

Table S1

A

Genotype	N	% Total
<i>Ephx1</i> ^{+/+} <i>Ephx2</i> ^{+/+}	35	6.5
<i>Ephx1</i> ^{+/+} <i>Ephx2</i> ^{+/-}	74	13.7
<i>Ephx1</i> ^{+/+} <i>Ephx2</i> ^{-/-}	33	6.1
<i>Ephx1</i> ^{+/-} <i>Ephx2</i> ^{+/+}	64	11.9
<i>Ephx1</i> ^{+/-} <i>Ephx2</i> ^{+/-}	156	28.9
<i>Ephx1</i> ^{+/-} <i>Ephx2</i> ^{-/-}	56	10.4
<i>Ephx1</i> ^{-/-} <i>Ephx2</i> ^{+/+}	32	5.9
<i>Ephx1</i> ^{-/-} <i>Ephx2</i> ^{+/-}	62	11.5
<i>Ephx1</i> ^{-/-} <i>Ephx2</i> ^{-/-}	28	5.2

Table S1. Breeding statistics of the first 90 litters generated by *Ephx1*^{+/-} *Ephx2*^{+/-} X *Ephx1*^{+/-} *Ephx2*^{+/-} in-crossing.

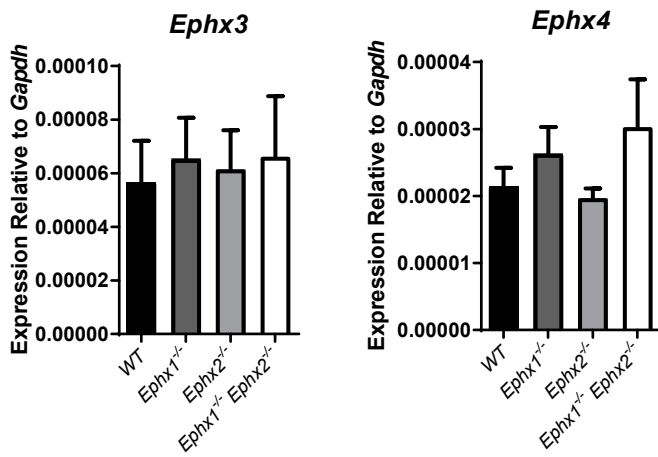
Table S2

	Age	Weight	Heart/body	Lung/body	Liver/body	Kidney/body
<i>WT</i>	70.3 (3)	20.9 (1.0)	4.7 (0.1)	7.1 (0.6)	47.1 (1.1)	13.7 (0.7)
<i>Ephx1^{-/-}</i>	72.7 (1.7)	21.6 (1.0)	4.6 (0.1)	6.6 (0.3)	44.2 (1.2)	13.2 (0.4)
<i>Ephx2^{-/-}</i>	67.6 (1.2)	18.6 (1.4)	4.7 (0.1)	7.2 (0.7)	47.3 (2.4)	12.7 (0.4)
<i>Ephx1^{-/-} Ephx2^{-/-}</i>	79.4 (2.2)	22.6 (1.2)	4.7 (0.2)	6.6 (0.5)	49.1 (1.6)	13 (0.7)

Table S2. Gross morphological analysis of wild type (WT), *Ephx1^{-/-}*, *Ephx2^{-/-}*, and *Ephx1^{-/-} Ephx2^{-/-}* mice. Age (days), weight (grams), and organ/body weights (mg/gram) are shown as mean (SEM), N=5-9 per group. None of the parameters were statistically different by genotype.

