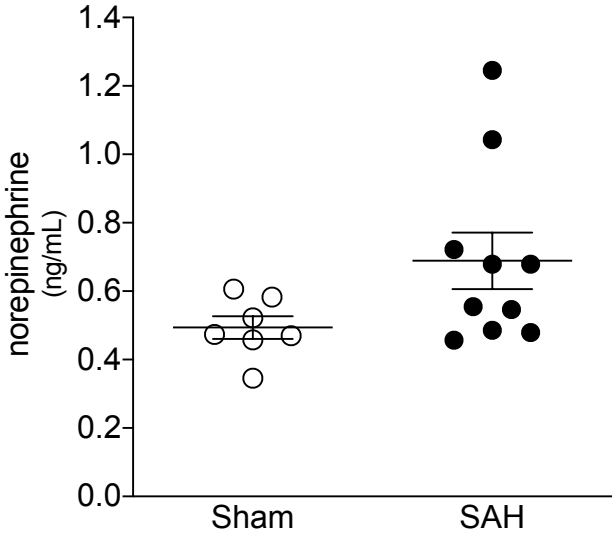
Supplementary Material

SUPPLEMENTARY FIGURE 1

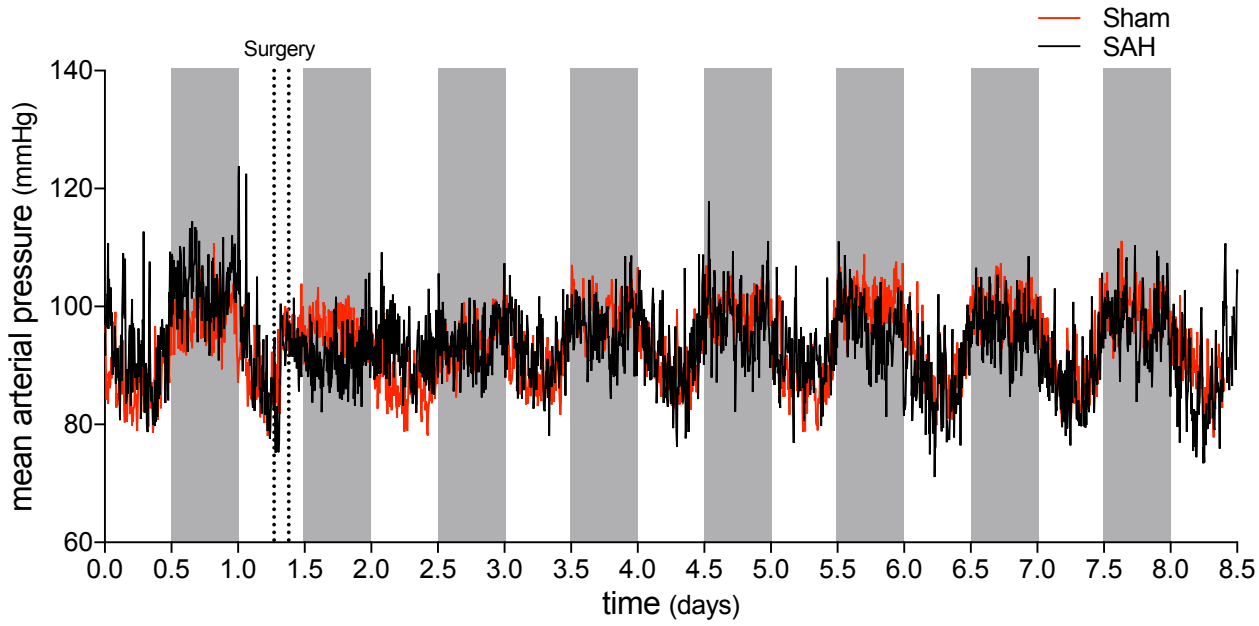


Plasma norepinephrine levels mice with subarachnoid hemorrhage

At 2-days post-subarachnoid hemorrhage (SAH) induction, circulating plasma norepinephrine levels are not different between SAH and sham-operated control mice (sham n=7, SAH n=10). The SAH group did not pass the Shapiro-Wilk normalicy test; the data are therefore compared with a non-parametric Mann-Whitney test (P=NS).

