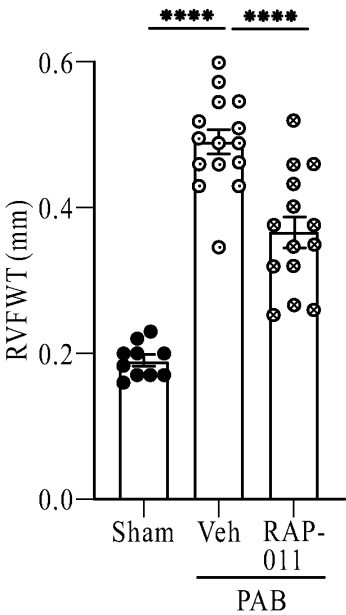


FIG. 17C

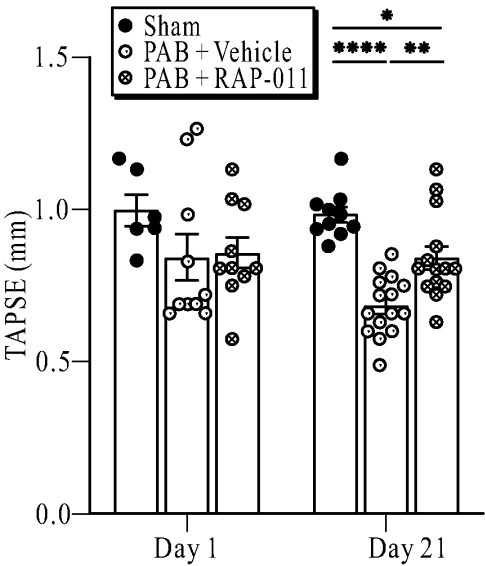


FIG. 17D

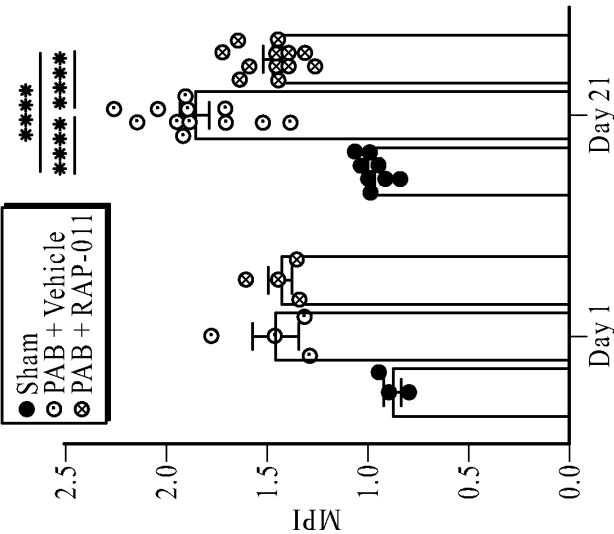


FIG. 17E

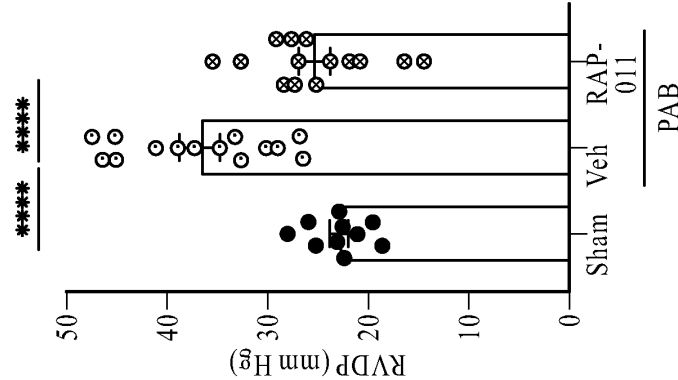


FIG. 17F

