Supporting Information

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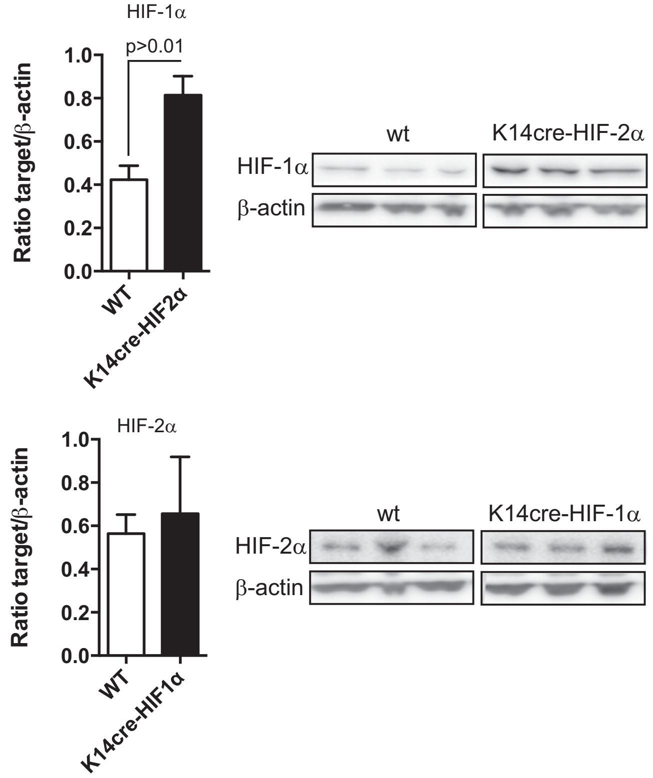

Fig. S1. Representative Western blots and densitometry analysis of hypoxia-inducible factor 1 alpha (HIF-1α) (*Upper*) and HIF-2α (*Lower*) stability in skin samples from K14cre-HIF2α and K14cre-HIF-1α mice, respectively, compared with WT controls. Densitometry data are stated as the ratio of target protein to β-actin and are shown as mean ± SEM ($n = 6$).

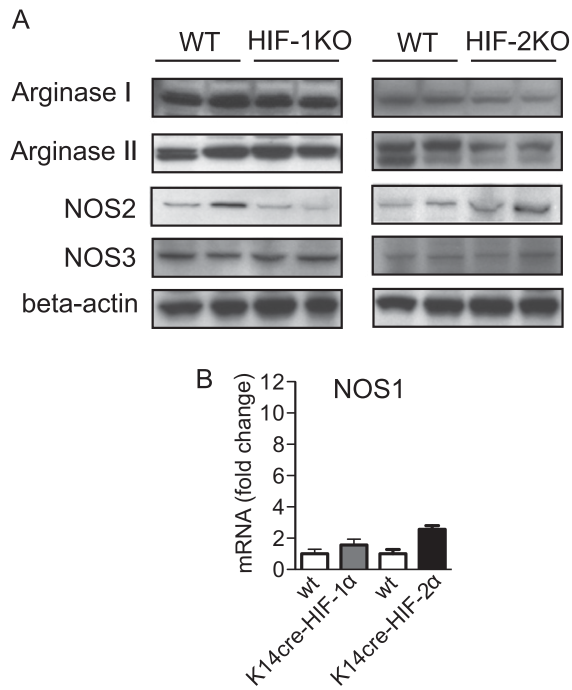

Fig. S2. (*A*) Representative Western blots of arginase-I/-II, nitric oxide synthase 2 (NOS2)/3, and β-actin control basally expressed in the skin of K14cre-HIF1α and -HIF2α mice compared with littermate controls. (*B*) Baseline quantitative PCR (qPCR) analysis for NOS1 expression in skin samples from keratinocyte-specific HIF-1α– and HIF-2α–deleted mice compared to littermate controls. Data are shown as mean fold change ± SEM (*n* = 8).