Supplementary Material

SUPPLEMENTARY FIGURE 2

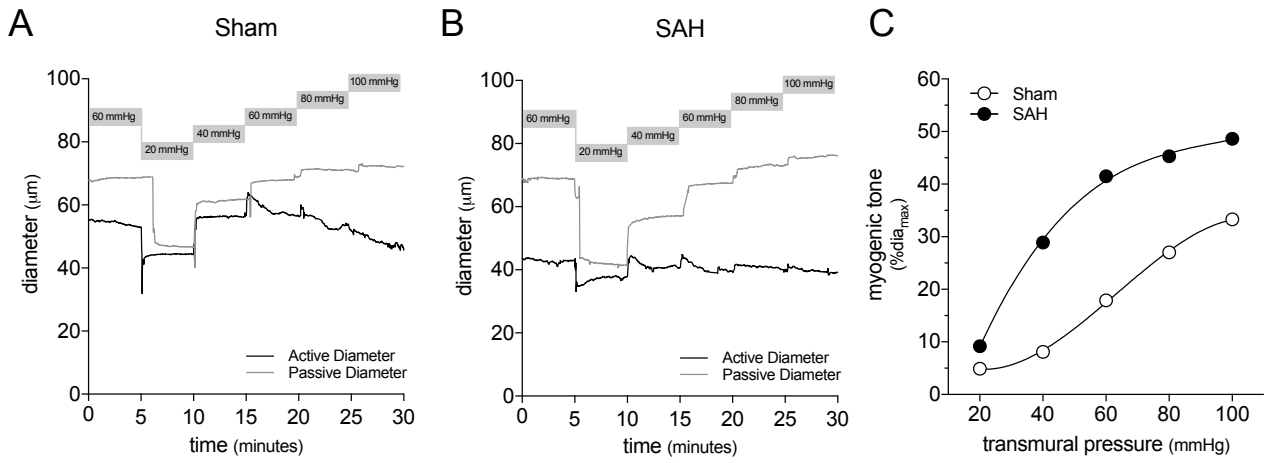


Telemetric blood pressure measurements in mice with subarachnoid hemorrhage

Telemetric mean arterial blood pressure measurements in conscious mice indicate that mice with subarachnoid hemorrhage (SAH; n=3) *do not* develop hypertension within 1-week post-SAH induction (sham n=5). Baseline measurements were collected 1 day prior to SAH or sham surgery; the surgical window is delineated by dotted vertical lines. White and gray shading indicate "lights on" and "lights off" periods, respectively.

Supplementary Material

SUPPLEMENTARY FIGURE 3

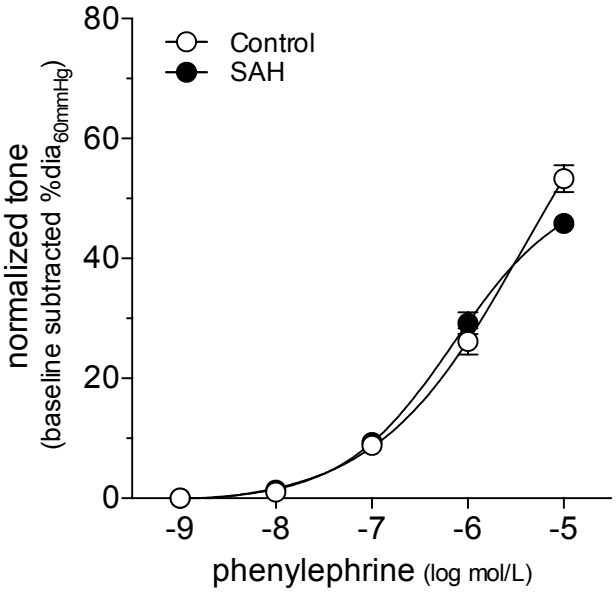


Representative diameter measurements

Stepwise increases in transmural pressure (20-100mmHg) are indicated in the boxes above the tracing. The active diameter tracing is acquired first ("dia_{active}"; black line), followed by measurement of passive diameter under calcium-free conditions ("dia_{max}"; gray line). Shown are representative diameter tracings from cremaster skeletal muscle resistance arteries isolated from **(A)** sham-operated mice (dia_{max} = 68 μm) and **(B)** mice with subarachnoid hemorrhage (SAH; dia_{max} = 68 μm). Myogenic tone is calculated as the percent constriction in relation to the maximal diameter at each respective transmural pressure: tone (% of dia_{max}) = [(dia_{max}-dia_{active})/dia_{max}]x100. ***Panel C*** displays the calculated myogenic tone measures for the arteries displayed in *Panels A and B*.

Supplementary Material

SUPPLEMENTARY FIGURE 4

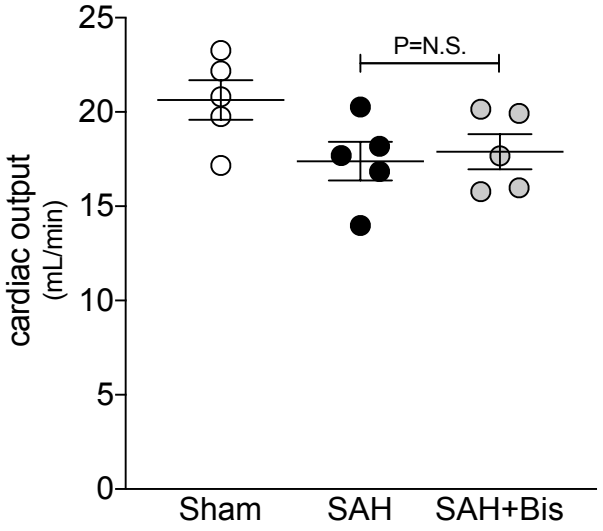


Baseline-normalized phenylephrine responses mice with subarachnoid hemorrhage

When baseline tone is normalized, phenylephrine-stimulated vasoconstriction in cremaster skeletal muscle resistance arteries isolated from mice with subarachnoid hemorrhage (SAH; at 2 days post-induction) are not different from sham-operated controls. Data were statistically compared with a 2-way ANOVA (P=N.S.; sham dia_{max}: 78±2 μm, n=26; SAH 78±2 μm, n=22).

