# Text S1

Supplementary Material for "The Relative Influences of Phosphometabolites and pH on Action Potential Morphology During Myocardial Reperfusion: A Simulation Study."

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Table S1: Action Potential Duration (90) During Initial 10 Minutes of Reperfusion (ms)

| | Pre | R0 | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 | R9 | R10 | Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 109.0 | 16.5 | 88.5 | 92.0 | 88.5 | 84.5 | 82.0 | 81.0 | 80.0 | 79.5 | 79.5 | 79.5 | 83.5 |
| Dual Clamp | 109.0 | 16.5 | 66.5 | 67.5 | 64.5 | 61.5 | 59.5 | 57.5 | 56.0 | 54.5 | 53.5 | 52.5 | 59.4 |
| pH Clamp | 109.0 | 16.5 | 87.5 | 90.0 | 86.5 | 83.0 | 80.5 | 79.0 | 77.0 | 75.5 | 74.5 | 73.5 | 80.7 |
| pH 6.4 | 109.0 | 16.5 | 88.0 | 91.5 | 88.0 | 83.5 | 80.0 | 78.0 | 76.0 | 74.5 | 73.5 | 72.5 | 80.6 |
| pH 6.9 | 109.0 | 16.5 | 88.5 | 92.0 | 88.0 | 84.0 | 81.0 | 79.5 | 78.0 | 77.0 | 76.5 | 76.5 | 82.1 |
| pH 7.9 | 109.0 | 16.5 | 88.5 | 92.0 | 88.5 | 85.0 | 82.5 | 82.0 | 81.5 | 81.5 | 81.5 | 81.5 | 84.4 |
| ATP Clamp | 109.0 | 16.5 | 66.5 | 66.5 | 61.5 | 57.0 | 53.5 | 51.5 | 49.5 | 48.5 | 47.5 | 47.0 | 54.9 |
| ATP 25 | 109.0 | 16.5 | 48.0 | 48.5 | 45.0 | 41.5 | 38.5 | 37.0 | 35.5 | 34.5 | 33.5 | 33.0 | 39.5 |
| ATP 50 | 109.0 | 16.5 | 72.5 | 73.0 | 68.0 | 63.0 | 59.0 | 56.0 | 54.5 | 53.0 | 52.0 | 51.5 | 60.2 |
| ATP 75 | 109.0 | 16.5 | 83.0 | 85.0 | 80.0 | 75.5 | 72.0 | 70.0 | 68.0 | 67.0 | 66.5 | 66.5 | 73.4 |
| ATP 150 | 109.0 | 16.5 | 95.5 | 102.0 | 101.0 | 99.5 | 99.0 | 99.0 | 99.0 | 99.0 | 99.0 | 99.0 | 99.2 |
| ATP 200 | 109.0 | 16.5 | 101.0 | 109.5 | 111.0 | 111.0 | 110.5 | 111.0 | 111.0 | 111.0 | 110.5 | 110.5 | 109.7 |

Table S2: Action Potential Amplitude During Initial 10 Minutes of Reperfusion (mV)

