

Supplemental Digital Content 1: Means and SD

		Action Potential Characteristics		
		<i>Control</i>	<i>10 μM Bupivacaine</i>	<i>10 μM Bupivacaine + 10 % Lipovenös®</i>
V_m (mV)	Epicardial	-87.8 ± 2.5	-88.3 ± 2.2 *	-88.2 ± 2.1 *
	Endocardial	-86.4 ± 2.1	-86.8 ± 2.3	-87.1 ± 1.7
Overshoot (mV)	Epicardial	38.1 ± 5.5	21.8 ± 9.7 ***	28.5 ± 7.2 *** †††
	Endocardial	41.2 ± 6.6	26.6 ± 14.1 ***	33.6 ± 10.1 *** ††
dV/dt_{max} (Vs ⁻¹)	Epicardial	258.9 ± 68.1	114.9 ± 52.0 ***	150.4 ± 64.1 *** †††
	Endocardial	278.1 ± 126.8	141.9 ± 90.4 ***	181.1 ± 102.9 *** ††
APD _{0mV} (ms)	Epicardial	4.5 ± 2.0	5.4 ± 4.5	4.8 ± 2.7
	Endocardial	25.3 ± 17.7	28.2 ± 21.8	20.3 ± 12.3 †
APD ₂₀ (ms)	Epicardial	2.7 ± 0.7	6.1 ± 5.8 *	3.4 ± 1.0 †
	Endocardial	7.6 ± 3.3	20.3 ± 9.5 ***	10.8 ± 4.6 †††
APD ₅₀ (ms)	Epicardial	11.3 ± 6.6	18.2 ± 13.0 **	13.1 ± 6.5 ††
	Endocardial	48.3 ± 31.4	61.3 ± 33.5 *	40.5 ± 20.0 ††
APD ₉₀ (ms)	Epicardial	50.0 ± 21.1	63.6 ± 25.3 ***	49.6 ± 15.5 †††
	Endocardial	119.4 ± 56.3	132.0 ± 55.3	93.6 ± 34.6 *** †††
n	Epicardial	12	12	12
	Endocardial	7	7	7
		<i>Control</i>	<i>40 μM Mepivacaine</i>	<i>40 μM Mepivacaine + 10 % Lipovenös®</i>
V_m (mV)	Epicardial	-87.9 ± 2.5	-88.1 ± 2.1	-87.6 ± 1.9 * ††
	Endocardial	-88.2 ± 2.5	-88.4 ± 2.5	-88.0 ± 2.3 †
Overshoot (mV)	Epicardial	35.9 ± 5.6	26.3 ± 8.9 ***	25.1 ± 9.3 ***
	Endocardial	41.5 ± 4.2	35.6 ± 6.8 ***	35.6 ± 6.9 ***
dV/dt_{max} (V s ⁻¹)	Epicardial	208.8 ± 52.5	136.1 ± 50.0 ***	124.1 ± 48.2 *** †
	Endocardial	294.5 ± 63.4	198.8 ± 58.5 ***	191.6 ± 57.6 ***
APD _{0mV} (ms)	Epicardial	3.4 ± 1.1	3.3 ± 1.2	3.9 ± 1.5 *** †††
	Endocardial	28.4 ± 32.9	28.4 ± 32.2	23.2 ± 25.9 * ††
APD ₂₀ (ms)	Epicardial	2.3 ± 0.7	3.0 ± 1.2 ***	4.1 ± 2.4 *** ††
	Endocardial	10.0 ± 14.6	15.1 ± 21.5 ***	12.0 ± 14.3 †
APD ₅₀ (ms)	Epicardial	10.1 ± 5.6	13.0 ± 7.7	19.5 ± 16.7 *** ††
	Endocardial	56.9 ± 56.8	59.7 ± 57.8	48.7 ± 49.4 *** †††
APD ₉₀ (ms)	Epicardial	50.0 ± 20.4	56.2 ± 22.3	63.5 ± 27.6 ** †
	Endocardial	125.2 ± 89.6	125.2 ± 87.1	102.2 ± 76.2 *** †††
n	Epicardial	25	25	25
	Endocardial	34	34	34