Supplementary Material

SUPPLEMENTARY FIGURE 5

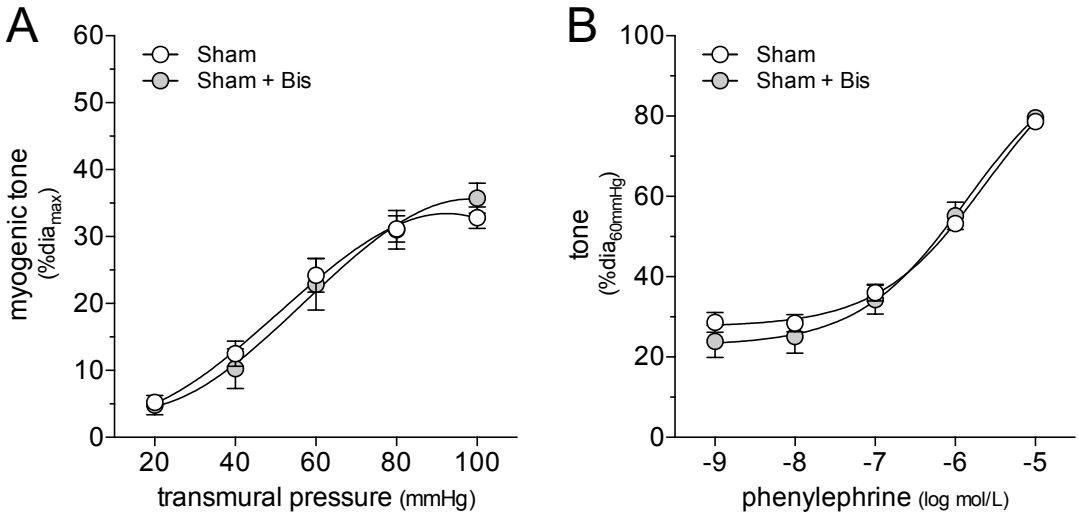


Post-operative bisoprolol treatment does not protect cardiac function following subarachnoid hemorrhage

When delivered immediately following experimental subarachnoid hemorrhage (SAH) induction, bisoprolol treatment (Bis; twice daily for 2 days with i.p. injections; 10 mg/kg initial pre-operative dose followed by 5 mg/kg for all subsequent injections) does not prevent the reduction in cardiac output at 2-days post-SAH (n=5 for all groups). The SAH and SAH+Bis groups were statistically compared with a Student's t test (P=N.S.).

Supplementary Material

SUPPLEMENTARY FIGURE 6

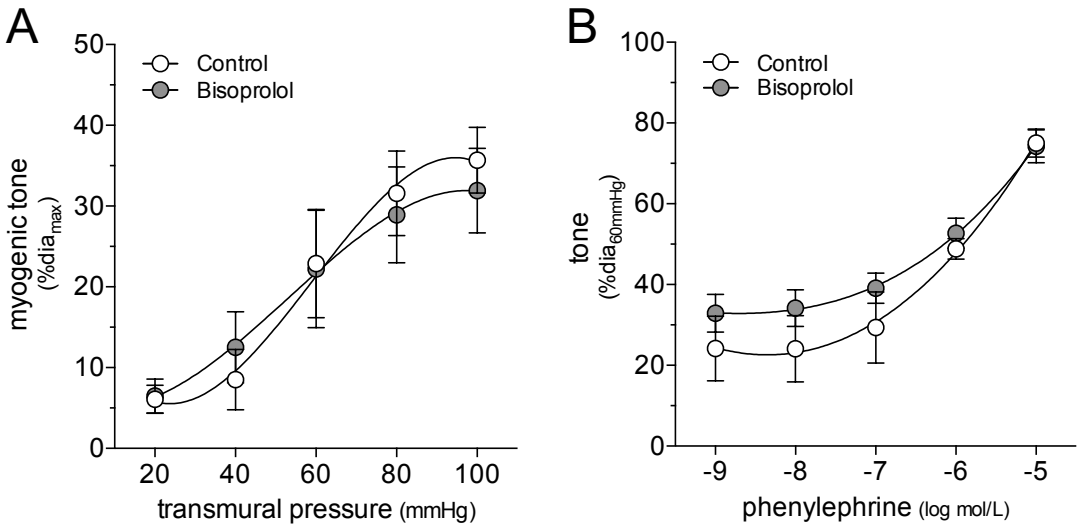


Bisoprolol does not alter cremaster artery reactivity in sham animals

In sham-operated mice, *in vivo* bisoprolol treatment (Bis; twice daily for 2 days with i.p. injections; 10 mg/kg initial pre-operative dose followed by 5 mg/kg for all subsequent injections) has no effect on **(A)** myogenic reactivity or **(B)** phenylephrine responses in cremaster skeletal muscle resistance arteries isolated at 2 days post-surgery/treatment (sham dia$_{max}$: 80±2 μm, n=13; Sham+Bis dia$_{max}$: 70±4 μm, n=9). The sham data in both panels are reproduced from *Figure 2* for comparison to the Sham+Bis data. Data were statistically compared with a 2-way ANOVA (P=N.S.)