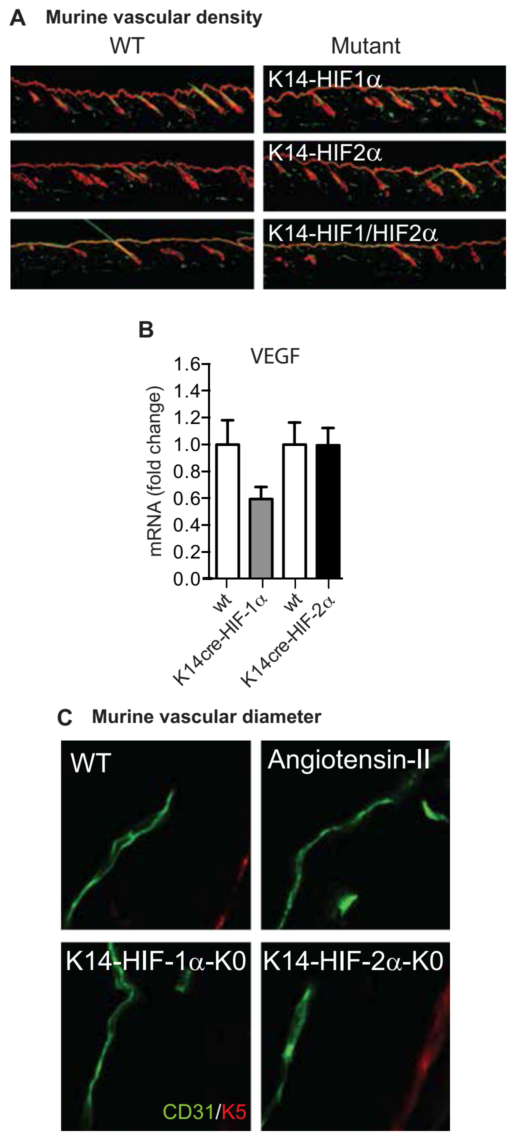

Fig. S3. (*A*) Representative photomicrographs of histological analysis for skin vascular density. Frozen 8-μM skin sections were immunostained for PCAM-1 (CD31). ImageJ software (National Institutes of Health) was used for quantitative analysis to determine the percentage vessel density. (*B*) Baseline qPCR analysis for VEGF expression in skin samples from keratinocyte-specific HIF-1α– and HIF-2α–deleted mice compared with WT controls. Data are shown as mean fold change ± SEM ($n = 8$). (*C*) Representative photomicrographs of histological analysis of vascular diameter. Frozen 8-μM skin sections were immunostained for PCAM-1 (CD31). ImageJ software was used for quantitative analysis to determine the vessel cross-section.

