Materials and Methods:

Inducible Nkx2-5 knockout mice

Floxed-Nkx2-5 homozygous mice (Nkx2-5^{flox/flox})¹ were bred with transgenic mice carrying the Cre-ERTM gene under CMV promoter, Tg(CMV-Cre-ERTM).² Subsequent matings between offsprings generated Nkx2-5^{flox/flox}/Tg(CMV-Cre-ERTM)(flox/flox/Cre), Nkx2-5^{wild/wild}/Tg(CMV-Cre-ERTM) (wild/wild/Cre) and Nkx2-5^{flox/flox} (flox/flox). For perinatal deletion of the floxed-Nkx2-5 genes, a single injection of tamoxifen (0.5-1 mg/g body weight, ip) was administered to pregnant mice on gestation day 19. Male Tg(CMV-Cre-ERTM)² were also crossed to females that carried the Rosa reporter allele, R26R³. All animal care protocols fully conformed to the Association for the Assessment and Accreditation of Laboratory Animal Care, with approvals from the University of Florida Institutional Animal Care and Use Committees.

Southern, Northern and Western blotting and immunostaining

Southern and Northern blot analyses were performed using the following probes: Nkx2-5 5' genomic probe, NotI-ClaI fragment of mouse Nkx2-5 genomic DNA; Nkx2-5 coding probe, PfIMI-EcoRI fragment of mouse Nkx2-5 cDNA; Cre-recombinase probe, EcoRI-BamHI fragment of pCAGGS-nls-Cre plasmid (gift from Dr. H. Xin); RT-PCR products amplified by the following primer sets: KcneI/minK (476 bp, F', 5'- CTTGACGCCCAGGATGAGC -3'; R, 5'- GGTGCCCCTACAATAAAGACTATGG -3'); HOD/HOP (703 bp, F', 5'-

AGCAGACAGGCACCAGCATC -3'; R'- AAGGGAGCACAGGGAAGTGAAC -3'). Western blot analyses and immunostaining using frozen sections were performed with the following primary antibodies: anti-Nkx2-5 pAb⁴, sarcomeric actinin (A7811, SIGMA), Nav1.5(α) (ASC-005, alomone labs), GAPDH (RDI-TRK5G4-6C5, Research Diagnostic Inc), RyR2 (MA3-916, Affinity BioReagents), SERCA2a (sc-8095, Santa Cruz), phospholamban (05-205, Upstate). For detection of RyR and pentamer of phospholamban, protein samples were heated at 37°C for 15 min before loading on SDS-PAGE gels.⁵ Fluorescent microscopic images were obtained using ZEISS Axiovert200M with or without Apotome.

Surface ECG recording and ultrasound imaging

Recordings of six limb leads surface ECG (ADInstruments, Milford, MA) were performed without anesthesia as described previously with some modifications.⁶ ECG recordings were analyzed using PowerLab software (ADInstruments).⁶ M-mode ultrasound imaging of the left ventricle was obtained at the level of the papillary muscle from a parasternal window using an ultrasound biomicroscope with a single transducer with a frequency 55 MHz (VisualSonics, Tronto, Canada).

Histological analyses

X-gal staining of whole hearts and frozen sections were performed according to standard protocol.⁷ Tissues were fixed in 4% paraformaldehyde/PBS overnight, dehydrated, embedded in paraffin, sectioned, and stained with hematoxylin/eosin or Masson's trichrome. Acetylcholine esterase staining in frozen tissue sections was performed as described previously with some modifications.⁸ Whole mount acetylcholine esterase staining was performed with the incisions on right ventricular and atrial free wall, with addition of 0.1% TritonTM X-100 in all the solutions except for Cu²⁺-glycine solution. After fixation with paraformaldehyde, tissue images were captured by a stereomicroscope (Nikon SMZ800) attached to a CCD camera (QImaging MicroPublisher3.3, BC, Canada), with scale bars present. The same magnifications and zoom

were applied for the hearts dissected from flox/flox or flox/flox/Cre mice at the same ages. Digitalized AV nodal surface size was measured using NIH Image software.

Gene expression profiling

Total RNA pooled from 3-4 hearts of postnatal day 4 (PD4) flox/flox or flox/flox/Cre mice with tamoxifen administration was analyzed in the CodeLink Bioarrays followed by CodeLink and GeneSpring software (Genus Biosystems, Northbrook, IL). Four sets of relative expression values between flox/flox and flox/flox/Cre were averaged and are listed.