Figure S1

A



B

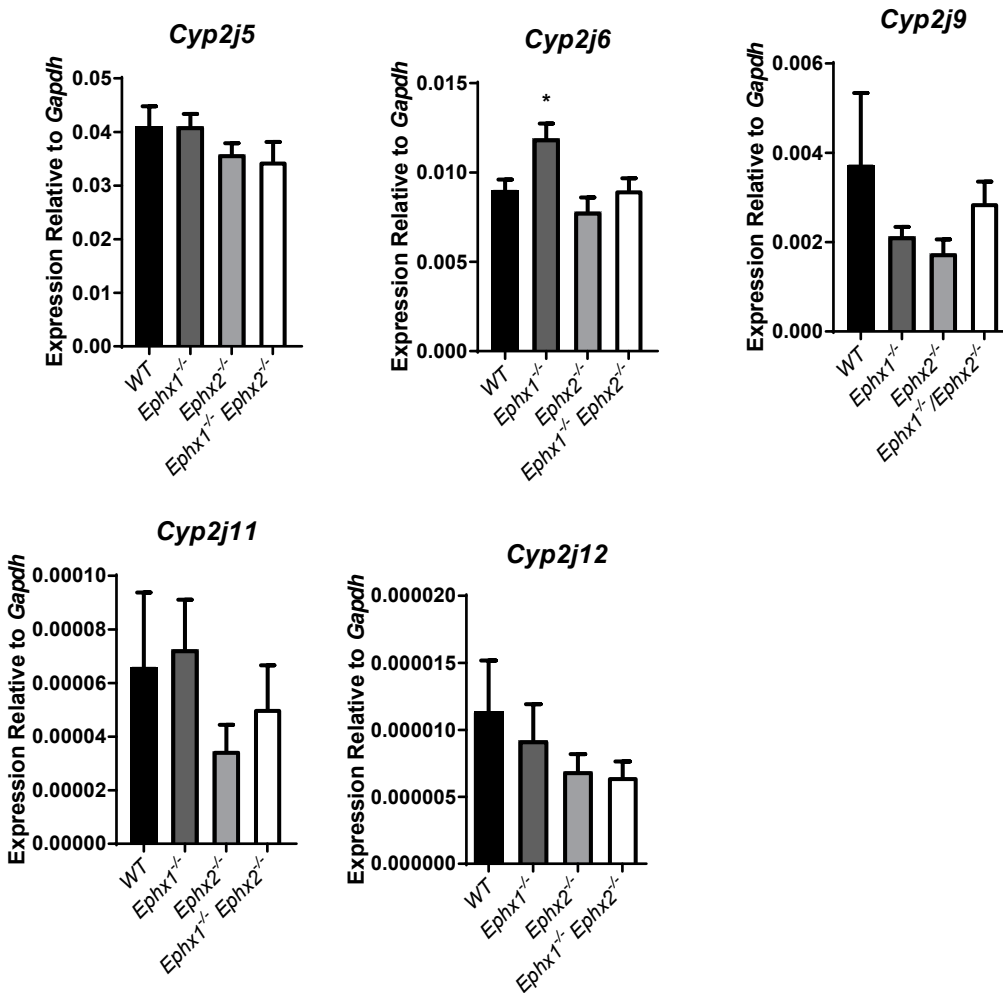


Figure S1

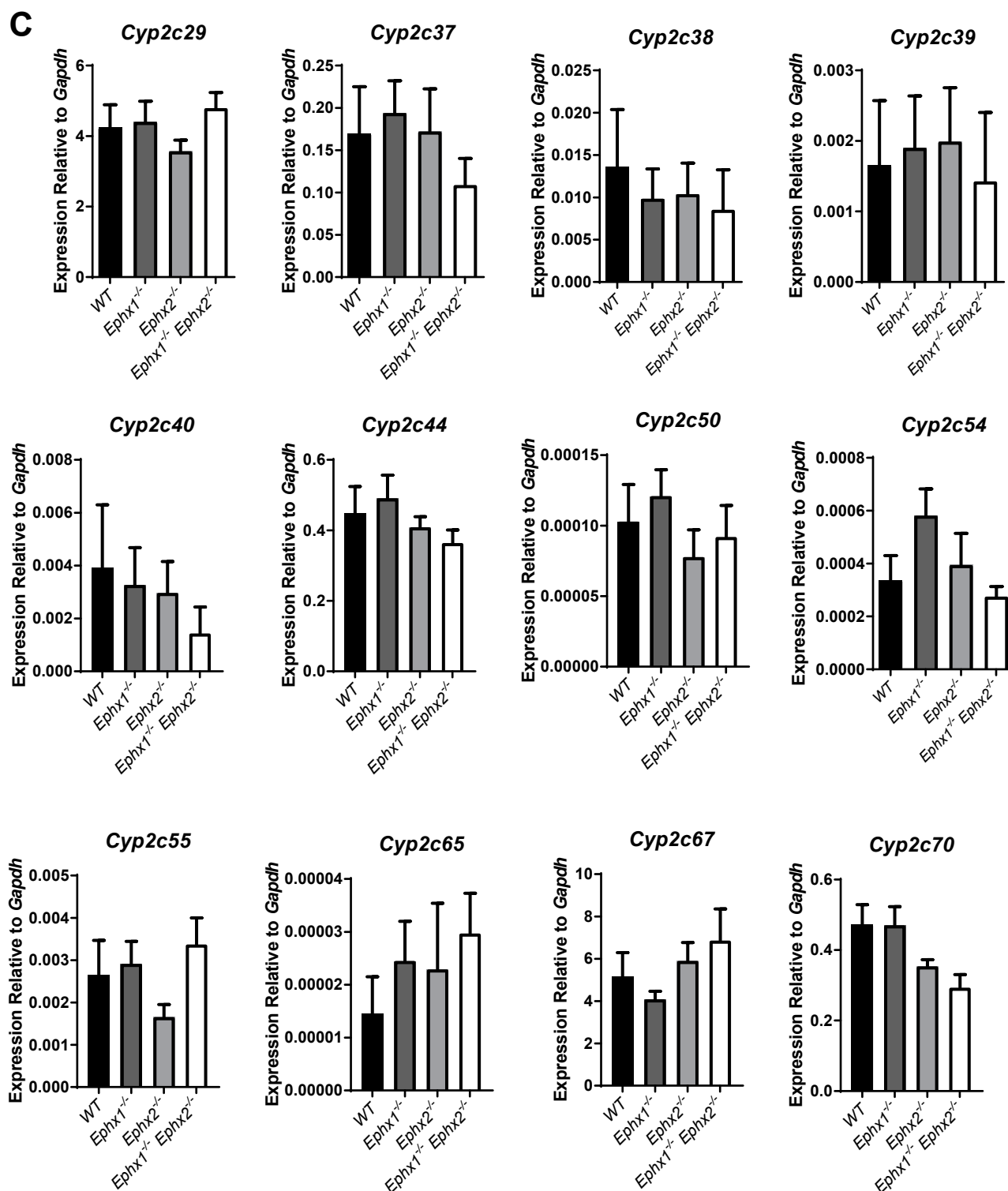


Figure S1. Expression of (A) epoxide hydrolases, (B) *Cyp2j* subfamily, and (c) *Cyp2c* subfamily enzymes in livers of WT, *Ephx1*^{-/-}, *Ephx2*^{-/-} and *Ephx1*^{-/-} *Ephx2*^{-/-} mice. Values are expressed as arbitrary units (mean ± SEM) of 4-8 mice per group after normalization for expression of *Gapdh*. *p<0.05 vs WT.

