

## Supplemental Digital Content 2: 95% Confidence Intervals

		<b>Action Potential Characteristics</b>		
		<i>Control</i>	<i>10 μM Bupivacaine</i>	<i>10 μM Bupivacaine + 10 % Lipovenös®</i>
$V_m$ (mV)	Epicardial	-89.4 - -86.1	-89.7 - -86.9 <sup>*</sup>	-89.5 - -86.9 <sup>*</sup>
	Endocardial	-88.3 - -84.5	-88.9 - -84.6	-88.7 - -85.5
Overshoot (mV)	Epicardial	34.5 - 41.6	15.6 - 27.9 <sup>***</sup>	23.9 - 33.1 <sup>*** †††</sup>
	Endocardial	35.1 - 47.2	13.7 - 39.6 <sup>***</sup>	24.3 - 43.0 <sup>** ††</sup>
$dV/dt_{max}$ ( $Vs^{-1}$ )	Epicardial	215.6 - 302.2	81.8 - 147.9 <sup>***</sup>	109.6 - 191.1 <sup>*** †††</sup>
	Endocardial	160.8 - 395.4	58.2 - 225.5 <sup>***</sup>	86.7 - 277.1 <sup>*** ††</sup>
APD <sub>0mV</sub> (ms)	Epicardial	3.3 - 5.8	2.5 - 8.2	3.0 - 6.5
	Endocardial	9.0 - 41.6	8.0 - 48.3	8.9 - 31.7 <sup>†</sup>
APD <sub>20</sub> (ms)	Epicardial	2.2 - 3.2	2.4 - 9.7 <sup>*</sup>	2.7 - 4.1 <sup>†</sup>
	Endocardial	4.6 - 10.7	11.5 - 29.0 <sup>***</sup>	6.5 - 15.0 <sup>†††</sup>
APD <sub>50</sub> (ms)	Epicardial	7.1 - 15.5	9.9 - 26.5 <sup>**</sup>	9.0 - 17.2 <sup>††</sup>
	Endocardial	19.2 - 77.3	30.3 - 92.3 <sup>*</sup>	22.0 - 59.0 <sup>††</sup>
APD <sub>90</sub> (ms)	Epicardial	36.6 - 63.3	47.5 - 79.6 <sup>***</sup>	39.7 - 59.4 <sup>†††</sup>
	Endocardial	67.3 - 171.4	80.8 - 183.1	61.7 - 125.6 <sup>** †††</sup>
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	-89.0 - -86.9	-89.0 - -87.3	-88.3 - -86.8 <sup>††</sup>
	Endocardial	-89.1 - -87.3	-89.3 - -87.5	-88.8 - -87.2 <sup>†</sup>
Overshoot (mV)	Epicardial	33.6 - 38.2	22.7 - 30.0 <sup>***</sup>	21.3 - 29.0 <sup>***</sup>
	Endocardial	40.0 - 43.0	33.2 - 38.0 <sup>***</sup>	33.2 - 38.0 <sup>***</sup>
$dV/dt_{max}$ ( $V s^{-1}$ )	Epicardial	187.1 - 230.4	115.5 - 156.8 <sup>***</sup>	104.2 - 144.0 <sup>*** †</sup>
	Endocardial	272.4 - 316.6	178.4 - 219.2 <sup>***</sup>	171.6 - 211.7 <sup>***</sup>
APD <sub>0mV</sub> (ms)	Epicardial	3.0 - 3.9	2.8 - 3.8	3.3 - 4.6 <sup>*** †††</sup>
	Endocardial	17.0 - 39.9	17.2 - 39.7	14.2 - 32.3 <sup>* ††</sup>
APD <sub>20</sub> (ms)	Epicardial	2.1 - 2.6	2.6 - 3.5 <sup>***</sup>	3.1 - 5.1 <sup>*** ††</sup>
	Endocardial	4.9 - 15.0	7.6 - 22.6 <sup>***</sup>	7.0 - 17.0 <sup>†</sup>
APD <sub>50</sub> (ms)	Epicardial	7.8 - 12.5	9.8 - 16.1	12.6 - 26.4 <sup>*** ††</sup>
	Endocardial	37.1 - 76.7	39.5 - 79.9	31.5 - 66.0 <sup>** †††</sup>
APD <sub>90</sub> (ms)	Epicardial	41.6 - 58.4	47.0 - 65.4	52.1 - 74.9 <sup>** †</sup>
	Endocardial	94.0 - 156.5	94.8 - 155.6	75.6 - 128.8 <sup>*** †††</sup>
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>
$I_{Na}$ (pApF <sup>-1</sup> )	-51.3 - -33.3	-23.4 - -15.2 <sup>***</sup>	-32.4 - -20.4 <sup>*** ††</sup>	-54.3 - -32.8 <sup>††† ###</sup>
n	17	17	17	17
	<i>Control</i>	<i>10 μM Bupivacaine</i>	<i>Centrifuged 10 μM Bupivacaine + 10 % Lipovenös®</i>	<i>Control</i>
$I_{Na}$ (pApF <sup>-1</sup> )	-58.5 - -41.7	-26.5 - -19.4 <sup>***</sup>	-31.5 - -19.4 <sup>*** ††</sup>	-54.8 - -39.4 <sup>*** ††† ###</sup>
n	17	17	17	17
	<i>Control</i>	<i>40 μM Mepivacaine</i>	<i>40 μM Mepivacaine + 10 % Lipovenös®</i>	<i>Control</i>
$I_{Na}$ (pApF <sup>-1</sup> )	-55.5 - -33.1	-37.1 - -22.8 <sup>***</sup>	-43.1 - -27.0 <sup>*** ††</sup>	-60.7 - 37.1 <sup>*** ††† ###</sup>
n	24	24	24	24
	<i>Control</i>	<i>40 μM Mepivacaine</i>	<i>Centrifuged 40 μM Mepivacaine + 10 % Lipovenös®</i>	<i>Control</i>
$I_{Na}$ (pApF <sup>-1</sup> )	-57.4 - -39.0	-41.7 - -28.4 <sup>***</sup>	-45.3 - -30.4 <sup>*** ††</sup>	-61.7 - -40.8 <sup>*** ††† ###</sup>
n	23	23	23	23
	<i>Control</i>	<i>Control</i>	<i>10 % Lipovenös®</i>	<i>Control</i>
$I_{Na}$ (pApF <sup>-1</sup> )	-58.5 - -32.5	-54.7 - -29.9	-69.2 - -34.1 <sup>††</sup>	-66.8 - 33.7 <sup>††</sup>
n	7	7	7	7
	<i>Control</i>	<i>1 μM Bupivacaine</i>	<i>5 μM Bupivacaine</i>	<i>10 μM Bupivacaine</i>
$I_{Na}$ (pApF <sup>-1</sup> )	-60.0 - -32.7	-44.5 - -25.3	-33.4 - -17.3	-26.3 - -13.8
n	7	7	7	7