I_{Na}

	<i>Control</i>	<i>10 μM Bupivacaine</i>	<i>10 μM Bupivacaine + 10 % Lipovenös®</i>	<i>Control</i>
<i>I_{Na}</i> (pApF ⁻¹)	-42.3 ± 17.6	-19.3 ± 7.9 ^{***}	-26.4 ± 11.7 ^{*** †††}	-43.5 ± 20.1 ^{††† ###}
<i>n</i>	17	17	17	17
	<i>Control</i>	<i>10 μM Bupivacaine</i>	<i>Centrifuged 10 μM Bupivacaine + 10 % Lipovenös®</i>	<i>Control</i>
<i>I_{Na}</i> (pApF ⁻¹)	-50.1 ± 16.3	-23.0 ± 6.8 ^{***}	-27.3 ± 8.1 ^{*** †††}	-47.1 ± 15.0 ^{*** ††† ###}
<i>n</i>	17	17	17	17
	<i>Control</i>	<i>40 μM Mepivacaine</i>	<i>40 μM Mepivacaine + 10 % Lipovenös®</i>	<i>Control</i>
<i>I_{Na}</i> (pApF ⁻¹)	-44.3 ± 26.6	-30.0 ± 16.9 ^{***}	-35.1 ± 19.0 ^{*** †††}	-48.9 ± 28.0 ^{*** ††† ###}
<i>n</i>	24	24	24	24
	<i>Control</i>	<i>40 μM Mepivacaine</i>	<i>Centrifuged 40 μM Mepivacaine + 10 % Lipovenös®</i>	<i>Control</i>
<i>I_{Na}</i> (pApF ⁻¹)	-48.2 ± 21.3	-35.1 ± 15.4 ^{***}	-37.9 ± 17.2 ^{*** ††}	-51.2 ± 24.2 ^{** ††† ###}
<i>n</i>	23	23	23	23
	<i>Control</i>	<i>Control</i>	<i>10 % Lipovenös®</i>	<i>Control</i>
<i>I_{Na}</i> (pApF ⁻¹)	-45.5 ± 14.1	-42.3 ± 13.4	-51.6 ± 19.0 ^{†††}	-50.0 ± 17.9 ^{††}
<i>n</i>	7	7	7	7
	<i>Control</i>	<i>1 μM Bupivacaine</i>	<i>5 μM Bupivacaine</i>	<i>10 μM Bupivacaine</i>
<i>I_{Na}</i> (pApF ⁻¹)	-46.4 ± 14.8	-34.9 ± 10.4	-25.4 ± 8.7	-20.0 ± 6.8
<i>n</i>	7	7	7	7

Concentrations of Local Anesthetics

	LA	LA +10 % Lipovenös®	LA + 10 % Lipovenös® Water Phase	LA + 10 % Lipovenös® Lipid-Enriched Phase
Bupivacaine (µM)				
10 µM		8.8 ± 0.8	6.5 ± 0.4 ^{†††}	45.4 ± 12.3
n		6	6	6
100 µM	91.8 ± 2.6	93.7 ± 3.1	64.7 ± 8.2 ^{†††}	445.2 ± 145.1
n	7	7	7	7
Mepivacaine (µM)				
10 µM		11.5 ± 1.6	10.1 ± 2.1 [‡]	13.8 ± 2.3
n		6	6	6
100 µM	102.8 ± 2.6	105.8 ± 8.5	103.9 ± 9.4 (p = 0.08)	115.9 ± 7.8
n	7	7	7	7

Concentration-response Analysis on hKv4.2+hKChIP2b Currents in *Xenopus laevis* Oocytes

	Bupivacaine	Bupivacaine +10 % Lipovenös®	Mepivacaine	Mepivacaine +10 % Lipovenös®
IC ₅₀ (µM)	126.6 ± 67	218.2 ± 113.8 *	1,688 ± 845	1,203 ± 637
Hillslope	1.1 ± 0.3	1.3 ± 0.3	1.0 ± 0.1	0.9 ± 0.2
n	14	15	13	19

Effect of Increasing Lipovenös® Concentrations on hKv4.2+hKChIP2b Currents Blocked by 300 µM Bupivacaine

	0 %	10 %	20 %	40 %	80 %	Control
Charge (nC)	551 ± 144	793 ± 222	1,033 ± 309	1,359 ± 345	1,516 ± 282	1,667 ± 340
n	13	13	13	13	13	13

Effect of the Ultra-Centrifuged Bupivacaine-Lipid Mixture on hKv4.2+hKChIP2b Currents

	100 µM Bupivacaine	100 µM Bupivacaine + 10 % Lipovenös®	100 µM Bupivacaine	100 µM Bupivacaine + 10 % Lipovenös® Ultra-Centrifuged
Charge (nC)	557.7 ± 224	747.7 ± 295.1 ***	514 ± 124.4	714.9 ± 178.2 ***
n	10	10	10	10

Data are given as mean ± SD. * p < 0.05, ** p < 0.01, *** p < 0.001 vs. control; † p < 0.05, †† p < 0.01, ††† p < 0.001 vs. 10 µM bupivacaine or 40 µM mepivacaine; ### p < 0.001 vs. 10 µM bupivacaine + 10 % Lipovenös® or 40 µM mepivacaine + 10 % Lipovenös®; ‡ p < 0.05, ‡‡‡ p < 0.001 vs. LA + 10 % Lipovenös®.

APD_{0mV} = action potential duration at 0 mV; APD₂₀ = action potential duration at 20 % repolarization; APD₅₀ = action potential duration at 50 % repolarization; APD₉₀ = action potential duration at 90 % repolarization; dV/dt_{max} = maximal upstroke velocity of the action potential; Hillslope = slope of the Hill function fitted to the charge of hKv4.2+hKChIP2b currents inhibited by the LAs; IC₅₀ = concentration at which the charge of hKv4.2+hKChIP2b

currents was inhibited to 50%; I_{Na} = cardiac fast Na^+ current; LA = local anesthetic; Lipid-enriched Phase = the lipid-enriched phase of the solution after ultracentrifugation; Lipovenös[®] = Lipovenös[®] MCT 20%, Fresenius Kabi AG, Bad Homburg, Germany; n = number of cells investigated; Overshoot = overshoot of the action potential; V_m = resting membrane potential; Water Phase = the water phase of the solution after ultracentrifugation.