Figure S2

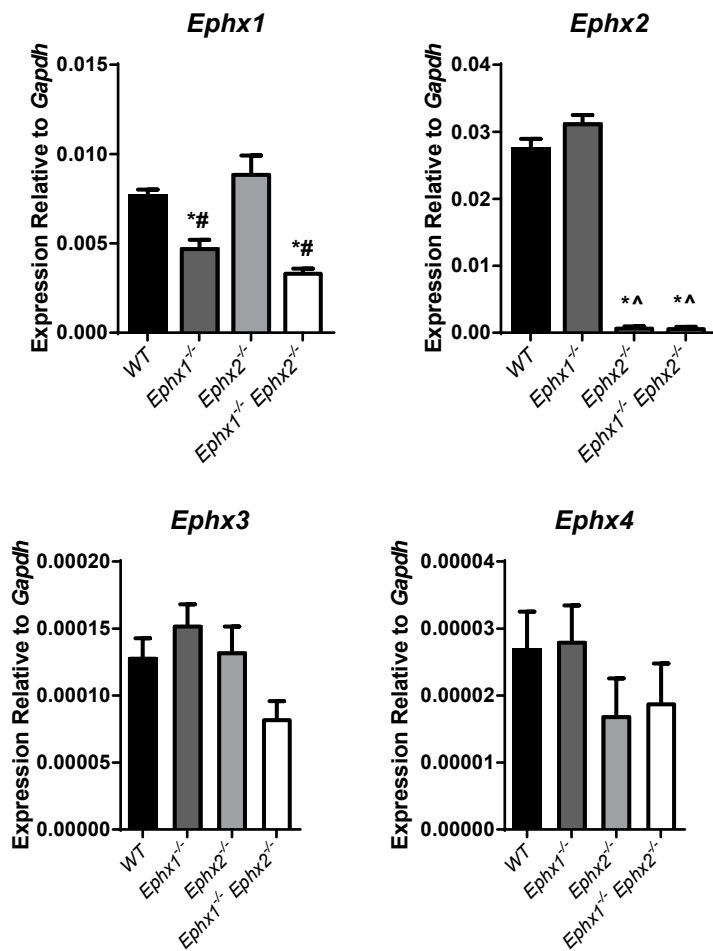


Figure S2. Heart expression of epoxide hydrolases in WT, *Ephx1*^{-/-}, *Ephx2*^{-/-} and *Ephx1*^{-/-} *Ephx2*^{-/-} mice. Values are expressed as arbitrary units (mean ± SEM) of 5 mice per group after normalization for expression of *Gapdh*. *p<0.05 vs. WT, #p<0.05 vs. *Ephx2*^{-/-} and ^p<0.05 vs. *Ephx1*^{-/-}.

Table S3

	<i>WT</i>	<i>Ephx1</i> ^{-/-}	<i>Ephx2</i> ^{-/-}	<i>Ephx1</i> ^{-/-} <i>Ephx2</i> ^{-/-}
TXB₂	19 (4)	20 (3)	23 (5)	46 (18)
PGD₂	121 (56)	121 (55)	134 (57)	57 (9)
PGE₂	35 (14)	28 (15)	27 (8)	45 (15)
PGF_{2α}	373 (63)	306 (21)	479 (114)	369 (33)
19,20-EpDPE	4287 (1474)	5206 (867)	4394 (514)	6762 (383)*#
17,18-EpETE	425 (132)	632 (178)	865 (120)*	1324 (26)*#
14,15-EET	496 (96)	594 (97)	2323 (293)*	2069 (211)*
11,12-EET	296 (105)	352 (38)	603 (139)	1169 (157)*#
8,9-EET	470 (115)	462 (69)	1198 (215)*	1045 (136)
5,6-EET	906 (242)	1649 (455)	2711 (1016)	2114 (925)
12,13-EpOME	8852 (1512)	7216 (462)	118718 (13234)*	99289 (15021)*
9,10-EpOME	2503 (532)	2341 (256)	15283 (3394)*	14508 (3032)*
19,20-DiHDPA	16343 (3353)	7643 (590)*	12527 (1901)	305 (61)*#
17,18-DHET	56669 (12310)	35840 (4123)	34093 (5962)	2082 (403)*#
14,15-DHET	7849 (1512)	5457 (729)	2600 (552)*	329 (35)*#
11,12-DHET	3186 (534)	2527 (279)	1802 (380)	116 (10)*#
8,9-DHET	2317 (340)	1609 (134)*	1438 (236)	0 (0)*#
5,6-DHET	1080 (125)	785 (67)*	754 (159)	385 (59)*
12,13-DiHOME	134215 (11757)	144686 (20785)	18553 (2690)*	19369 (3604)*
9,10-DiHOME	35937 (3022)	37174 (4504)	27823 (5215)	7916 (1352)*#
20-HETE	2008 (292)	2022 (264)	2332 (270)	1766 (335)
19-HETE	4151 (823)	4395 (547)	4894 (991)	2756 (572)
15-HETE	1067 (79)	852 (67)	1034 (163)	1108 (176)
12-HETE	77217 (29217)	67281 (14786)	45325 (10682)	132759 (66333)
11-HETE	1090 (137)	859 (63)	1118 (204)	1032 (115)
8-HETE	102647 (16089)	85014 (9167)	94888 (14675)	105128 (14091)
5-HETE	4031 (466)	3664 (365)	4662 (1004)	4219 (663)
13-HODE	200620 (14629)	177396 (17612)	196257 (15923)	233089 (47699)
9-HODE	119843 (7052)	109401 (7919)	115882 (8913)	134696 (25168)

Table S3. Oxylipin levels in plasma from WT, *Ephx1*^{-/-}, *Ephx2*^{-/-} and *Ephx1*^{-/-} *Ephx2*^{-/-} mice. Values are expressed as mean (SEM) in pg/ml plasma. N=9-11 per group, *p<0.05 vs. WT, #p<0.05 vs. *Ephx2*^{-/-} and ^p<0.05 vs. *Ephx1*^{-/-}.