Supplementary Material

SUPPLEMENTARY FIGURE 7

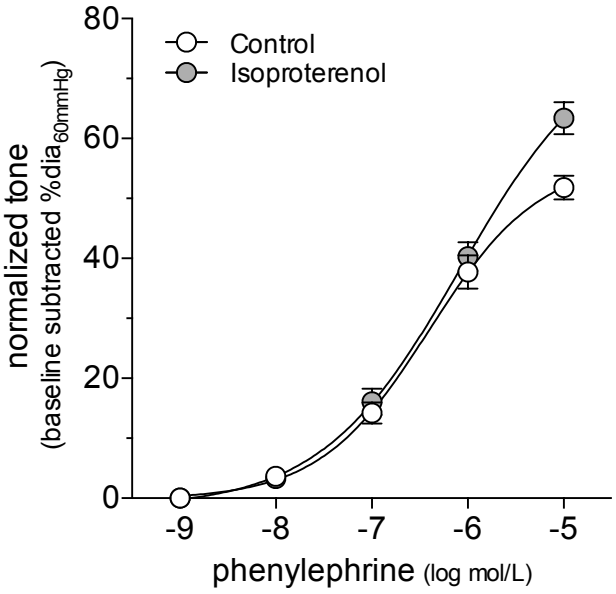


Bisoprolol does not alter cremaster artery reactivity in vitro

In vitro, bisoprolol (5 μmol/L for 30 minutes) does not affect cremaster skeletal muscle resistance artery **(A)** myogenic reactivity or **(B)** phenylephrine responses (dia_{max} = 76±5, n=4). Data were statistically compared with a repeated measures 2-way ANOVA (P=N.S.).

Supplementary Material

SUPPLEMENTARY FIGURE 8

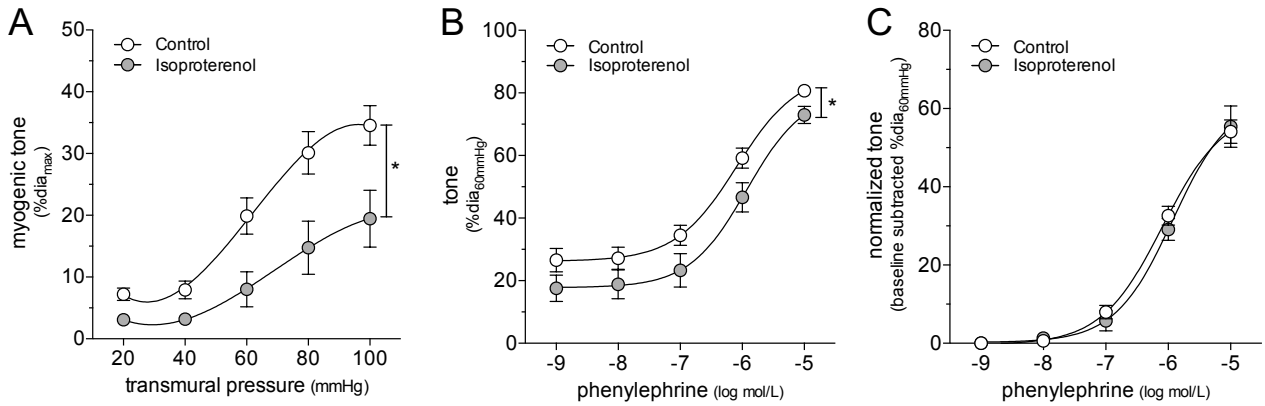


Baseline-normalized phenylephrine responses for isoproterenol-treated mice

When baseline tone is normalized, phenylephrine responses in cremaster skeletal muscle resistance arteries isolated from isoproterenol-treated mice (150 mg/kg/day i.p. for 2 days) are not different from saline-treated controls. Data were statistically compared with a 2-way ANOVA (P=N.S.; control dia_{max}: 80±4 μm, n=8; isoproterenol dia_{max}: 79±2 μm, n=8).

Supplementary Material

SUPPLEMENTARY FIGURE 9

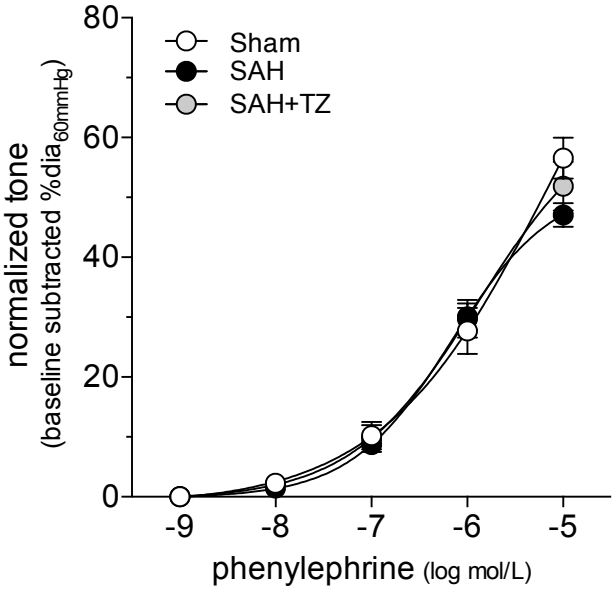


Isoproterenol alters cremaster artery myogenic reactivity in vitro

(A) *In vitro*, isoproterenol (1µmol/L for 30 minutes) attenuates cremaster skeletal muscle resistance artery myogenic reactivity. **(B)** Phenylephrine responses are also attenuated by isoproterenol treatment, due to a shift in basal tone. **(C)** When baseline tone is normalized, phenylephrine responses are unaffected by isoproterenol treatment. All data were statistically compared with a paired 2-way ANOVA (dia_{max} = 73±3, n=8). * denotes $P<0.05$.