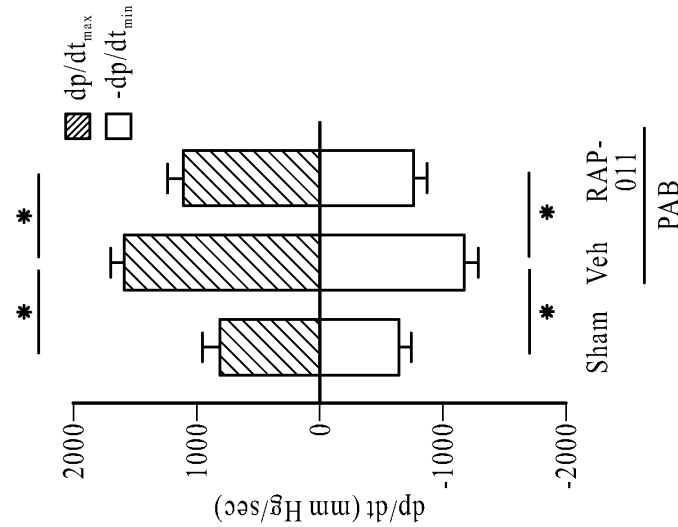


FIG. 17G

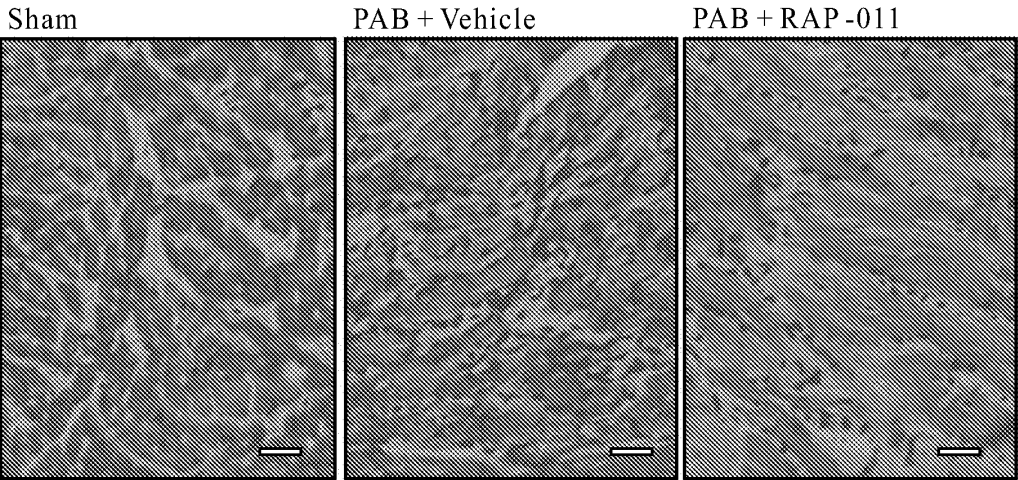


FIG. 17H

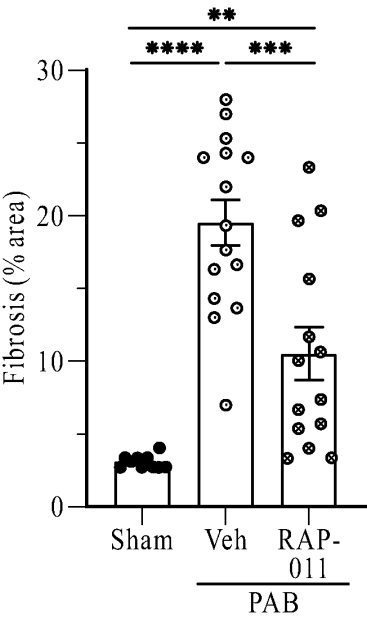


FIG. 17I

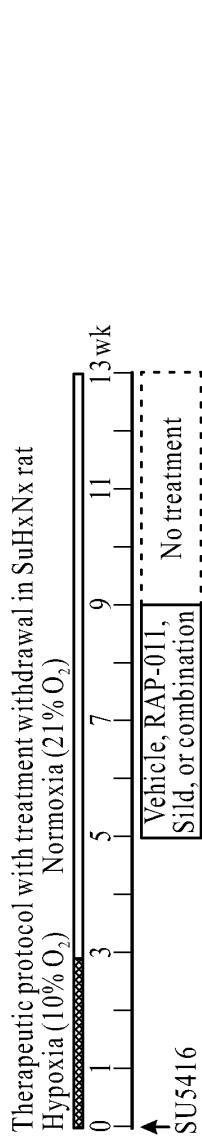


FIG. 18A