| | Pre | R0 | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 | R9 | R10 | Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 118.4 | 36.1 | 101.9 | 110.1 | 110.9 | 109.7 | 109.5 | 109.1 | 108.9 | 108.9 | 108.9 | 108.9 | 108.7 |
| Dual Clamp | 118.4 | 36.1 | 90.2 | 105.1 | 105.2 | 102.2 | 99.1 | 97.1 | 94.8 | 92.6 | 90.5 | 88.6 | 96.5 |
| pH Clamp | 118.4 | 36.1 | 101.8 | 111.2 | 111.6 | 109.2 | 106.8 | 105.7 | 104.7 | 103.9 | 103.2 | 102.6 | 106.0 |
| pH 6.4 | 118.4 | 36.1 | 101.9 | 110.3 | 110.6 | 108.5 | 107.8 | 106.7 | 106.3 | 105.8 | 105.4 | 105.2 | 106.9 |
| pH 6.9 | 118.4 | 36.1 | 101.9 | 110.0 | 110.7 | 109.1 | 108.7 | 108.1 | 107.7 | 107.5 | 107.4 | 107.3 | 107.8 |
| pH 7.9 | 118.4 | 36.1 | 101.9 | 110.2 | 111.1 | 110.5 | 110.1 | 109.9 | 109.8 | 109.8 | 109.8 | 109.9 | 109.3 |
| ATP Clamp | 118.4 | 36.1 | 89.9 | 103.5 | 103.7 | 101.8 | 99.8 | 98.9 | 97.7 | 96.5 | 95.4 | 94.6 | 98.2 |
| ATP 25 | 118.4 | 36.1 | 78.9 | 103.7 | 104.5 | 102.2 | 100.6 | 99.5 | 98.1 | 96.7 | 95.4 | 95.0 | 97.5 |
| ATP 50 | 118.4 | 36.1 | 94.7 | 105.0 | 105.6 | 103.6 | 101.7 | 101.0 | 100.0 | 99.1 | 98.3 | 97.5 | 100.6 |
| ATP 75 | 118.4 | 36.1 | 99.5 | 107.2 | 108.0 | 106.4 | 105.7 | 105.0 | 104.6 | 104.3 | 104.2 | 104.1 | 104.9 |
| ATP 150 | 118.4 | 36.1 | 104.5 | 113.8 | 117.0 | 116.6 | 116.2 | 116.1 | 116.3 | 116.3 | 116.1 | 115.9 | 114.9 |
| ATP 200 | 118.4 | 36.1 | 106.2 | 119.1 | 122.0 | 122.1 | 121.8 | 121.8 | 121.9 | 121.8 | 121.5 | 121.2 | 119.9 |

Table S3: Resting Membrane Potential During Initial 10 Minutes of Reperfusion (mV)

| | Pre | R0 | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 | R9 | R10 | Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | -78.0 | -48.4 | -69.2 | -75.9 | -77.3 | -77.4 | -77.4 | -77.2 | -77.1 | -77.0 | -76.9 | -76.8 | -76.2 |
| Dual Clamp | -78.0 | -48.4 | -68.5 | -75.2 | -76.4 | -76.1 | -75.5 | -75.0 | -74.4 | -73.9 | -73.4 | -73.0 | -74.1 |
| pH Clamp | -78.0 | -48.4 | -69.3 | -76.2 | -77.5 | -77.5 | -77.1 | -76.8 | -76.4 | -76.1 | -75.8 | -75.5 | -75.8 |
| pH 6.4 | -78.0 | -48.4 | -69.3 | -75.9 | -77.2 | -77.2 | -77.0 | -76.8 | -76.6 | -76.4 | -76.2 | -76.1 | -75.9 |
| pH 6.9 | -78.0 | -48.4 | -69.2 | -75.9 | -77.2 | -77.3 | -77.2 | -77.0 | -76.8 | -76.7 | -76.6 | -76.4 | -76.0 |
| pH 7.9 | -78.0 | -48.4 | -69.2 | -75.9 | -77.4 | -77.6 | -77.5 | -77.4 | -77.3 | -77.2 | -77.2 | -77.1 | -76.4 |
| ATP Clamp | -78.0 | -48.4 | -68.3 | -75.0 | -76.3 | -76.2 | -75.9 | -75.6 | -75.2 | -75.0 | -74.7 | -74.5 | -74.7 |
| ATP 25 | -78.0 | -48.4 | -68.2 | -74.9 | -76.2 | -76.1 | -75.7 | -75.4 | -75.1 | -74.8 | -74.5 | -74.3 | -74.5 |
| ATP 50 | -78.0 | -48.4 | -68.5 | -75.2 | -76.5 | -76.5 | -76.2 | -75.9 | -75.7 | -75.4 | -75.2 | -75.0 | -75.0 |
| ATP 75 | -78.0 | -48.4 | -68.9 | -75.5 | -76.9 | -76.9 | -76.8 | -76.6 | -76.4 | -76.2 | -76.1 | -75.9 | -75.6 |
| ATP 150 | -78.0 | -48.4 | -69.7 | -76.7 | -78.2 | -78.5 | -78.5 | -78.4 | -78.4 | -78.3 | -78.3 | -78.2 | -77.3 |
| ATP 200 | -78.0 | -48.4 | -70.1 | -77.3 | -79.0 | -79.3 | -79.3 | -79.2 | -79.2 | -79.1 | -79.1 | -79.0 | -78.1 |