Measurement of sodium current and simultaneous recording of cardiac contraction and Ca²⁺

After genotyping, neonatal ventricular cardiomyocytes were isolated from flox/flox or flox/flox/Cre mice side by side at PD3, cultured for 4-5 days before measuring sodium currents (equivalent to PD7-8). Sodium currents were (I_{Na}) obtained by voltage clamp recordings in the whole cell patch clamp configuration at room temperature (~22°C). Myocytes were bathed in low sodium buffer containing, in mmol/L: NaCl 10, CsCl 80, CaCl₂ 2, MgCl₂ 1, HEPES 10, 4- aminopyridine 10, tetraethylammonium-Cl 30, dextrose 10, CdCl 0.1; and nifedipine 5 μ M with an osmolarity of 290 mOsm and pH of 7.4 adjusted with CsOH. Recordings were obtained using Molecular Devices Axon 200A amplifier (Sunnyvale, CA) filtered at 2 kHz and digitized using Molecular Devices, Digidata 1322A, at 10 kHz. Data were acquired using Molecular Devices PClamp 9.0 software. Myocytes were impaled with Drummond Wiretrol II capillary pipettes (Drummond Scientific Company, Broomall, PA) pulled with Sutter instrument P-97 horizontal pipette puller and polished with Narishige MF-830 microforge with series resistance of 0.5 to 1.5

m Ω when filled with solution containing, in mmol/L: CsOH 105, glutamic acid 105, tetraethylammonium-Cl 20, HEPES 10, Cs₂-EGTA 5, MgATP 5, NaGTP 0.1 with osmolarity of 285 and pH adjusted to 7.2 with CsOH. A -9.7 mV correction for liquid junction potential, between the patch pipette and bath solution, was set upon access to the cell cytosol. Cell capacitance and input series resistance were electronically compensated to approximately 90 percent using online circuitry. Leak currents were subtracted online with P/4 protocol.

Data analysis was performed using Molecular devices Clampfit 9.0, Microsoft Excel, and GraphPad Prism 4.0 (San Diego, CA). I_{Na} current density was derived by dividing current amplitude from each recording by their respective cell capacitance obtained from amplifier upon compensation. Experiments that showed inadequate voltage control, such as space clamp error or inappropriate steep increase in current amplitude in the negative slope of current voltage relation, were discarded. Steady state activation curves were generated from data used to obtain current voltage relation plots fitted to a Boltzman equation: $I/I_{Max} = 1/[1+exp(V - V_{1/2} / K_V)]$ where I/I_{Max} is the current expressed as fraction of maximal current; $V_{1/2}$ is the voltage to obtain half maximal current and K_{mV} is the slope factor.

Cardiomyocytes were isolated from 3 weeks old flox/flox or flox/flox/Cre mice. Only rod-shaped cardiomyocytes with staircase ends, clear cross striations and surface membranes free from blebs were studied for simultaneous measurements of cell shortening and intracellular free calcium cardiomyocyte contraction and simultaneous Ca²⁺ measurement as described previously.⁹

Real-time reverse transcriptase (RT)-PCR

Real-time RT-PCR was performed using the inventoried Taqman Gene Expression Assays (Applied Biosystems): Scn5a, Mm00451971_m1; RyR2, Mm00465877_m1; T-type Ca channel α1G, Mm00486549_m1; T-type Ca channel α1H, Mm00445369_m1; Scn1a, Mm00450580; Scn3a, Mm00658167; Scn4a, Mm00500103; Scn7a, Mm00801952; Scn8a, Mm00488110; Scn9a, Mm00450762; Scn1b, Mm0041210. Data were normalized with betaactin expression (product No, 4352933E). Duplicate experiments were averaged.