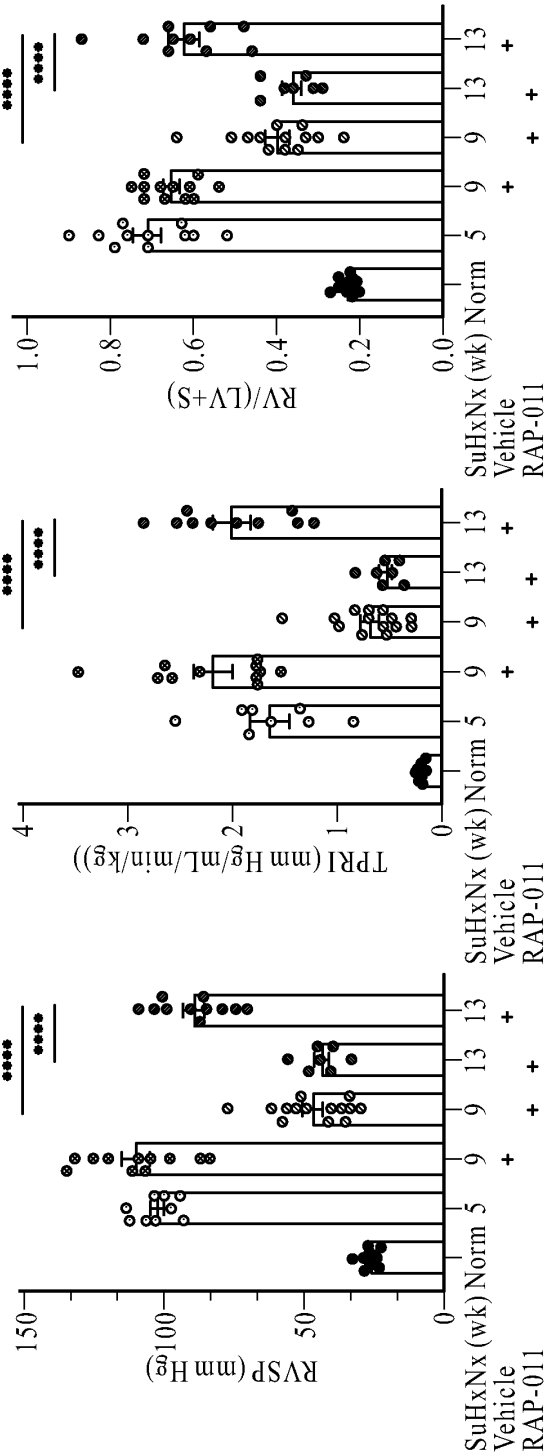


FIG. 18B

FIG. 18C

FIG. 18D

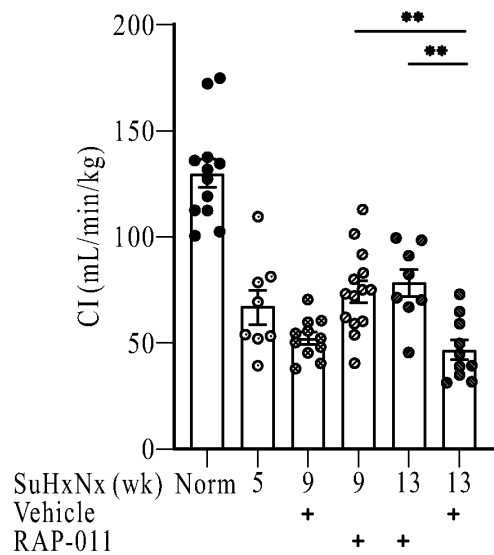


FIG. 18E

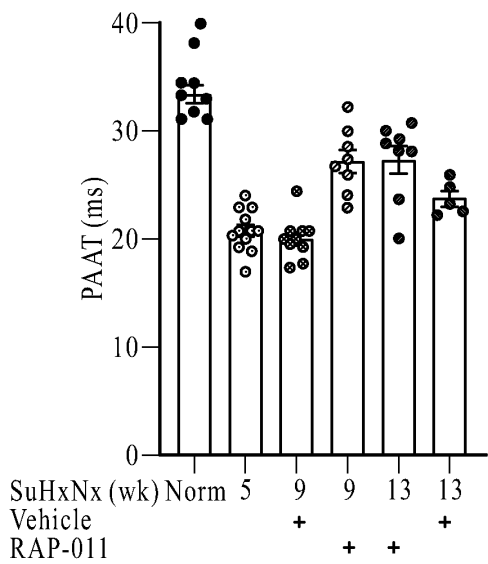


FIG. 18F

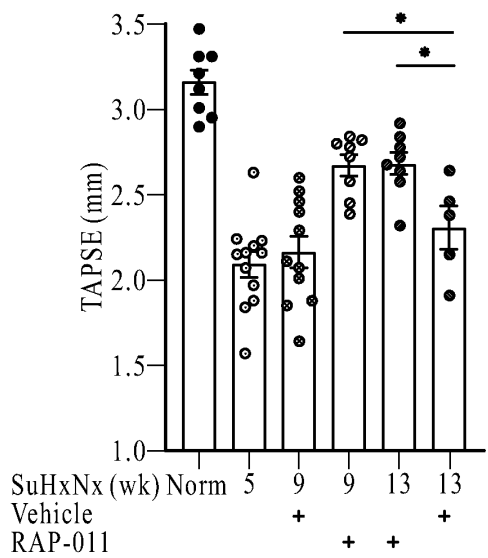