Supplementary Material

SUPPLEMENTARY FIGURE 10

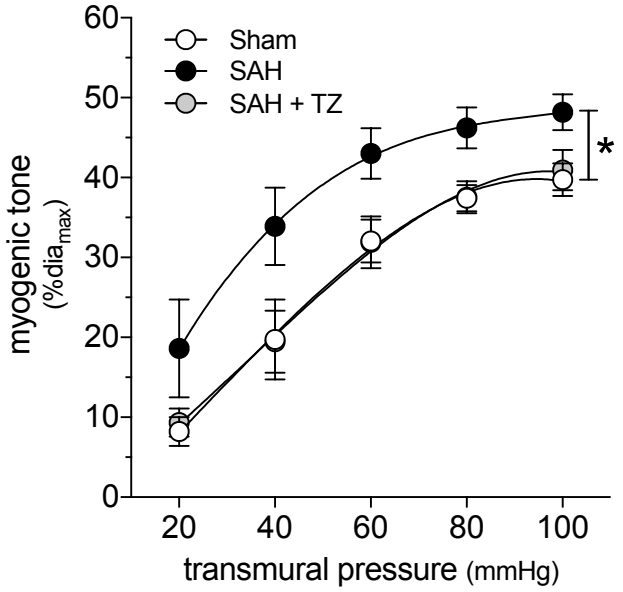


Baseline-normalized phenylephrine responses for terazosin-treated mice

When baseline tone is normalized, phenylephrine responses in cremaster skeletal muscle resistance arteries isolated from SAH mice are not different from those isolated from sham-operated controls. Normalized phenylephrine responses in cremaster skeletal muscle resistance arteries isolated from terazosin-treated mice (TZ; twice daily for 2 days with i.p. injections; 1 mg/kg initial pre-operative dose followed by 0.5 mg/kg for all subsequent injections) are also not different from sham-operated controls. Data were statistically compared with a 2-way ANOVA (P=N.S.; sham dia_{max}: 76±3 μm, n=13; SAH dia_{max}: 76±3 μm, n=12; SAH+TZ dia_{max}: 74±2 μm, n=13).

Supplementary Material

SUPPLEMENTARY FIGURE 11

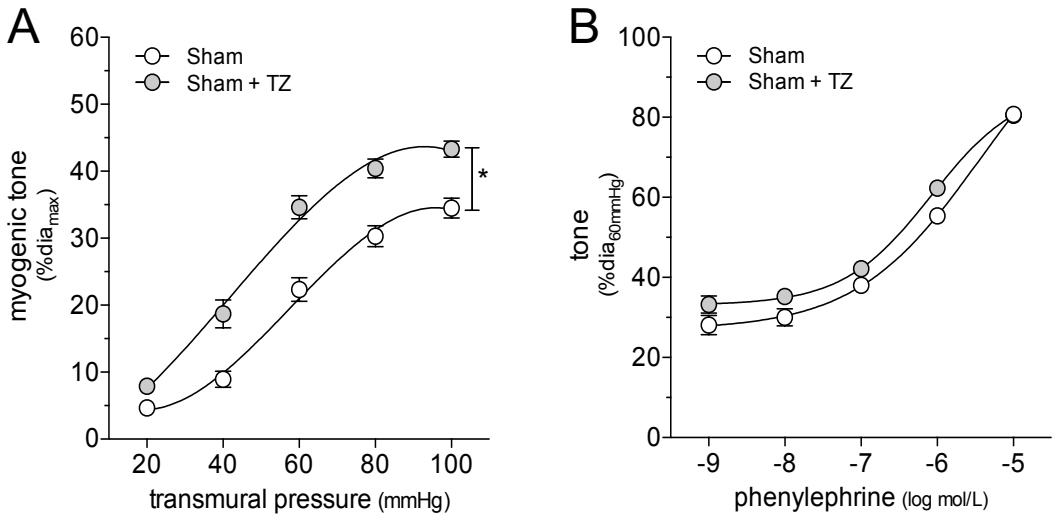


Post-operative terazosin treatment normalizes myogenic reactivity following subarachnoid hemorrhage

When delivered immediately following experimental subarachnoid hemorrhage (SAH) induction, terazosin (TZ; twice daily for 2 days with i.p. injections; 1 mg/kg initial dose followed by 0.5 mg/kg for all subsequent injections) normalizes the augmented myogenic vasoconstriction observed in cremaster skeletal muscle resistance arteries at 2-days post-SAH. Data were statistically compared with a 2-way ANOVA (sham dia_{max}: 72±4 μm, n=5; SAH dia_{max}: 76±6 μm, n=5; SAH+TZ dia_{max}: 72±5 μm, n=6). * denotes $P<0.05$.