Table S4: Mean Currents (uA/uF) During Reperfusion (pH Simulations)

| | Control | Dual Clamp | pH Clamp | pH 6.4 | pH 6.9 | pH 7.9 |
|---|---|---|---|---|---|---|
| $I_{Na}$ | -0.2022 | -0.1739 | -0.1948 | -0.1958 | -0.1992 | -0.2044 |
| $I_{Na,b}$ | -0.2269 | -0.2223 | -0.2225 | -0.2237 | -0.2255 | -0.2278 |
| $I_{Na\text{-}L}$ | -0.0119 | -0.0074 | -0.0109 | -0.0111 | -0.0116 | -0.0121 |
| NCX | -0.3058 | -0.0445 | -0.1745 | -0.2246 | -0.2704 | -0.3292 |
| NaK | 0.4911 | 0.0783 | 0.3000 | 0.3838 | 0.4433 | 0.5215 |
| $I_{Ca(L),Na}$ | -0.1218 | -0.0500 | -0.1056 | -0.1095 | -0.1163 | -0.1256 |
| $I_{Ca(L),K}$ | 0.0613 | 0.0182 | 0.0535 | 0.0546 | 0.0580 | 0.0639 |
| $I_{Ca(L)}$ | -1.0362 | -0.4851 | -0.9138 | -0.9514 | -0.9991 | -1.0609 |
| $I_{Cl}$ | -0.3560 | -0.5343 | -0.4431 | -0.4300 | -0.3890 | -0.3330 |
| $I_{Kr}$ | 0.1445 | 0.0793 | 0.1356 | 0.1369 | 0.1411 | 0.1470 |
| $I_{Ks}$ | 0.1119 | 0.0205 | 0.1027 | 0.1004 | 0.1063 | 0.1164 |
| $I_{Kp}$ | 0.0604 | 0.0313 | 0.0600 | 0.0576 | 0.0589 | 0.0617 |
| $I_{K1}$ | 0.8181 | 0.6872 | 0.6794 | 0.7634 | 0.7983 | 0.8287 |
| $I_{Ca(T)}$ | -0.0740 | -0.0767 | -0.0720 | -0.0726 | -0.0733 | -0.0744 |
| $I_{Ca,b}$ | –0.4852 | -0.5001 | -0.4717 | -0.4791 | -0.4826 | -0.4869 |
| $I_{pCa}$ | 0.9589 | 0.9700 | 1.0960 | 1.0328 | 0.9904 | 0.9385 |
| $I_{K(ATP)}$ | 0.3115 | 0.3243 | 0.2961 | 0.2976 | 0.3051 | 0.3161 |

Table S5: Mean Currents (uA/uF) During Reperfusion (Phosphometabolite Simulations)