FIG. 18G

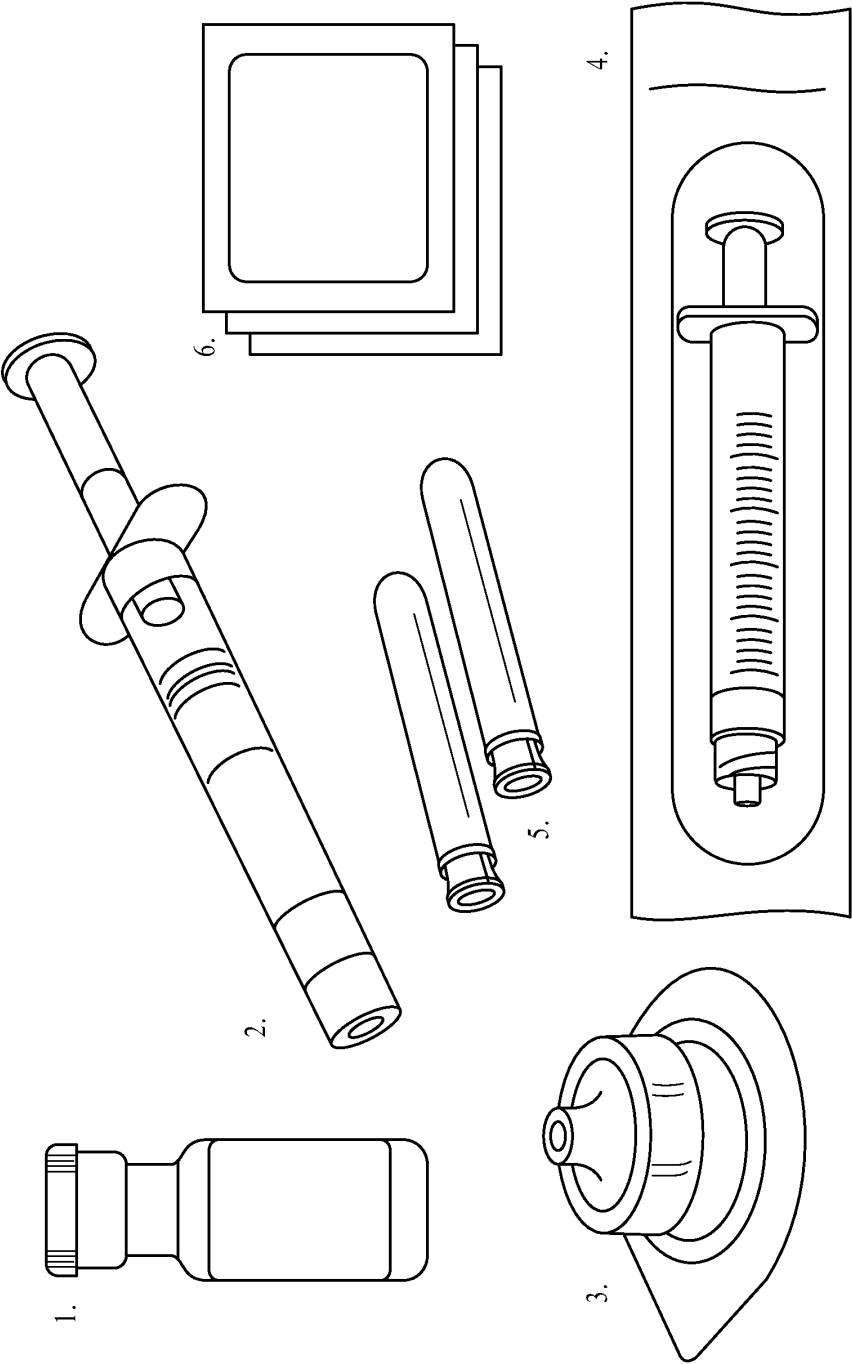


FIG. 19

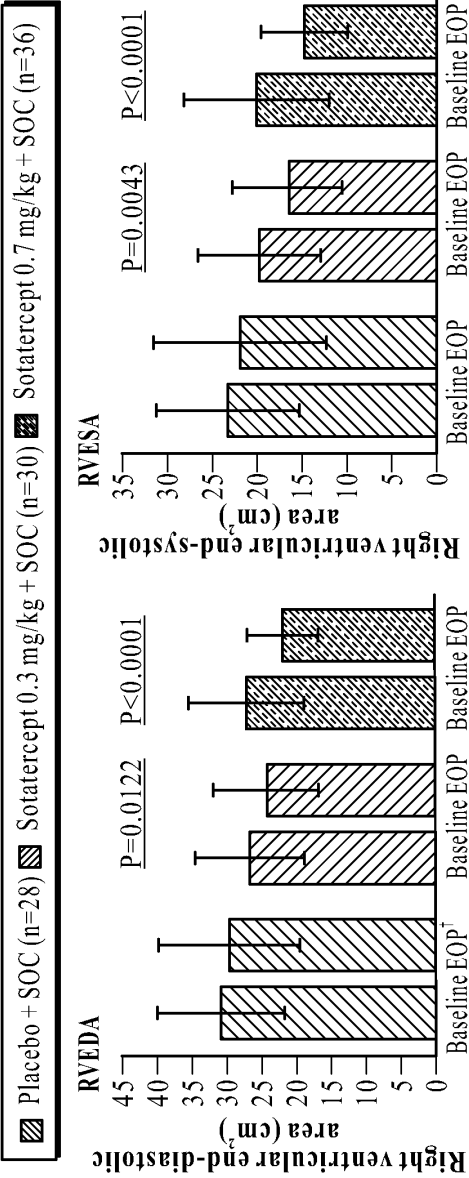


FIG. 20B

Placebo + SOC [†]		Sotatercept 0.3 mg/kg + SOC		Sotatercept 0.7 mg/kg + SOC	
Endpoint	LS mean [‡]	LS mean	LS mean difference (95% CI)	P value	P value
RVEDA (cm ²)	-0.00 (0.68)	-2.5 (0.66)	-2.5(-4.4, -0.55)	0.0122	<0.0001
RVESA (cm ²)	-0.50 (0.63)	-3.1 (0.61)	-2.6(-4.3, -0.83)	0.0043	<0.0001