Supplementary Material

SUPPLEMENTARY FIGURE 12

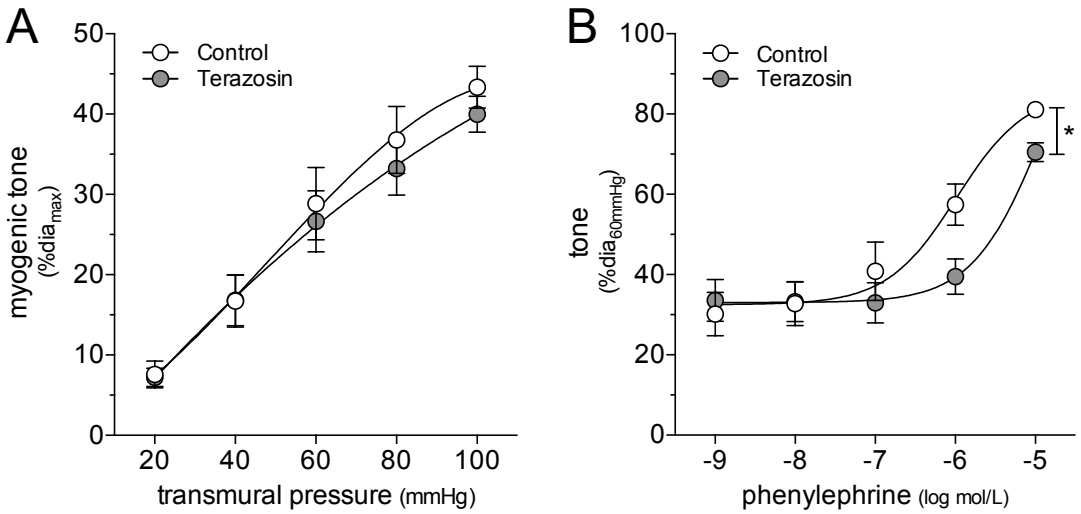


Terazosin augments cremaster artery myogenic reactivity in sham animals

In sham-operated mice, *in vivo* terazosin treatment (TZ; twice daily for 2 days with i.p. injections; 1 mg/kg initial pre-operative dose followed by 0.5 mg/kg for all subsequent injections) **(A)** augments myogenic reactivity in cremaster skeletal muscle resistance arteries isolated at 2 days post-surgery/treatment, but **(B)** does not alter phenylephrine responses (sham dia$_{max}$: 75±2 μm, n=19; Sham+TZ dia$_{max}$: 76±3 μm, n=26). * denotes P<0.05.

Supplementary Material

SUPPLEMENTARY FIGURE 13

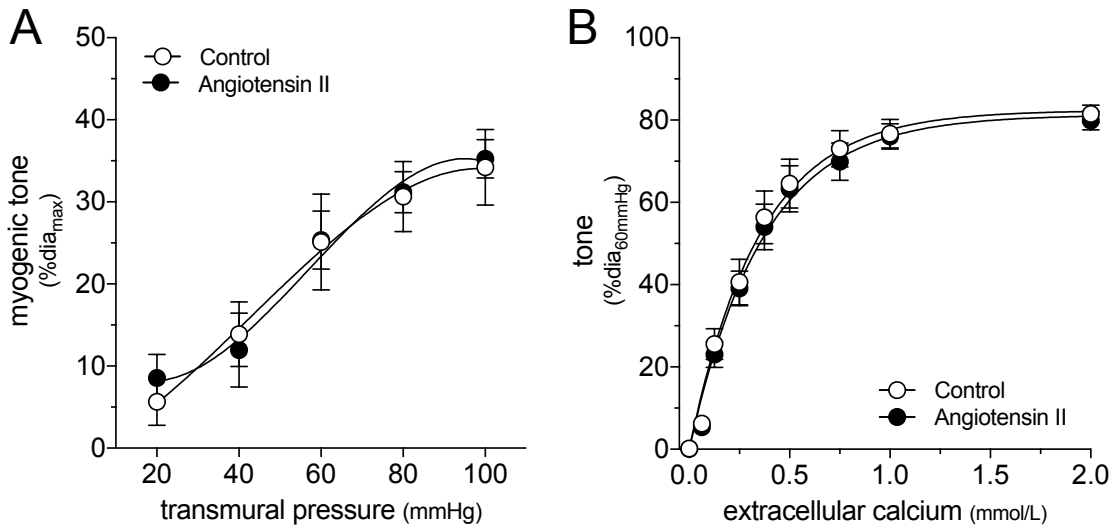


Terazosin does not alter cremaster artery myogenic reactivity in vitro

(A) *In vitro*, terazosin (25nmol/L for 30 minutes) has no effect on cremaster skeletal muscle resistance artery myogenic reactivity. **(B)** However, *in vitro* terazosin treatment attenuates phenylephrine-stimulated vasoconstriction. Data were statistically compared with a repeated measures 2-way ANOVA (dia_{max} = 78±4, n=6). * denotes $P<0.05$.

Supplementary Material

SUPPLEMENTARY FIGURE 14

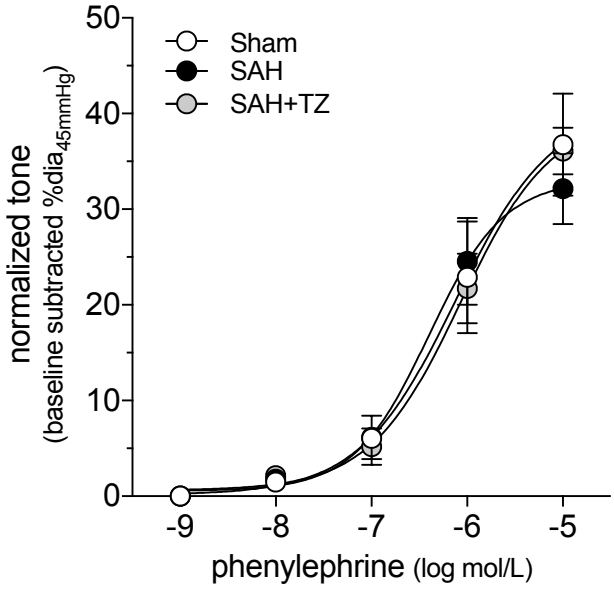


In vitro angiotensin II treatment does not alter cremaster artery myogenic reactivity or calcium sensitivity