Table S4

	<i>WT</i>		<i>Ephx1^{-/-}</i>		<i>Ephx2^{-/-}</i>		<i>Ephx1^{-/-} Ephx2^{-/-}</i>	
	Baseline	Reperfusion	Baseline	Reperfusion	Baseline	Reperfusion	Baseline	Reperfusion
6-keto-PGF_{1α}	33024 (3872)	38830 (4691)	23521 (3365)	49978 (3490) [^]	29749 (7880)	51756 (7416) [^]	32713 (4019)	40452 (9555)
TXB₂	349 (53)	2413 (310) [^]	384 (71)	1778 (302) [^]	530 (64)	1528 (363) [^]	482 (79)	1247 (236) [^] [^]
PGD₂	8055 (1277)	43716 (5341) [^]	8012 (948)	30296 (3225) [^]	10459 (752)	27051 (5017) [^]	9796 (2236)	18445 (3125) [^] [^]
PGE₂	2675 (304)	4809 (807) [^]	2183 (372)	4732 (558) [^]	2682 (416)	4107 (517)	2976 (597)	3500 (493)
PGF_{2α}	2795 (375)	5826 (1054) [^]	3101 (533)	5333 (533) [^]	4035 (662)	5165 (531)	3242 (560)	4705 (707)
8-iso-PGF_{2α}	146 (14)	360 (41) [^]	156 (21)	303 (38) [^]	206 (22)	300 (41)	152 (34)	265 (45)
19,20-EpDPE	391 (37)	1426 (271) [^]	890 (82) [*]	1583 (191) [^]	542 (208)	1306 (256) [^]	1023 (189) [*]	1561 (230) [^]
17,18-EpETE	86 (15)	214 (41) [^]	96 (16)	227 (49) [^]	157 (14) [*]	189 (18)	213 (45) [*]	401 (84) [#] [^]
14,15-EET	385 (124)	4255 (990) [^]	774 (335)	3078 (750) [^]	1078 (345)	3165 (466) [^]	856 (177)	2504 (695) [^]
11,12-EET	421 (150)	1469 (342) [^]	237 (17)	1071 (331)	585 (236)	1337 (278)	426 (72)	934 (222) [^]
8,9-EET	288 (35)	1615 (389) [^]	350 (43)	1090 (372)	583 (141)	1417 (316) [^]	433 (119)	1172 (358) [^]
5,6-EET	306 (212)	3195 (1693)	509 (378)	1923 (1224)	791 (388)	2620 (1903)	592 (303)	1429 (859)
12,13-EpOME	5695 (1069)	19602 (6332)	7260 (2120)	11397 (1521)	11279 (1077) [*]	14962 (1114) [^]	9868 (1087) [*]	16274 (2879) [^]
9,10-EpOME	4150 (730)	13160 (4294)	5239 (1369)	8281 (1270)	7645 (1112) [*]	10818 (1015)	6101 (538)	11468 (2725)
19,20-DiHDPA	802 (91)	1301 (161) [^]	536 (63) [*]	1012 (77) [^]	933 (201)	1424 (404)	7 (7) ^{*#}	0 (0) ^{*#}
17,18-DHET	7122 (747)	15577 (1857) [^]	7787 (786)	17201 (2201) [^]	6010 (365)	11960 (1735) [^]	253 (253) ^{*#}	635 (432) ^{*#}
14,15-DHET	113 (21)	194 (21) [^]	117 (17)	211 (25) [^]	100 (7)	162 (16) [^]	24 (9) ^{*#}	93 (9) ^{*#} [^]
11,12-DHET	292 (68)	724 (184) [^]	207 (43)	411 (45) [^]	178 (6)	258 (33) [^]	31 (15) ^{*#}	112 (11) ^{*#} [^]
8,9-DHET	125 (27)	165 (28)	101 (24)	153 (21) [^]	116 (19)	159 (33)	37 (16) ^{*#}	35 (14) ^{*#}
5,6-DHET	44 (6)	104 (26)	61 (11)	77 (10)	73 (16)	80 (12)	31 (3) [#]	75 (16) [^]
12,13-DHOME	1498 (526)	1767 (433)	979 (164)	1189 (131)	668 (100)	1013 (116) [^]	715 (122)	1094 (192) [^]
9,10-DHOME	865 (179)	1295 (289)	951 (268)	1017 (103)	771 (38)	815 (160)	634 (73)	782 (127)
20-HETE	807 (119)	1125 (81)	969 (115)	1109 (78)	1053 (205)	1159 (130)	1010 (186)	1408 (321)
19-HETE	519 (114)	496 (91)	400 (80)	536 (68)	419 (63)	503 (55)	419 (66)	602 (126)
15-HETE	722 (72)	1260 (167) [^]	644 (66)	1006 (123) [^]	966 (181)	1330 (202)	720 (62)	847 (91) ^{*#}
12-HETE	10320 (1992)	8884 (1661)	7803 (2292)	7278 (2324)	13352 (2037)	11541 (1748)	7396 (1222) [#]	5898 (670) [#]
11-HETE	558 (69)	997 (150) [^]	424 (43)	760 (98)	731 (116)	1077 (197)	580 (72)	643 (93)
8-HETE	5425 (540)	13044 (2342) [^]	6084 (1903)	12724 (1991) [^]	11234 (1881) [*]	17098 (3205)	5235 (374) [#]	9822 (1882) [^]
5-HETE	325 (41)	1512 (157) [^]	375 (54)	1152 (219) [^]	584 (100)	1713 (497)	333 (43) [#]	819 (122) ^{*^}
13-HODE	5414 (1158)	7842 (2110)	6032 (974)	5332 (820) [^]	7692 (1246)	7317 (612)	8073 (2187)	6514 (868)
9-HODE	6501 (1374)	9041 (2139)	6770 (1086)	6520 (922) [^]	9306 (1508)	9125 (953)	9046 (2376)	8002 (1122)