| | Control | Dual Clamp | ATP Clamp | ATP 25 | ATP 50 | ATP 75 | ATP 150 | ATP 200 |
|---|---|---|---|---|---|---|---|---|
| $I_{Na}$ | -0.2022 | 0.1739 | -0.1793 | -0.1811 | -0.1844 | -0.1922 | -0.2217 | -0.2357 |
| $I_{Na,b}$ | -0.2269 | -0.2223 | -0.2261 | -0.2373 | -0.2266 | -0.2249 | -0.2334 | -0.2391 |
| $I_{Na\text{-}L}$ | -0.0119 | -0.0074 | -0.0070 | -0.0050 | -0.0081 | -0.0101 | -0.0156 | -0.0187 |
| NCX | -0.3058 | -0.0445 | -0.0632 | -0.0089 | -0.1145 | -0.2140 | -0.4355 | -0.4883 |
| NaK | 0.4911 | 0.0783 | 0.1352 | 0.0920 | 0.2140 | 0.3527 | 0.6941 | 0.7856 |
| $I_{Ca(L),Na}$ | 0.1218 | -0.0500 | -0.0495 | -0.0187 | -0.0646 | -0.0962 | -0.1620 | -0.1814 |
| $I_{Ca(L),K}$ | 0.0613 | 0.0182 | 0.0176 | 0.0052 | 0.0257 | 0.0444 | 0.0912 | 0.1050 |
| $I_{Ca(L)}$ | -1.0362 | -0.4851 | -0.4805 | -0.1892 | -0.6096 | -0.8626 | -1.2527 | -1.3384 |
| $I_{Cl}$ | -0.3560 | -0.5343 | -0.4781 | -0.5419 | -0.4568 | -0.4012 | -0.2812 | -0.2355 |
| $I_{Kr}$ | 0.1445 | 0.0793 | 0.0713 | 0.0370 | 0.0874 | 0.1200 | 0.1808 | 0.2046 |
| $I_{Ks}$ | 0.0723 | 0.0132 | 0.0162 | 0.0017 | 0.0274 | 0.0658 | 0.2303 | 0.3315 |
| $I_{Kp}$ | 0.0604 | 0.0313 | 0.0278 | 0.0130 | 0.0331 | 0.0477 | 0.0818 | 0.0934 |
| $I_{K1}$ | 0.8181 | 0.6872 | 0.7108 | 0.7823 | 0.7414 | 0.7738 | 0.8412 | 0.8136 |
| $I_{Ca(T)}$ | -0.0740 | -0.0767 | -0.0767 | -0.0703 | -0.0751 | -0.0742 | -0.0733 | -0.0717 |
| $I_{Ca,b}$ | -0.4852 | -0.5001 | -0.5079 | -0.5366 | -0.5034 | -0.4905 | -0.4796 | -0.4760 |
| $I_{pCa}$ | 0.9589 | 0.9700 | 0.9332 | 0.7655 | 0.9378 | 0.9747 | 0.9083 | 0.8749 |
| $I_{K(ATP)}$ | 0.3115 | 0.3243 | 0.3034 | 0.2372 | 0.3164 | 0.3248 | 0.2648 | 0.2106 |

Table S6: $pH_i$ and Ion Concentrations (mM) During Reperfusion (pH Simulations)

| | Control | Dual Clamp | pH Clamp | pH 6.4 | pH 6.9 | pH 7.9 |
|---|---|---|---|---|---|---|
| Peak $[Na^+_i]$ | 19.50 | 32.17 | 25.61 | 23.49 | 20.91 | 18.69 |
| Mean $[Na^+_i]$ | 17.48 | 23.89 | 19.59 | 19.17 | 18.17 | 17.06 |
| Peak $[Ca^{2+}_i]$ | 0.001702 | 0.001218 | 0.001715 | 0.001974 | 0.001842 | 0.001603 |
| Mean $[Ca^{2+}_i]$ | 0.000738 | 0.000758 | 0.001044 | 0.000886 | 0.000796 | 0.000704 |
| Mean $[Ca_{SR}]$ | 3.081 | 0.701 | 2.827 | 3.022 | 3.059 | 3.083 |
| Mean CaiT Ampl | 0.001000 | 0.000282 | 0.000635 | 0.000938 | 0.000998 | 0.000981 |
| Mean $[K^+_i]$ | 108.75 | 99.33 | 105.76 | 106.79 | 107.78 | 109.49 |
| End $pH_i$ | 7.09 | 6.09 | 6.13 | 6.69 | 6.93 | 7.17 |
| Mean $pH_i$ | 6.93 | 6.23 | 6.25 | 6.64 | 6.81 | 7.01 |
| Mean [ADP] | 0.0197 | 0.1448 | 0.0042 | 0.0097 | 0.0146 | 0.0237 |