Cremaster skeletal muscle resistance arteries isolated from naïve mice were treated for 4 hours with either 10 nmol/L angiotensin II or control buffer *in vitro*. The arteries were then washed and assessed in normal buffer. Angiotensin treatment does not affect **(A)** myogenic tone or **(B)** calcium sensitivity (control dia$_{max}$: 69±4 μm, n=5; angiotensin II dia$_{max}$: 78±5 μm, n=6). Data were statistically compared with a 2-way ANOVA.

Supplementary Material

SUPPLEMENTARY FIGURE 15

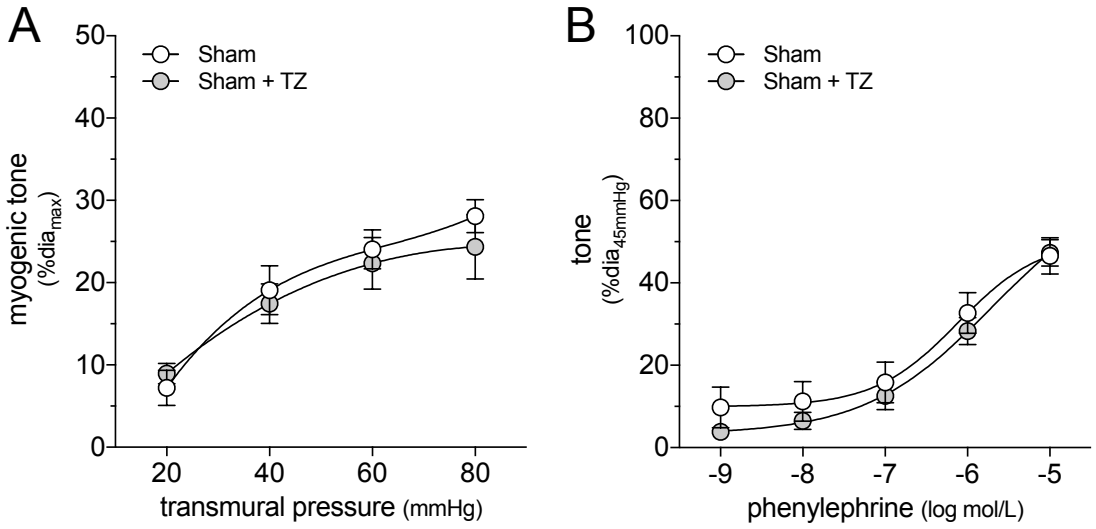


Baseline-normalized phenylephrine responses in terazosin-treated cerebral arteries

When baseline tone is normalized, phenylephrine responses in olfactory cerebral arteries isolated from SAH mice are not different from those isolated from sham-operated controls. Normalized phenylephrine responses in olfactory cerebral arteries isolated from terazosin-treated mice (TZ; twice daily for 2 days with i.p. injections; 1 mg/kg initial pre-operative dose followed by 0.5 mg/kg for all subsequent injections) are also not different from sham-operated controls. Data were statistically compared with a 2-way ANOVA (P=N.S.; sham dia_{max}: 108±4 μm, n=6, SAH dia_{max}: 104±7 μm, n=5, SAH+TZ dia_{max}: 108±10 μm, n=6).

Supplementary Material

SUPPLEMENTARY FIGURE 16



Terazosin does not alter olfactory cerebral artery reactivity in sham animals.

In sham-operated mice, *in vivo* terazosin treatment (TZ; twice daily for 2 days with i.p. injections; 1 mg/kg initial pre-operative dose followed by 0.5 mg/kg for all subsequent injections) has no effect on **(A)** myogenic reactivity (sham dia$_{max}$: 108±4 μm, n=6; Sham+TZ dia$_{max}$: 110±5 μm, n=5) or **(B)** phenylephrine responses (sham dia$_{max}$: 110±4 μm, n=5; Sham+TZ dia$_{max}$: 110±5 μm, n=5) in olfactory cerebral arteries isolated at 2 days post-surgery/treatment. The sham data in both panels are reproduced from *Figure 6*, for comparison to the Sham+TZ data. Data were statistically compared with a 2-way ANOVA (P=N.S.).

Supplementary Material

SUPPLEMENTARY TABLE 1

Echocardiographic measures in mice with subarachnoid hemorrhage

	Sham	SAH
Mouse Body Weight (g)	22.9 ± 0.3	22.5 ± 0.3
Wall Thickness (mm)	0.658 ± 0.016	0.654 ± 0.022
Systolic Diameter (mm)	2.66 ± 0.06	2.68 ± 0.07
Diastolic Diameter (mm)	3.87 ± 0.05	3.75 ± 0.06
Systolic Volume (µl)	17.8 ± 1.0	18.0 ± 1.1
Diastolic Volume (µl)	48.0 ± 1.6	44.2 ± 1.6
Fractional Shortening (%)	31.3 ± 0.8	28.9 ± 0.9
LVEF (%)	64 ± 1	60 ± 1
Stroke Volume (µl)	30.2 ± 0.9	**26.2 ± 0.7 ***
Heart Rate (min^{-1})	510 ± 7	**477 ± 10 ***
Cardiac Output (ml/min)	15.3 ± 0.4	**12.4 ± 0.4 ***

Data are means ± SEM (n=35 in both groups). * denotes $P<0.05$ for an unpaired comparison (Student's t test). Acronyms: LVEF − Left ventricular ejection fraction; SAH – subarachnoid hemorrhage.