Reporter assays

C57BL/6 genomic DNA or BAC clone (Invitrogen, RPC 123.C, Clone ID: 190M7) was subjected to PCR for amplification of Scn5a genomic DNA fragments using specific primers: (fragment -736 to +119, F, 5'-TGGCGGTGTGTTTGATTTCAG-3'; R, 5'-GGGCTCGGTTCGGCGTAG-3'), (fragment -2308 to +119, F, 5'-GGCTGGAAGTGGTGACATTAGAG-3'; R, 5'-TGGCGGTGTGTTTGATTTCAG-3'), (fragment -9282 to -8098, F, 5'- TGGCAACCGCAGAACGAC -3'; R, 5'-CCCTCCTCCCCGCAATCAC -3'), (fragment -10419 to -9917, F, 5'-TGTGTGGGGTGTATGGGTGACC-3'; R, 5'-GGAGGTAGTGCGTCTGTTCCTATC-3'), (fragment -17405 to -16448, F, 5'-ATGTTCCTGGCATAACCCGAG-3'; R, 5'-AAACCCTTTCCTCCCCCG-3'), (fragment -27145 to -26589, F, 5'-CCCAAGCCACACTCTCAGGTCAC-3'; R, 5'-GCAAGCACAGGGGGACTGG-3'). PCR fragments were cloned into pCR-Blunt II-TOPO or pCR2.1 vector (Invitrogen), sequenced, and inserted into pGL3 basic plasmid (Promega) using appropriate restriction enzyme sites. Nkx2-5 non-binding mutant of -736 to +119 bp fragments were generated by PCR using two primers; F, 5'-

TGTGGTTCT<u>GG</u>GTGTCCCGGTGTCAGTGTGTCAATGGATGTGTCTCT<u>GG</u>GTCACGTG GTA-3'; R, 5'-

TACCACGTGAC<u>CC</u>AGAGACACATCCATTGACACACTGACACCGGGACAC<u>CC</u>AGAAC CACA-3'.

10T1/2 fibroblast cells cultured in six-well plates were cotransfected with 3 µg of luciferease reporter constructs, 1 µg of pcDNA3 or pcDNA3-Nkx2-5 expression plasmid and 0.5 µg of Rous sarcoma virus β-galactosidase construct using the calcium phosphate method as described previously.¹⁰

Statistical analyses

Results among groups except for analyses of sodium currents (see above) were compared using ANOVA and Fisher's PLSD or Bonferroni's post-hoc test (StatView version 5.01).

References:

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Table S1. The six most reduced ion channels in Nkx2-5 knockout hearts by gene expression profiling.

PD4

PD4			fold difference KO vs. control
Protein	Gene	UniGene No.	(mean ± S.E., n=4)
calcium channel, voltage-dependent, T type, alpha 1H subunit	Cacna1h	Mm.268378	0.321 ± 0.012
potassium voltage-gated channel, Isk-related subfamily, member 1	Kcne1	Mm.299425	0.367 ± 0.002