Table S7: $pH_i$ and Ion Concentrations (mM) During Reperfusion (Phosphometabolite Simulations)

| | Control | Dual Clamp | ATP Clamp | ATP 25 | ATP 50 | ATP 75 | ATP 150 | ATP 200 |
|---|---|---|---|---|---|---|---|---|
| Peak $[Na^+_i]$ | 19.50 | 32.17 | 27.79 | 25.93 | 25.61 | 22.91 | 14.11 | 12.63 |
| Mean $[Na^+_i]$ | 17.48 | 23.89 | 23.07 | 21.60 | 21.70 | 19.91 | 13.41 | 11.07 |
| Peak $[Ca^{2+}_i]$ | 0.001702 | 0.001218 | 0.001164 | 0.001085 | 0.001800 | 0.001911 | 0.001424 | 0.001592 |
| Mean $[Ca^{2+}_i]$ | 0.000738 | 0.000758 | 0.000685 | 0.000459 | 0.000700 | 0.000769 | 0.000654 | 0.000614 |
| Mean $[Ca_{SR}]$ | 3.081 | 0.701 | 0.786 | 1.805 | 2.556 | 2.925 | 3.501 | 4.103 |
| Mean CaiT Ampl | 0.001000 | 0.000282 | 0.000335 | 0.000372 | 0.000841 | 0.001027 | 0.000935 | 0.001155 |
| Mean $[K^+_i]$ | 108.75 | 99.33 | 100.81 | 100.64 | 102.53 | 105.48 | 114.13 | 117.17 |
| End $pH_i$ | 7.09 | 6.09 | 7.07 | 7.07 | 7.08 | 7.08 | 7.10 | 7.10 |
| Mean $pH_i$ | 6.93 | 6.23 | 6.92 | 6.92 | 6.93 | 6.93 | 6.94 | 6.94 |
| Mean [ADP] | 0.0197 | 0.1448 | 0.7173 | 0.0314 | 0.0274 | 0.0235 | 0.0119 | 0.0039 |

## Phosphometabolite Equations

During pre-ischemia, all metabolites are held at their initial values. During ischemia:

$$[\mathrm{ATP}] = 0.0006549\mathrm{t}^3 - 0.02305\mathrm{t}^2 - 0.104837\mathrm{t} + 7.216 \tag{S.1}$$

$$[\mathrm{PCr}] = -0.01259 + 12.339\mathrm{e}^{-0.92559\mathrm{t}} + 0.96819\mathrm{e}^{-0.078496\mathrm{t}} \tag{S.2}$$

During reperfusion:

$$[\mathrm{ATP}]_\mathrm{t} = [\mathrm{ATP}]_{\mathrm{t}\text{-}\Delta\mathrm{t}} - \frac{[\mathrm{ATP}]_{\mathrm{t}\text{-}\Delta\mathrm{t}} - 0.4[\mathrm{ATP}_{\mathrm{preischemic}}]}{5\mathrm{x}10^3\mathrm{ms}}\Delta\mathrm{t} \tag{S.3}$$

$$[\mathrm{PCr}]_\mathrm{t} = [\mathrm{PCr}]_{\mathrm{t}\text{-}\Delta\mathrm{t}} - \frac{[\mathrm{PCr}]_{\mathrm{t}\text{-}\Delta\mathrm{t}} - 0.75[\mathrm{ion}_{\mathrm{preischemic}}]}{5\mathrm{x}10^3\mathrm{ms}}\Delta\mathrm{t} \tag{S.4}$$

During ischemia and reperfusion:

$$[\mathrm{Cr}] = 22.2 - [\mathrm{PCr}] \tag{S.5}$$

$$[\mathrm{ADP}] = \frac{[\mathrm{ATP}] * [\mathrm{Cr}]}{[\mathrm{PCr}] * [\mathrm{H}_\mathrm{i}^+] * 1.66\mathrm{x}10^6} \tag{S.6}$$

$$[\mathrm{AMP}] = \frac{[\mathrm{ADP}] * [\mathrm{ADP}] * 1.05}{[\mathrm{ATP}]} \tag{S.7}$$

$$[\mathrm{Pi}_{\mathrm{free}}] = [\mathrm{Pi}_{\mathrm{total}} - (3 * [\mathrm{ATP}] + 2 * [\mathrm{ATP}] + [\mathrm{AMP}] + [\mathrm{PCr}]) \tag{S.8}$$