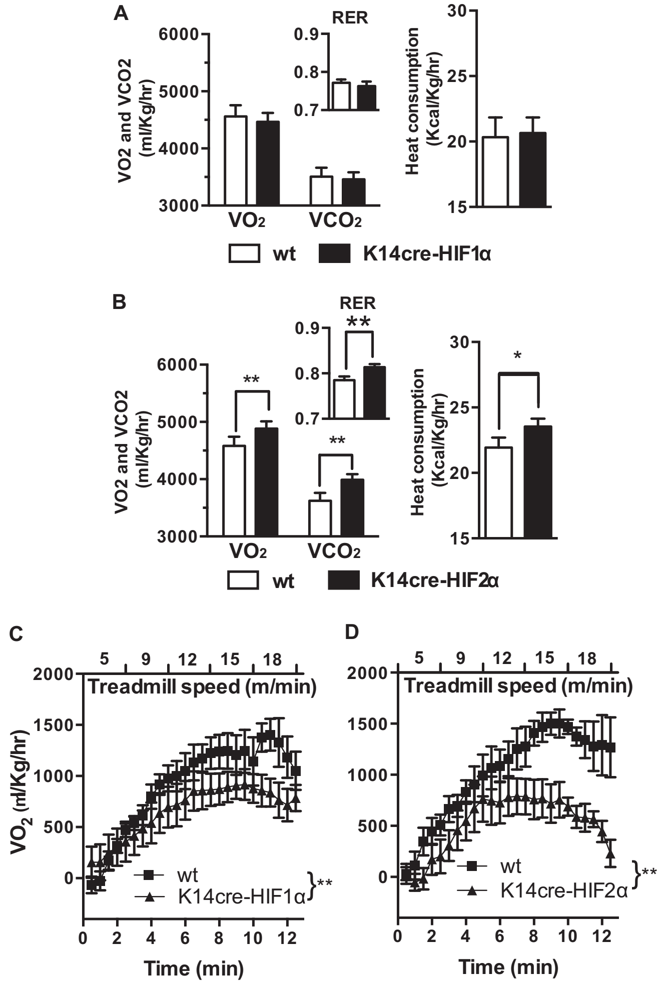

Fig. S4. Metabolic characterization of K14cre-HIF-1α and K14cre-HIF-2α. (*A* and *B*) Measurement of VO_2 and VCO_2 from resting K14cre-HIF-1α (*A*) or K14cre-HIF-2α (*B*) mice (data are shown as mean VO_2 or VCO_2 ± SEM in $mL^{-1} \cdot kg^{-1} \cdot h^{-1}$), respiratory exchange ration (RER) (data are shown as mean ratio ± SEM), and metabolic heat production (data are shown as mean $Kcal^{-1} \cdot kg^{-1} \cdot h^{-1}$ ± SEM) ($n = 5$). *$P < 0.05$, **$P < 0.005$. (*C* and *D*) Whole-body O_2 consumption (VO_2) in response to accumulating exercise stress. K14-HIF-1α ($n = 5$) (*C*) or K14-HIF-2α ($n = 5$) (*D*) mice were compared with littermate controls ($n = 4$). **$P < 0.005$, ANOVA. Data are shown as mean VO_2 ± SEM $mL^{-1} \cdot kg^{-1} \cdot h^{-1}$ accumulating with time as the intensity of the exercise increases.

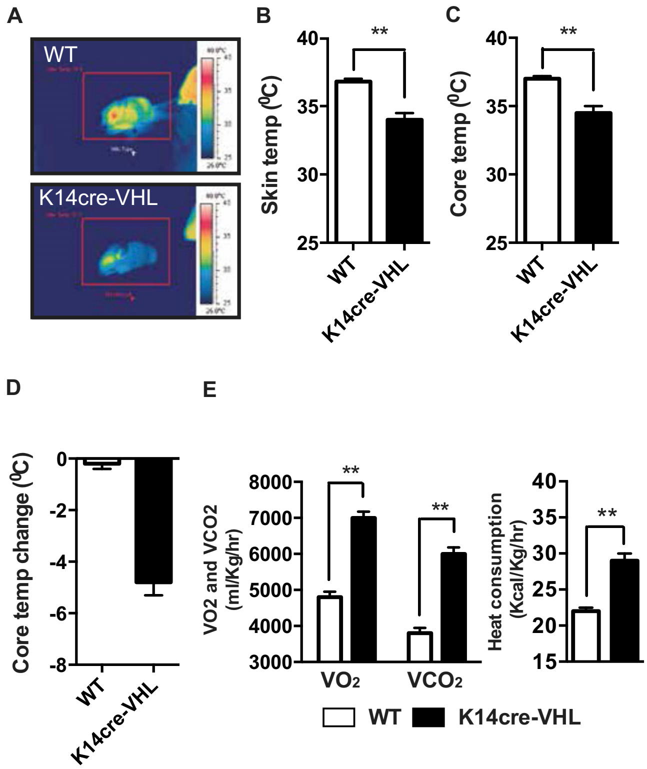

Fig. S5. K14cre-VHL mice are hypothermic. (*A* and *B*) Skin-surface temperature was measured by a thermal infrared camera and expressed as average temperature (°C) ± SEM (*n* = 8). (*C*) Basal core body temperature was measured using a rectal probe and expressed as average temperature (°C) ± SEM (*n*=8). (*D*) Core body temperature was monitored during acclimation of K14cre-VHL mice to an environmental temperature of 4 °C compared with WT controls. Data are shown as the mean drop in core temperature (°C) ± SEM following a 3-h exposure (*n* = 8). (*E*) Measurement of VO_2 and VCO_2 from resting K14cre-VHL mice. Data are shown as mean VO_2 or VCO_2 ± SEM $mL^{-1} \cdot kg^{-1} \cdot h^{-1}$ metabolic heat production. Data are shown as mean $Kcal^{-1} \cdot kg^{-1} \cdot h^{-1}$ ± SEM (*n* = 8). **$P < 0.005$.

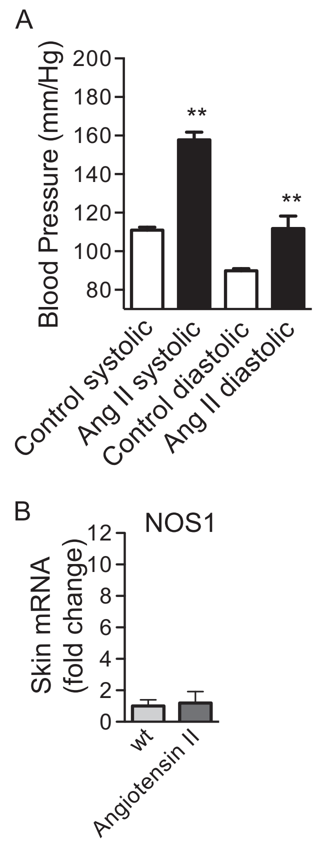

Fig. S6. WT mice develop severe hypertension when Angiotensin II (2 $ug^{-1}{\cdot}kg^{-1}{\cdot}min^{-1}$) is infused over 14 d. Data are shown as mean (mmHg) ± SEM ($n = 6$).