Table S4. Oxylipin levels in cardiac perfusates from WT, *Ephx1^{-/-}*, *Ephx2^{-/-}* and *Ephx1^{-/-} Ephx2^{-/-}* mice at baseline and after postischemic reperfusion. Values are expressed as mean (SEM) in pg/gram heart tissue/minute. N=6-7/group, *p<0.05 vs. WT, #p<0.05 vs. *Ephx2^{-/-}* and ^p<0.05 vs. Baseline of the same genotype.

Table S5

Parameter	WT	<i>Ephx1</i> ^{-/-}	<i>Ephx2</i> ^{-/-}	<i>Ephx1</i> ^{-/-} <i>Ephx2</i> ^{-/-}
N=	10	8	9	8
Heart Rate (baseline)	336 (9)	332 (17)	329 (16)	325 (8)
LVDPbaseline (cm H ₂ O)	118 (5)	125 (8)	109 (6)	118 (9)
dp/dt max (cm H ₂ O/sec)	5601 (152)	6389 (468)	5408 (265)	5906 (512)
dp/dt min (cm H ₂ O/sec)	3558 (324)	3867 (249)	3268 (175)	3554 (339)
Rate Pressure Product (cmH ₂ O x HR)	396441 (2041)	44738 (2417)	36199 (3422)	38224 (2320)
TIC (min)	7.43 (0.83)	5.88 (0.51)	8.12 (0.68)	7.38 (0.85)
Cmax (cm H ₂ O)	112 (9)	123 (9)	132 (13)	122 (14)

Table S5. Cardiac parameters from WT, *Ephx1*^{-/-}, *Ephx2*^{-/-} and *Ephx1*^{-/-} *Ephx2*^{-/-} mice at baseline or during ischemia. Values are expressed as mean +/- SEM, N=8-10/group. No significant differences were observed. Abbreviations: LVDP, Left Ventricular Developed Pressure; dp/dt, change in pressure/change in time; HR, Heart Rate; TIC, Time to Ischemic Contracture; Cmax, maximum ischemic contracture.