**Concentrations of Local Anesthetics**

	LA	LA +10 % Lipovenös®	LA + 10 % Lipovenös® Water Phase	LA + 10 % Lipovenös® Lipid-Enriched Phase
<b>Bupivacaine (µM)</b>				
10 µM		7.9 - 9.7	6.0 - 6.9 <sup>†††</sup>	32.5 - 58.3
n		6	6	6
100 µM	89.4 - 94.3	90.9 - 96.5	57.3 - 72.2 <sup>†††</sup>	311.8 - 578.6
n	7	7	7	7
<b>Mepivacaine (µM)</b>				
10 µM		9.9 - 13.2	7.9 - 12.3 <sup>‡</sup>	11.4 - 16.2
n		6	6	6
100 µM	100.4 - 105.3	98.0 - 113.7	95.2 - 112.6 (p = 0.08)	108.6 - 123.1
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 <sub>50</sub> (µM)	87.9 - 165.3	155.2 - 281.2 *	1,178 - 2,199	895 - 1,510
Hillslope	0.9 - 1.3	1.1 - 1.4	0.9 - 1.1	0.8 - 1.0
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)	465 - 638	659 - 927	846 - 1,219	1,150 - 1,567	1,346 - 1,687	1,462 - 1,872
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)	397.4 - 718	536.6 - 958.9 <sup>***</sup>	425.5 - 603.5	587.5 - 842.3 <sup>***</sup>
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<sub>0mV</sub> = action potential duration at 0 mV; APD<sub>20</sub> = action potential duration at 20 % repolarization; APD<sub>50</sub> = action potential duration at 50 % repolarization; APD<sub>90</sub> = action potential duration at 90 % repolarization; dV/dt<sub>max</sub> = 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; IC<sub>50</sub> = 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<sup>®</sup> = Lipovenös<sup>®</sup> 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.