FIG. 20C

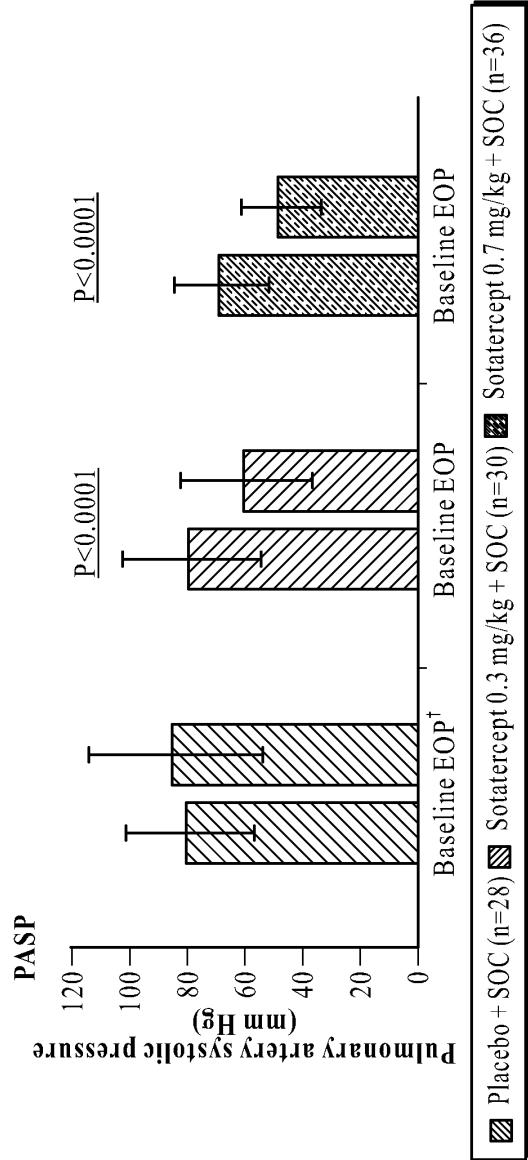
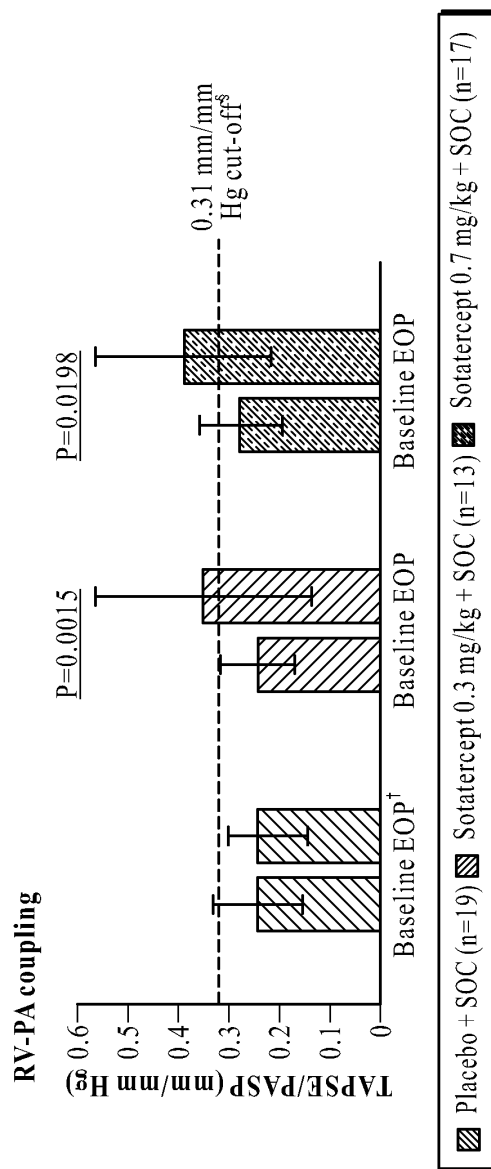


FIG. 21A

	Placebo + SOC	Sotatercept 0.3 mg/kg + SOC		Sotatercept 0.7 mg/kg + SOC	
Endpoint, n	LS mean, n [†]	LS mean, n (95% CI)	P value	LS mean, n (95% CI)	P value
PASP(mm Hg), 54	4.8 (4.1), 20	-24.3 (4.7), 16	<0.0001	-21.9 (4.6), 18	<0.0001

FIG. 21B



	Placebo + SOC	Sotatercept 0.3 mg/kg + SOC				Sotatercept 0.7 mg/kg + SOC			
Endpoint	LS mean [†]	LS mean	LS mean difference (95% CI)	P value		LS mean	LS mean difference (95% CI)	P value	
RV -PA coupling (mm/mm Hg)	-0.02 (0.03)	0.13 (0.03)	0.15 (0.06, 0.24)	0.0015		0.09 (0.03)	0.10 (0.02, 0.2)	0.0198	