calcium channel, voltage-dependent, T type, alpha 1G subunit	Cacna1g	Mm.29585	0.518 ± 0.018
sodium channel, voltage-gated, type V, alpha polypeptide	Scn5a	Mm.103584	0.745 ± 0.009
ryanodine receptor 2, cardiac	Ryr2	Mm.239871	0.766 ± 0.057
gap junction membrane channel protein alpha 5 (connexin 40)	Gja5	Mm.281816	0.767 ± 0.029

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gap junction membrane channel protein beta 4 $Gjb4$ Mm.56906 0.914 ± 0.066	nnel 5	Clen5	Mm.254370	0.910 ± 0.121
	interacting protein 2	Kenip2	Mm.213204	0.911 ± 0.013
potassium voltage-gated channel, shaker-related subfamily, member 4 $Kcna4$ $Mm.142718$ 0.920 ± 0.068	n membrane channel protein beta 4	Gjb4	Mm.56906	0.914 ± 0.066
	oltage-gated channel, shaker-related subfamily, member 4	Kcna4	Mm.142718	0.920 ± 0.068
purinergic receptor P2X, ligand-gated ion channel 4 $P2rx4$ Mm.290884 0.921 ± 0.034	eceptor P2X, ligand-gated ion channel 4	P2rx4	Mm.290884	0.921 ± 0.034
potassium voltage-gated channel, subfamily Q, member 4 Kcnq4 Mm.249977 0.921 ± 0.029	oltage-gated channel, subfamily Q, member 4	Kenq4	Mm.249977	0.921 ± 0.029
calcium channel, voltage-dependent, alpha 2/delta subunit 2 Cacna2d2 Mm.273084 0.921 ± 0.030	nnel, voltage-dependent, alpha 2/delta subunit 2	Cacna2d2	Mm.273084	0.921 ± 0.030
purinergic receptor P2X, ligand-gated ion channel, 1 $P2rx1$ Mm.25722 0.924 ± 0.019	eceptor P2X, ligand-gated ion channel, 1	P2rx1	Mm.25722	0.924 ± 0.019
glutamate receptor, ionotropic, kainate 5 (gamma 2) Grik 5 Mm.2879 0.925 ± 0.040	eceptor, ionotropic, kainate 5 (gamma 2)	Grik5	Mm.2879	0.925 ± 0.040
potassium channel, subfamily K, member 13 Kcnk13 Mm.312335 0.927 ± 0.047	hannel, subfamily K, member 13	Kcnk13	Mm.312335	0.927 ± 0.047
	eptor potential cation channel, subfamily V, member 4	Trpv4	Mm.266450	0.929 ± 0.013
transient receptor potential cation channel, subfamily V, member 4 $Trpv4$ Mm.266450 0.929 ± 0.013	ane channel-like gene family 5	Tmc5	Mm.11068	0.929 ± 0.012
	hannel, subfamily K, member 16	Kcnk16	Mm.105571	0.932 ± 0.020