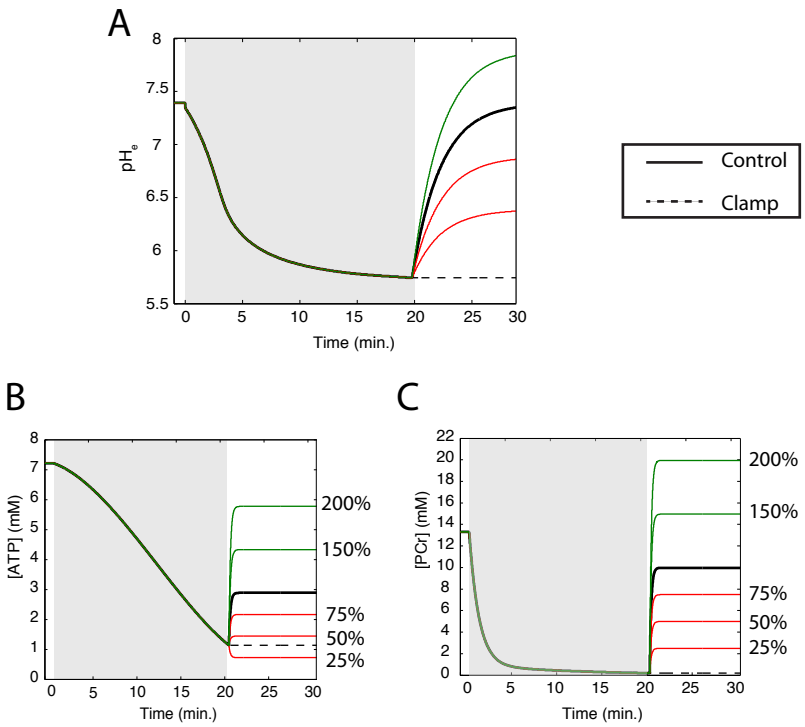


Figure S1: **Summary of simulations.** In each simulation, the end-reperfusion targets of extracellular pH ($pH_e$) (A) and/or ATP (B) and PCr (C) were controlled. Gray regions denote ischemic phase of simulations. See text for additional information.

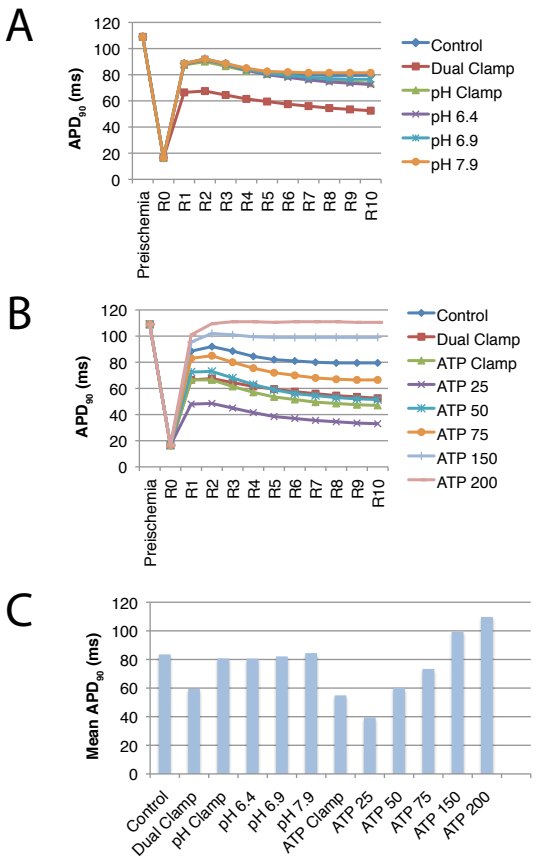


Figure S2: **Action potential duration (90) during simulated reperfusion.** The evolution of action potential duration (90) ($APD_{90}$) throughout reperfusion is shown for the series of simulations examining the effects of varying $pH_e$ (A) and phosphometabolite concentrations (B). Values recorded at the end of preischemia, at the beginning of reperfusion (R0), and once per minute of reperfusion (R1-R10) are shown. The mean $APD_{90}$ during reperfusion for each simulation is shown in (C).

