## **Supporting Information**

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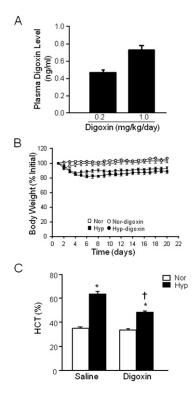


Fig. S1. Plasma digoxin levels and effect of digoxin treatment on body weight and hematocrit (HCT). (A) Plasma digoxin levels (mean  $\pm$  SEM) in mice treated by i.p. injection of digoxin (n=6 each). (B) Change in body weight (mean  $\pm$  SEM) during normoxic (Nor; 21%  $O_2$ ) and hypoxic (Hyp; 10%  $O_2$ ) exposure, expressed as percentage of initial weight (day 1), in mice injected with saline or digoxin (1.0 mg/kg per day). n=11 for Nor-saline, n=13 for Hyp-saline, and n=9 for Nor- and Hyp-digoxin. (C) Hematocrit (mean  $\pm$  SEM) in normoxic and hypoxic mice treated with saline or digoxin (1.0 mg/kg per day). n=8 for Nor-saline and Hyp-saline, n=9 for Nor-digoxin and Hyp-digoxin. \*Significantly different (P<0.05) from normoxia value within treatment; †significantly different (P<0.05) from Hyp-saline.

Table S1. Effect of hypoxia on right ventricle (RV) and left ventricle (LV) weights

Treatment	RV weight (mg)	LV weight (mg)	BW (g)	RV/BW (mg/g)	LV/BW (mg/g)	HR (beats/min)
Normoxia-prevention						
Saline	$20.7 \pm 0.7$	$89.5 \pm 3.3$	$28.8 \pm 0.9$	$0.72 \pm 0.01$	$3.1 \pm 0.04$	$393 \pm 46$
Digoxin (1.0 mg/kg)	$17.2 \pm 0.5$	$76.0 \pm 2.2$	$24.9 \pm 0.6$	$0.70\pm0.02$	$3.1 \pm 0.03$	$383 \pm 19$
Hypoxia-prevention						
Saline	32.2 ± 1.8*	81.9 ± 2.5	$23.4 \pm 0.5*$	$1.4 \pm 0.08*$	$3.4 \pm 0.1$	$395 \pm 17$
Digoxin (1.0 mg/kg)	$21.8 \pm 0.9^{\dagger}$	$71.4 \pm 1.9$	$23.9 \pm 0.8$	$0.92\pm0.05^{\dagger}$	$3.0 \pm 0.06$	$364 \pm 18$
Hypoxia-reversal						
Saline	$26.0 \pm 1.0$	$79.3 \pm 2.2$	$25.6 \pm 0.6$	$1.0 \pm 0.04$	$3.1 \pm 0.05$	$420 \pm 22$
Digoxin (0.2 mg/kg)	$22.0 \pm 0.9^{\dagger}$	$75.2 \pm 2.6$	$25.8 \pm 0.8$	$0.85 \pm 0.03^{\dagger}$	$2.9 \pm 0.05$	$383 \pm 18$
Digoxin (1.0 mg/kg)	$21.8 \pm 0.6^{\dagger}$	$71.5 \pm 2.9$	$23.7\pm0.8$	$0.91 \pm 0.03^{\dagger}$	$3.0\pm0.1$	$370 \pm 29$

Data are presented as mean  $\pm$  SEM [n=7 for saline hypoxia-reversal and digoxin (0.2 mg/kg/d) hypoxia-reversal and n=8 for all other groups]. BW, body weight.

<sup>\*</sup>Significant difference (P < 0.05) compared to normoxia value within a treatment (saline or digoxin).

<sup>&</sup>lt;sup>†</sup>Significant difference (*P* < 0.05) compared to saline value within an exposure (normoxia or hypoxia).

Table S2. Effect of acute exposure to digoxin on  $pH_i$  and  $[Ca^{2+}]_i$  in pulmonary arterial smooth muscle cells

Variable	Baseline	Digoxin	Change	n
pH (pH units)				
Normoxic	$6.89 \pm 0.04$	$6.90 \pm 0.04$	$0.01 \pm 0.03$	41
Hypoxic	$7.05 \pm 0.02*$	$7.02 \pm 0.02$	$-0.03 \pm 0.02$	53
[Ca <sup>2+</sup> ] <sub>i</sub> (nM)				
Normoxic	$108.2 \pm 6.1$	$116.5 \pm 6.3^{\dagger}$	9.1 ± 1.9 <sup>‡</sup>	34
Hypoxic	300.0 ± 24.1*	297.1 ± 21.7	$-2.9 \pm 8.7$	38

Data are presented as mean  $\pm$  SEM. Digoxin, 5 nM. n, number of cells tested.

Table S3. Nucleotide sequence of primers used for real-time PCR

mRNA	Accession no.	Species	Forward/reverse primers	Product size (bp)
GLUT1	NM_011400	Mouse	5′-TTCTCTGTCGGCCTCTTTGT-3′	98
			5'-GAGAAGCCCATAAGCACAGC-3'	
NHE1	NM_016981	Mouse	5'-CACCAGTGGAACTGGACCTT-3'	141
			5'-GGCAATGATGAACTGGTCCT-3'	
TRPC1	NM_053558	Mouse	5'-AGCCTCTTGACAAACGAGGA-3'	146
			5'-ACCTGACATCTGTCCGAACC-3'	
Cyclophilin	NM_011149	Mouse	5'-CAGCAAGTTCCATCGTGTCA-3'	100
			5'-GAAGCGCTCACCATAGATGC-3'	

<sup>\*</sup>Significant difference compared to normoxic value (P < 0.05; paired Student's t test).

 $<sup>^{\</sup>rm t}{\rm Significant}$  difference compared to baseline value (P < 0.05; paired Student's t test).

<sup>\*</sup>Significant difference (one-sample *t* test).