Table S2. Expression of ion channel-related genes in Nkx2-5 knockout heart.

transient receptor potential cation channel, subfamily M, member 7	Trpm7	Mm.244705	0.933 ± 0.037
calcium channel, voltage-dependent, beta 2 subunit	Cacnb2	Mm.313930	0.933 ± 0.032
sodium channel, voltage-gated, type IV, alpha polypeptide	Scn4a	Mm.432528	0.934 ± 0.038
glutamate receptor, ionotropic, kainate 2 (beta 2)	Grik2	Mm.332838	0.937 ± 0.052
chloride channel calcium activated 1	Clca1	Mm.20897	0.937 ± 0.034
calsenilin, presenilin binding protein, EF hand transcription factor	Csen	Mm.315292	0.945 ± 0.070
gap junction membrane channel protein beta 6	Gjb6	Mm.25652	0.949 ± 0.022
glutamate receptor, ionotropic, delta 2	Grid2	Mm.425327	0.950 ± 0.055
potassium voltage-gated channel, subfamily H (eag-related), member 2	Kcnh2	Mm.6539	0.950 ± 0.037
potassium voltage-gated channel, subfamily G, member 4	Kcng4	Mm.358699	0.951 ± 0.050
potassium voltage-gated channel, subfamily Q, member 1	Kenq1	Mm.356096	0.952 ± 0.020
chloride channel 7	Clcn7	Mm.270587	0.954 ± 0.053
Yip1 domain family, member 2	Yipf2	Mm.178115	0.954 ± 0.025
sodium channel, voltage-gated, type III, alpha	Scn3a	Mm.330256	0.954 ± 0.053
hydrogen voltage-gated channel	Hvcn1	Mm.28804	0.955 ± 0.042
potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4	Kcnn4	Mm.9911	0.957 ± 0.108
sodium channel, voltage-gated, type XI, alpha polypeptide	Scn11a	Mm.89981	0.957 ± 0.018
Shugoshin-like 2 (S. pombe)	Sgol2	Mm.339711	0.959 ± 0.016 0.959 ± 0.036
transient receptor potential cation channel, subfamily C, member 2	Trpc2	Mm.292904	0.967 ± 0.010
amiloride-sensitive cation channel 4, pituitary	Accn4	Mm.110790	0.967 ± 0.010 0.967 ± 0.051
chloride intracellular channel 6	Clic6	Mm.44747	0.968 ± 0.036
transient receptor potential cation channel, subfamily C, member 5	Trpc5	Mm.328378, Mm.434419	
gap junction membrane channel protein alpha 6	Gja6	Mm.123113	0.900 ± 0.001 0.970 ± 0.022
calcium channel, voltage-dependent, gamma subunit 7	Cacng7	Mm.214994	0.970 ± 0.022 0.970 ± 0.138
gap junction membrane channel protein alpha 12	Gja12	Mm.40016	0.970 ± 0.138 0.971 ± 0.040
hyperpolarization-activated, cyclic nucleotide-gated K+ 3	Hen3	Mm.389461	0.971 ± 0.040 0.972 ± 0.041
two pore segment channel 2	Tpen2	Mm.102235	0.972 ± 0.041 0.974 ± 0.025
gap junction membrane channel protein beta 2	Gjb2	Mm.102255 Mm.390683	0.974 ± 0.025 0.975 ± 0.045
transmembrane channel-like gene family 6	Tmc6	Mm.286963	0.975 ± 0.043 0.975 ± 0.063
calcium channel, voltage-dependent, L type, alpha 1C subunit	Cacna1c	Mm.436656	0.975 ± 0.003 0.976 ± 0.028
ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	Atp2a2	Mm.227583	0.977 ± 0.023
glutamate receptor, ionotropic, delta 1	Grid1	Mm.390745	0.977 ± 0.031 0.979 ± 0.023
potassium channel, subfamily K, member 4	Kenk4	Mm.12894	0.979 ± 0.023 0.981 ± 0.132
olfactomedin 1	Olfm1	Mm.12894 Mm.43278	0.981 ± 0.152 0.981 ± 0.059
chloride channel calcium activated 4	Clca4	Mm.43278 Mm.290600	
phospholamban	Pln	Mm.34145	0.982 ± 0.024 0.984 ± 0.041
trinucleotide repeat containing 6b	Tnrc6b Clenkb	Mm.131328	0.986 ± 0.053 0.989 ± 0.068
chloride channel Kb		Mm.24882	
bone morphogenetic protein 10	Bmp10	Mm.57171	0.990 ± 0.093
sodium channel, voltage-gated, type VI, alpha polypeptide	Scn7a	Mm.38127, Mm.389273	0.990 ± 0.050
Kv channel-interacting protein 1	Kenip1	Mm.252514	0.990 ± 0.013
potassium inwardly-rectifying channel, subfamily J, member 14	Kenj14	Mm.68170	0.994 ± 0.023
K+ voltage-gated channel, subfamily S, 1	Kens1	Mm.6217, Mm.439082	0.994 ± 0.063
potassium voltage-gated channel, subfamily G, member 3	Keng3	Mm.223506	0.994 ± 0.015
transient receptor potential cation channel, subfamily C, member 4 associated protein	Trpc4ap	Mm.268304, Mm.375116	
structure specific recognition protein 1	Ssrp1	Mm.219793	0.997 ± 0.054
potassium voltage-gated channel, shaker-related subfamily, member 7	Kcna7	Mm.12955	0.999 ± 0.027