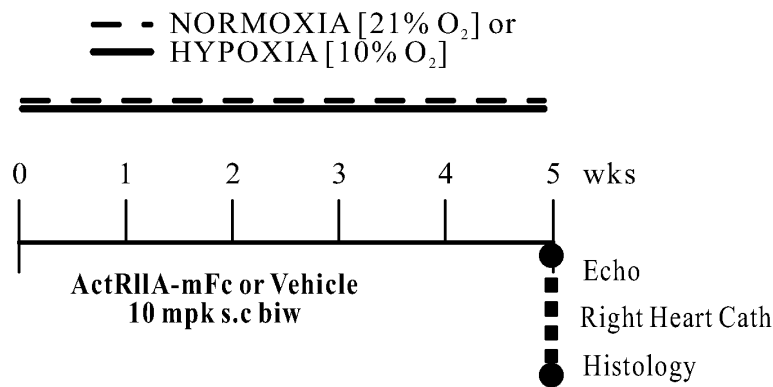


FIG. 23A

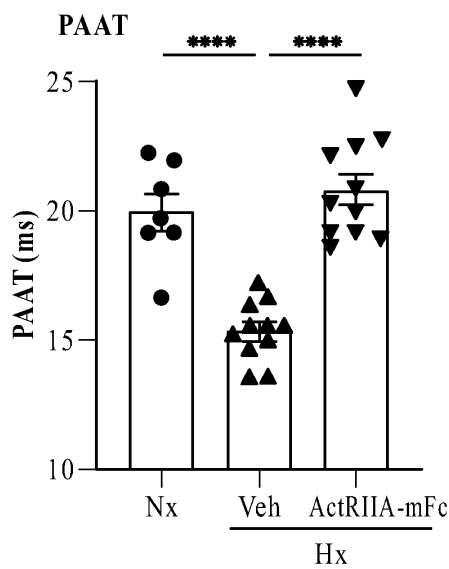


FIG. 23B

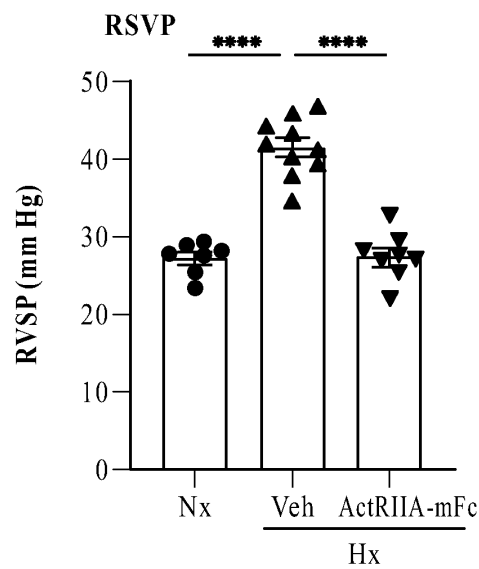


FIG. 23C

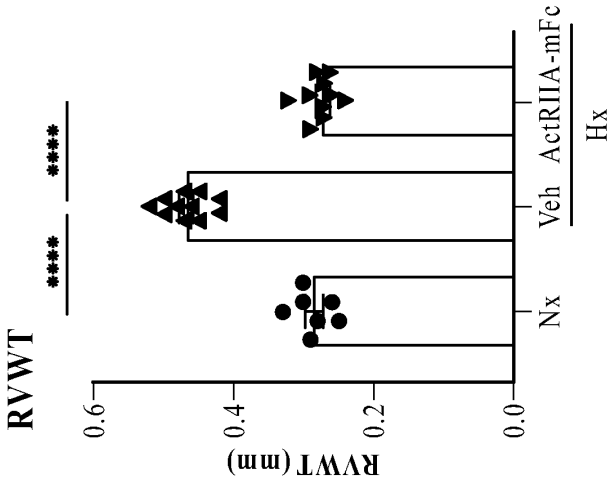


FIG. 23D