Figure S3

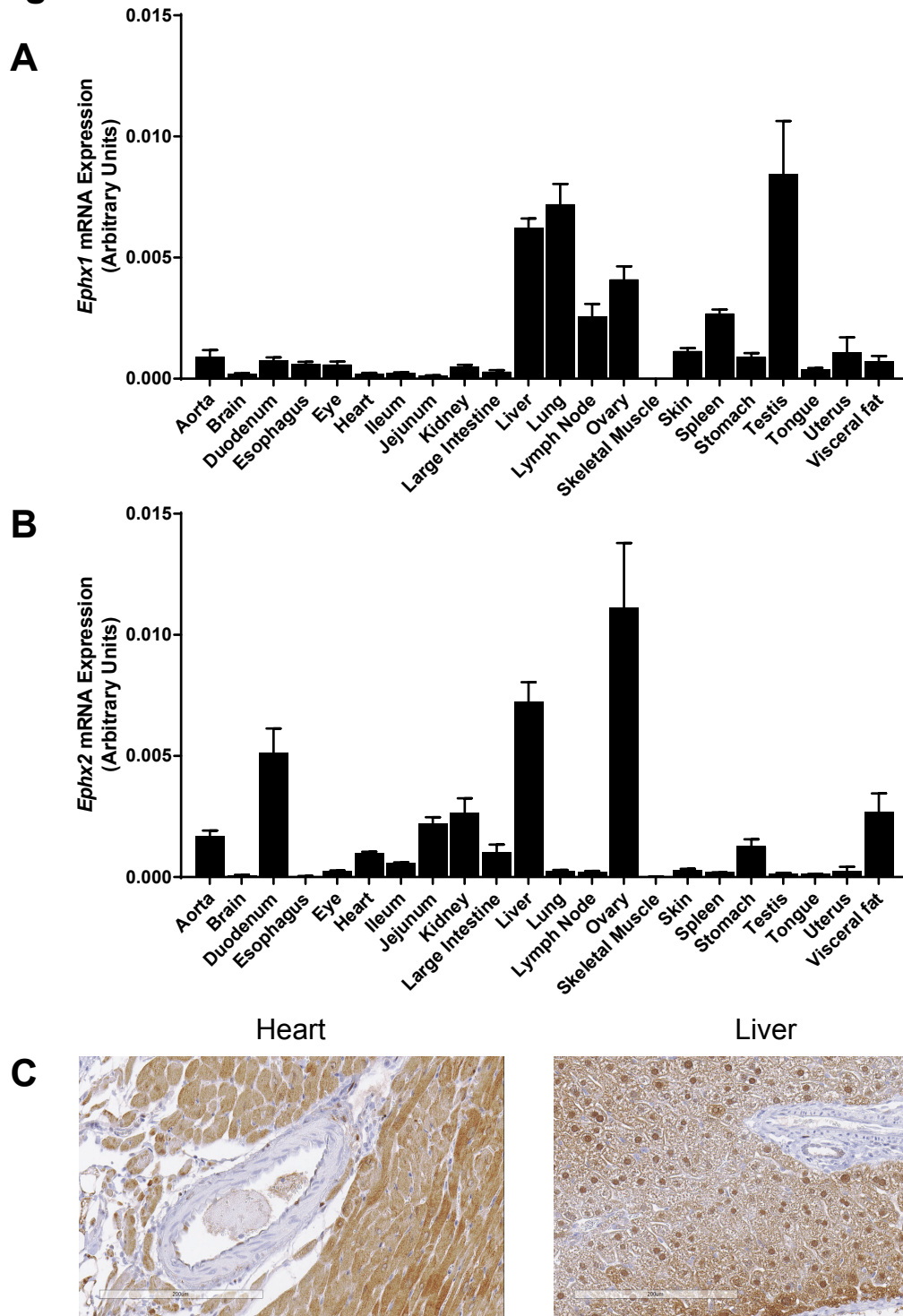


Figure S3. Expression of *Ephx1* (A) and *Ephx2* (B) in tissues collected from WT mice. Values are expressed as arbitrary units after normalization to *Gapdh* ($2^{-\Delta Ct}$). Data are expressed as mean \pm SEM, N=3-6/group. C) Heart and Liver from mice stained with anti-EPHX2 Ab (sc-22344; 1:100). Strong EPHX2 staining is observed in cardiomyocytes and hepatocytes, variable staining is observed in endothelial cells, and little or no EPHX2 is detected in smooth muscle or fibroblasts.