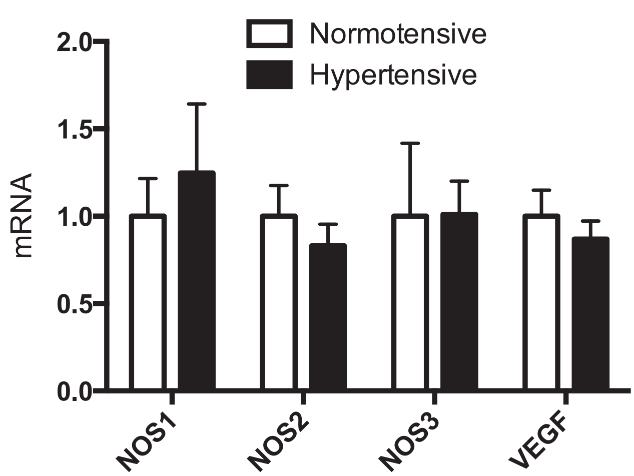

Fig. S7. qPCR analysis of NOS1, NOS2, NOS3, and VEGF from skin samples collected from normotensive (open bar; $n = 11$) and mildly hypertensive (closed bar; $n = 13$) volunteers. Data are shown as mean fold change ± SEM.

Table S1. Analysis of blood chemistry in K14cre-HIF1α mice and littermate controls (n = 10)

Blood components analyzed	K14-HIF-1α, range	Cre⁻, mean	Cre⁺, mean
Glucose, mg/dL	90–192	172.5	195.7
BUN, mg/dL	18–29	24	23.6
Creatinine, mg/dL	0.2–0.8	<0.2	<0.2
Albumin, g/dL	2.5–4.8	3.6	3.8
Globulin, g/dL	—	2	2
Total protein, g/dL	3.6–6.6	6.0	6.2
Sodium, mEg/L	126–182	149.6	151.75
Potassium, mWg/L	4.7–6.4	6.5	7.0
Calcium, mg/dL	5.9–9.4	10.1	10.1
Phosphorus, mg/dL	6.1–10.1	6.95	6.20
Bilirubin total, mg/dL	0.1–0.9	0.3	0.3
SGPT (ALT), U/L	28–132	42.75	42
Alk P, U/L	62–209	52	49
Amylase, U/L	169–-3,615	1,019	987

Table S2. Data from normotensive and hypertensive human volunteers

Subject	Age, y	Sex	Blood pressure at visit, diastolic/systolic, mmHG	Hypertensive medication	Other medications
1	46	F	144/71	Candesartan	Nil
2	28	M	141/96	Losartan	Nil
3	61	M	150/85	Perindopril, felodipine	Simvastatin, lanzoprazole
4	67	M	169/82	Lisinopril, doxazosin	Nil
5	48	M	142/89	Nil	Nil
6	50	M	167/109	Nil	Nil
7	62	M	173/94	Nil	Nil
8	51	M	165/99	Ramipril, amiodipine	Nil
9	65	F	173/98	Lisinopril	Latanoprost, Viscotears
10	53	M	140/90	Candesartan	Simvastatin, aspirin
11	51	F	159/96	Candesartan	Nil
12	70	M	150/73	Nil	Simvastatin, aspirin
13	68	F	133/66	Bendroflumethiazide	Pravastatin, diclofenac
14	58	M	134/82	Amiodipine, atenolol	Simvastatin, aspirin
15	56	M	173/105	Nil	Nil
16	63	F	172/70	Lisinopril	Nil
1	74	F	157/86	Nil	Aspirin
2	60	F	147/84	Nil	Nil
3	32	F	98/73	Nil	Nil
4	51	M	124/71	Nil	Lanzoprazole, aspirin
5	24	M	98/73	Nil	Nil
6	49	F	105/57	Nil	Nil
7	48	M	147/86	Nil	Nil
8	47	F	116/72	Nil	Nil
9	38	F	133/70	Nil	Nil
10	56	M	138/83	Nil	Nil
11	43	F	113/69	Nil	Nil
12	59	F	123/67	Nil	Nil
13	37	F	113/56	Nil	Nil
14	54	F	106/67	Nil	Nil
15	52	M	125/85	Nil	Nil
16	52	M	119/70	Nil	Nil
17	50	F	122/74	Nil	Nil
18	49	M	139/91	Nil	Nil
19	47	F	135/80	Nil	Nil
20	48	M	150/86	Nil	Nil
21	62	F	155/81	Nil	Nil
22	52	F	114/58	Nil	Nil
23	23	F	103/58	Nil	Nil
24	61	M	143/76	Nil	Nil