chloride channel 3	Clen3	Mm.259751, Mm.25263	0.999 ± 0.021
potassium inwardly-rectifying channel, subfamily J, member 6	Kenj6	Mm.328720	0.999 ± 0.043
potassium voltage-gated channel, shaker-related subfamily, member 2	Kcna2	Mm.56930	1.000 ± 0.020
transient receptor potential cation channel, subfamily V, member 3	Trpv3	Mm.75196	1.000 ± 0.055
potassium voltage-gated channel, shaker-related subfamily, beta member 3	Kenab3	Mm.232472	1.002 ± 0.008
potassium voltage gated channel, Shab-related subfamily, member 1	Kenb1	Mm.387390, Mm.395669	
potassium channel, subfamily K, member 2	Kcnk2	Mm.33304, Mm.387016	1.007 ± 0.035
sodium channel, voltage-gated, type X, alpha polypeptide	Scn10a	Mm.247042	1.001 ± 0.033
potassium channel tetramerisation domain containing 4	Kctd4	Mm.390712	1.011 ± 0.047
leucine-rich repeats and transmembrane domains 2	Lrtm2	Mm.121498	1.012 ± 0.085
Potassium channel tetramerisation domain containing 20	Ketd20	Mm.435	1.012 ± 0.014
potassium inwardly-rectifying channel, subfamily J, member 3	Kenj3	Mm.5127, Mm.406902	1.014 ± 0.015
potassium voltage-gated channel, subfamily G, member 2	Keng2	Mm.279568	1.015 ± 0.022
chloride channel 4-2	Clen4-2	Mm.297883	1.022 ± 0.019
Amiloride-sensitive cation channel 1, neuronal (degenerin)	Accn1	Mm.234998	1.023 ± 0.105
potassium voltage-gated channel, subfamily H (eag-related), member 3	Kenh3	Mm.374793	1.024 ± 0.042
InaD-like (Drosophila)	Inadl	Mm.90218	1.024 ± 0.042 1.026 ± 0.070
Potassium voltage-gated channel, subfamily Q, member 5	Kenq5	Mm.336519	1.029 ± 0.036 1.029 ± 0.036
ANKTM1	Anktm1	Mm.186329	1.020 ± 0.030 1.030 ± 0.033
potassium voltage-gated channel, subfamily H (eag-related), member 1	Kenh1	Mm.4489	1.030 ± 0.035 1.032 ± 0.048
Kelch-like 28 (Drosophila)	Klhl28	Mm.248678	1.032 ± 0.048 1.036 ± 0.034
transmembrane channel-like gene family 2	Tmc2	Mm.248078 Mm.219546	1.030 ± 0.034 1.037 ± 0.032
potassium voltage-gated channel, subfamily H (eag-related), member 7	Kenh7	Mm.242532	1.037 ± 0.032 1.038 ± 0.026
		Mm.242332 Mm.87663	
voltage dependent calcium channel gamma 5 subunit	Cacng5		1.038 ± 0.026
chloride channel, nucleotide-sensitive, 1A	Clns1a	Mm.21482	1.038 ± 0.009
potassium channel, subfamily U, member 1	Kenu1	Mm.289679	1.041 ± 0.015
potassium inwardly-rectifying channel, subfamily J, member 5	Kenj5	Mm.69472	1.044 ± 0.019
voltage-dependent anion channel 1	Vdac1	Mm.3555	1.044 ± 0.019
coenzyme Q2 homolog, prenyltransferase (yeast)	Coq2	Mm.260661	1.044 ± 0.049
potassium channel tetramerisation domain containing 10	Ketd10	Mm.238285	1.046 ± 0.020
transient receptor potential cation channel, subfamily C, member 3	Trpc3	Mm.74363	1.047 ± 0.018
chloride intracellular channel 1	Clic1	Mm.29524	1.048 ± 0.011
RIKEN cDNA 8230402K04 gene (8230402K04Rik), no gene name on unigene	not listed		1.052 ± 0.028
calcium channel, voltage-dependent, beta 3 subunit	Cacnb3	Mm.3544	1.052 ± 0.028
amiloride-sensitive cation channel 3	Accn3	Mm.299636	1.052 ± 0.047
potassium channel tetramerisation domain containing 2	Kctd2	Mm.276299	1.053 ± 0.078
potassium inwardly-rectifying channel, subfamily J, member 12	Kenj12	Mm.4970	1.053 ± 0.065
potassium voltage gated channel, Shaw-related subfamily, member 4	Kenc4	Mm.101976	1.056 ± 0.037
sodium channel modifier 1	Scnm1	Mm.182944	1.057 ± 0.026
chloride channel 6	Clen6	Mm.89987	1.059 ± 0.046
potassium channel tetramerisation domain containing 3	Kctd3	Mm.209880, Mm.406821, Mm.432948	1.063 ± 0.014
transient receptor potential cation channel, subfamily V, member 2	Trpv2	Mm.288064	1.064 ± 0.039
sodium channel and clathrin linker 1	Sclt1	Mm.331001	1.065 ± 0.046
potassium channel tetramerisation domain containing 9	Ketd9	Mm.6720	1.066 ± 0.018
potassium voltage-gated channel, shaker-related subfamily, member 3	Kcna3	Mm.30640	1.068 ± 0.057
sodium channel, voltage-gated, type II, beta	Scn2b	Mm.229373	1.070 ± 0.058
glutamate receptor, ionotropic, AMPA3 (alpha 3)	Gria3	Mm.327681	1.070 ± 0.005
o	0.140		