Supplementary Material

SUPPLEMENTARY TABLE 2

Echocardiographic measures in bisoprolol-treated mice

	Sham	SAH	SAH+Bis
Mouse Body Weight (g)	22.3 ± 0.4	21.9 ± 0.5	21.9 ± 0.5
Wall Thickness (mm)	0.665 ± 0.020	0.671 ± 0.033	0.653 ± 0.031
Systolic Diameter (mm)	2.46 ± 0.05	2.61 ± 0.09	2.49 ± 0.10
Diastolic Diameter (mm)	3.68 ± 0.05	3.65 ± 0.08	3.68 ± 0.10
Systolic Volume (µl)	15.3 ± 1.4	16.4 ± 1.7	14.2 ± 1.5
Diastolic Volume (µl)	41.4 ± 2.1	39.7 ± 2.2	41.1 ± 2.8
Fractional Shortening (%)	33.1 ± 1.3	28.4 ± 1.8	32.3 ± 2.1
LVEF (%)	64 ± 2	59 ± 3	66 ± 2
Stroke Volume (µl)	26.1 ± 1.0	23.3 ± 1.3	26.9 ± 1.7
Heart Rate (min^{-1})	542 ± 10	**485 ± 15** *	512 ± 16
Cardiac Output (ml/min)	14.2 ± 0.7	**11.4 ± 0.8** *	14.6 ± 0.8

Data are means ± SEM (sham n=12; SAH n=11; SAH+Bis n=10). * denotes $P<0.05$ for an unpaired comparison to the sham (ANOVA with Dunnett's post-test). Acronyms: Bis: – bisoprolol; LVEF − Left ventricular ejection fraction; SAH – subarachnoid hemorrhage.

Supplementary Material

SUPPLEMENTARY TABLE 3

Echocardiographic measures in isoproterenol-treated mice

	Naïve	Isoproterenol
Mouse Body Weight (g)	25.4 ± 0.5	24.9 ± 0.4
Wall Thickness (mm)	0.662 ± 0.033	0.691 ± 0.030
Systolic Diameter (mm)	3.07 ± 0.13	2.89 ± 0.99
Diastolic Diameter (mm)	4.24 ± 0.11	**3.87 ± 0.08 ***
Systolic Volume (µl)	23.1 ± 2.6	21.2 ± 1.6
Diastolic Volume (µl)	60.5 ± 4.2	**51.7 ± 1.7 ***
Fractional Shortening (%)	27.7 ± 1.2	25.4 ± 1.5
LVEF (%)	62 ± 2	59 ± 3
Stroke Volume (µl)	37.4 ± 2.5	**30.5 ± 1.0 ***
Heart Rate (min^{-1})	477 ± 12	471 ± 11
Cardiac Output (ml/min)	17.8 ± 0.9	**14.4 ± 0.6 ***

Data are means ± SEM (naïve n=5; isoproterenol n=9). * denotes $P<0.05$ for an unpaired comparison (Student's t test). Acronym: LVEF − Left ventricular ejection fraction.

Supplementary Material

SUPPLEMENTARY TABLE 4

Echocardiographic measures in terazosin-treated mice

	Sham	SAH	SAH+TZ
Mouse Body Weight (g)	23.9 ± 0.4	23.3 ± 0.3	23.8 ± 0.5
Heart Wall Thickness	0.669 ± 0.029	0.684 ± 0.031	0.673 ± 0.025
Systolic Diameter	2.74 ± 0.09	2.72 ± 0.10	2.80 ± 0.10
Diastolic Diameter	3.93 ± 0.08	3.81 ± 0.10	3.82 ± 0.09
Systolic Volume	18.2 ± 1.4	18.7 ± 1.8	21.0 ± 1.9
Diastolic Volume	50.4 ± 2.2	46.6 ± 2.5	48.5 ± 2.6
Fractional Shortening	30.6 ± 1.2	28.8 ± 1.0	26.9 ± 1.2
LVEF (%)	64 ± 2	61 ± 2	**57 ± 2 ***
Stroke volume (µl)	32.2 ± 1.3	**27.9 ± 1.0 ***	**27.5 ± 1.7 ***
Heart rate (min^{-1})	500 ± 9	480 ± 14	**443 ± 16 ***
Cardiac Output (ml/min)	16.0 ± 0.6	**13.3 ± 0.4 ***	**12.0 ± 0.3 ***

Data are means ± SEM (sham n=16; SAH n=16; SAH+TZ n=12). * denotes $P<0.05$ for an unpaired comparison to the sham (ANOVA with Dunnett's post-test). Acronyms: TZ: – terazosin; LVEF – Left ventricular ejection fraction; SAH – subarachnoid hemorrhage.