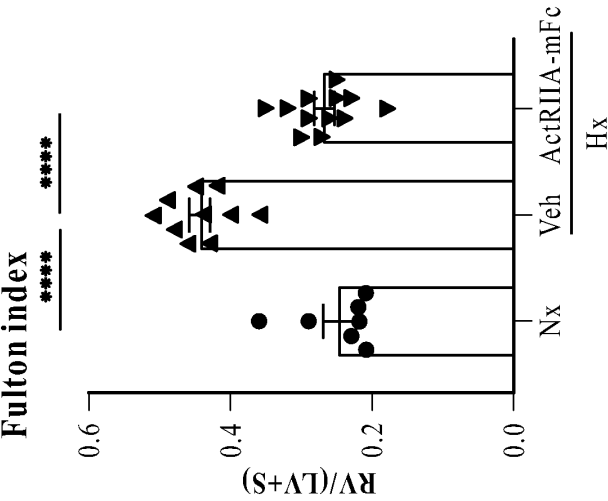


FIG. 23E

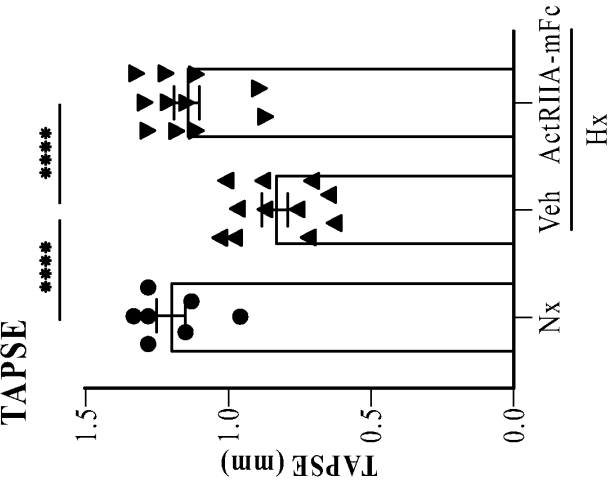


FIG. 23F

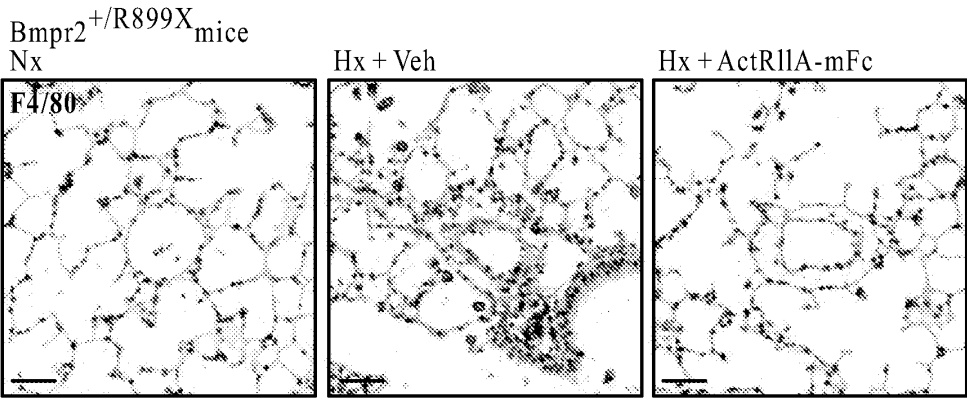


FIG. 24A

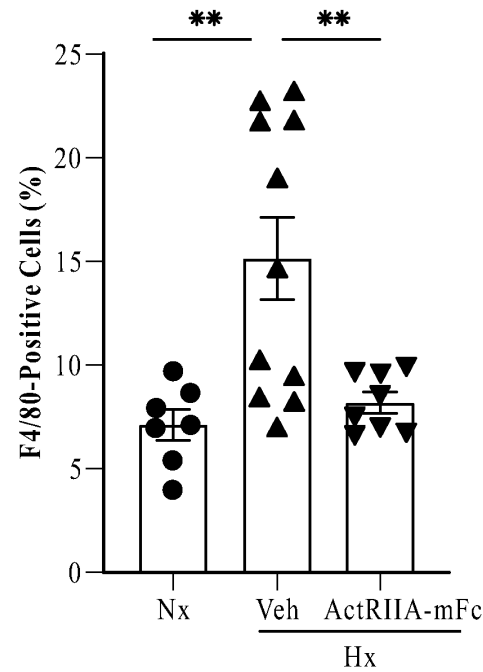


FIG. 24B