cation channel, sperm associated 2	Catsper2	Mm.384318	1.071 ± 0.018
solute carrier family 8 (sodium/calcium exchanger), member 3	Slc8a3	Mm.149463	1.071 ± 0.021
calcium channel, voltage-dependent, N type, alpha 1B subunit	Cacna1b	Mm.4424	1.075 ± 0.032
transient receptor potential cation channel, subfamily C, member 1	Trpc1	Mm.149633	1.076 ± 0.021
potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	Kenn3	Mm.120250	1.082 ± 0.024
potassium voltage gated channel, Shab-related subfamily, member 2	Kcnb2	Mm.156081	1.085 ± 0.032
transmembrane channel-like gene family 4	Tmc4	Mm.360398	1.086 ± 0.072
potassium voltage gated channel, Shaw-related subfamily, member 1	Kenc1	Mm.249386	1.089 ± 0.061
calcium channel, voltage-dependent, alpha 1F subunit	Cacna1f	Mm.289647	1.094 ± 0.013
proteasome maturation protein	Pomp	Mm.332855	1.100 ± 0.029
chloride intracellular channel 4 (mitochondrial)	Clic4	Mm.257765, Mm.430849	1.101 ± 0.033
potassium channel, subfamily V, member 1	Kcnv1	Mm.300079	1.106 ± 0.056
sodium channel, voltage-gated, type VIII, alpha polypeptide	Scn8a	Mm.385012	1.107 ± 0.074
calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	Cacnala	Mm.334658	1.111 ± 0.338
potassium inwardly-rectifying channel, subfamily J, member 10	Kcnj10	Mm.254563	1.111 ± 0.080
purinergic receptor P2X, ligand-gated ion channel, 2	P2rx2	Mm.55948	1.113 ± 0.019
ATPase, Na+/K+ transporting, beta 1 polypeptide	Atp1b1	Mm.4550	1.113 ± 0.011
potassium channel tetramerisation domain containing 12	Kctd12	Mm.246466	1.114 ± 0.026
tangerin (LOC114601), EH domain binding protein 1-like 1	Ehbp111	Mm.210447	1.115 ± 0.033
potassium channel tetramerisation domain containing 11	Kctd11	Mm.239498	1.117 ± 0.020
asparagine-linked glycosylation 10 homolog B (yeast, alpha-1,2-glucosyltransferase)	Alg10b	Mm.17853	1.117 ± 0.041
potassium voltage-gated channel, shaker-related subfamily, member 1	Kcna1	Mm.40424	1.118 ± 0.034
gap junction membrane channel protein alpha 8	Gja8	Mm.258183	1.118 ± 0.007
potassium channel tetramerisation domain containing 12b	Kctd12b	Mm.271572, Mm.433607	1.123 ± 0.017
calcium channel, voltage-dependent, gamma subunit 6	Cacng6	Mm.424047	1.124 ± 0.006
potassium channel modulatory factor 1	Kcmf1	Mm.29194	1.125 ± 0.023
calcium channel, voltage-dependent, alpha2/delta subunit 1	Cacna2d1	Mm.159842, Mm.173392	1.129 ± 0.079
potassium voltage-gated channel, shaker-related subfamily, beta member 1	Kenab1	Mm.316402	1.129 ± 0.114
voltage-dependent anion channel 2	Vdac2	Mm.262327	1.134 ± 0.058
topoisomerase (DNA) II alpha	Top2a	Mm.4237	1.135 ± 0.013
potassium inwardly-rectifying channel, subfamily J, member 8	Kcnj8	Mm.1482	1.139 ± 0.042
calcium channel, voltage-dependent, gamma subunit 8	Cacng8	Mm.357990	1.143 ± 0.098
potassium channel tetramerisation domain containing 13	Kctd13	Mm.245897	1.143 ± 0.038
potassium voltage-gated channel, Isk-related family, member 1-like	Kcne11	Mm.58507, Mm.299425	1.155 ± 0.026
gap junction membrane channel protein alpha 4	Gja4	Mm.24615	1.156 ± 0.041
potassium large conductance calcium-activated channel, subfamily M, beta member 1	Kenmb1	Mm.6206	1.165 ± 0.052
voltage-dependent anion channel 3	Vdac3	Mm.227704, Mm.426265	1.170 ± 0.054
epidermodysplasia verruciformis 2	Ever2	Mm.116675	1.171 ± 0.038
FXYD domain-containing ion transport regulator 5	Fxyd5	Mm.1870	1.173 ± 0.013
Mid-1-related chloride channel 1	Mclc	Mm.214545	1.178 ± 0.023
sodium channel, nonvoltage-gated, type I, alpha polypeptide	Scnn1a	Mm.144114 Mm.277338,	1.186 ± 0.010
calcium channel, voltage-dependent, gamma subunit 2	Cacng2	Mm.390811, Mm.400802	1.193 ± 0.050
Potassium inwardly-rectifying channel, subfamily K, member 6	Kcnk6	Mm.24877	1.195 ± 0.033
gap junction membrane channel protein beta 1	Gjb1	Mm.21198	1.197 ± 0.189
purinergic receptor P2X, ligand-gated ion channel, 5	P2rx5	Mm.156893	1.206 ± 0.053
potassium voltage-gated channel, Shal-related family, member 2	Kend2	Mm.320691	1.217 ± 0.039

TWIK-related individual K+ channel	Trik	Mm.329947	1.229 ± 0.056
glutamate receptor, ionotropic, AMPA4 (alpha 4)	Gria4	Mm.209263	1.242 ± 0.056
BTB (POZ) domain containing 5	Btbd5	Mm.248678	1.261 ± 0.107
calcium channel, voltage-dependent, beta 1 subunit, transcript variant 1	Cacnb1	Mm.41252, Mm.391757	1.262 ± 0.025
calcium channel mRNA, Two pore channel 1	Tpcn1	Mm.114054	1.359 ± 0.118
potassium voltage-gated channel, subfamily Q, member 2	Kenq2	Mm.40615	1.361 ± 0.100
protein distantly related to to the gamma subunit family	Pr1	Mm.24750	1.471 ± 0.032
potassium voltage-gated channel, Isk-related subfamily, gene 3	Kcne3	Mm.282386	1.488 ± 0.039
transmembrane channel-like gene family 7	Tmc7	Mm.69380	1.563 ± 0.071
sodium channel, voltage-gated, type I, beta polypeptide	Scn1b	Mm.1418	1.618 ± 0.033
transient receptor potential cation channel, subfamily C, member 7	Trpc7	Mm.62409	1.628 ± 0.146

Figure S1. Frozen sections of R26R/Tg-Cre-ERTM stained for β -galactosidase including aortic valve (A) and pulmonary valve (B). Bars = 500 um. AoV, aortic valve; PV, pulmonary valve.; LA, left atrium; LV, left ventricle, RV, right ventricle.

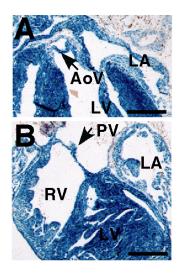


Figure S2. Conduction defects (A) and increased heart weight (B) in the mice survived at **PD28 in Nkx2-5 knockout (n=4) compared to control (n=5).** Either lead I (I) or lead II (II) ECG recording of each mouse is shown.

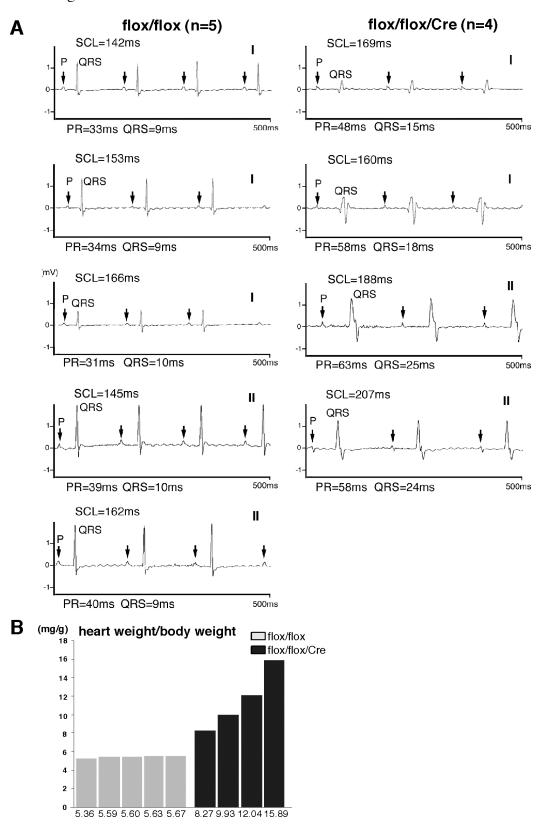


Figure S3. Specificity of Na_v1.5 staining. Anti-Na_v1.5(α) antibody (alomone labs, ASC-005) was utilized for immunohistochemistry in control flox/flox hearts in the absence (left) and presence (right) of pre-adsorption with antigen-peptide (1 µg peptide /1 µg antibody). Staining was performed side by side.

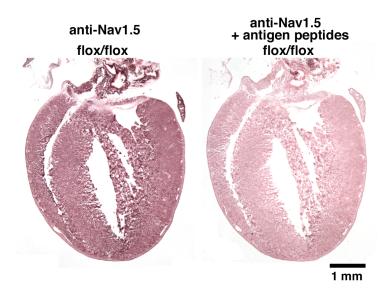


Figure S4. Immunostaining of Na_v1.5(α) in two additional flox/flox/Cre mouse hearts at PD12. Reduced staining of Na_v1.5(α) in ventricles, but preserved staining in atria, His bundles and inner layer of ventricles (likely Purkinje fibers) was noted.

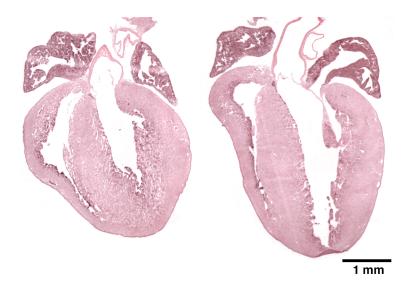


Figure S5. Western blotting demonstrates similar levels of $Na_v 1.5(\alpha)$ protein in atria of flox/flox and flox/flox/Cre mice (lanes 1 vs.2).