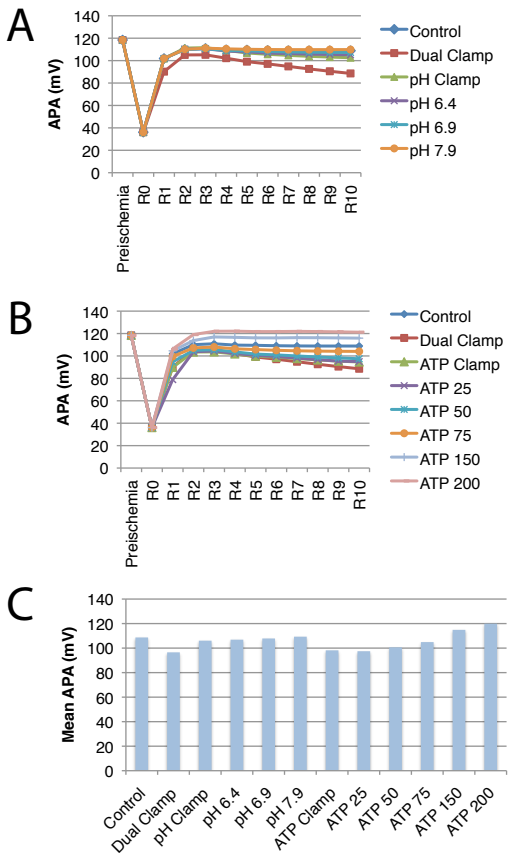


Figure S3: **Action potential amplitude during simulated reperfusion.** The evolution of action potential amplitude (APA) throughout reperfusion is shown for the series of simulations examining the effects of varying $pH_e$ (A) and phosphometabolite concentrations (B). Values recorded at the end of preischemia, at the beginning of reperfusion (R0), and once per minute of reperfusion (R1-R10) are shown. The mean APA during reperfusion for each simulation is shown in (C).

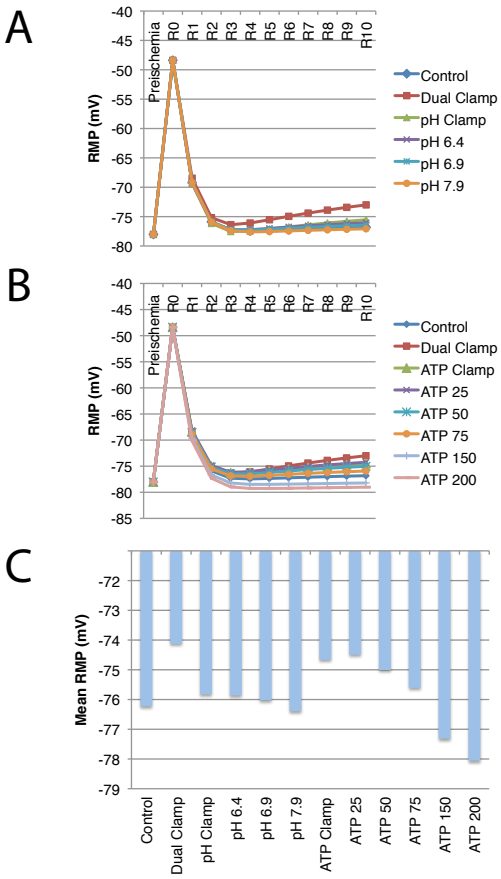


Figure S4: **Resting membrane potential during simulated reperfusion.** The evolution of resting membrane potential (RMP) throughout reperfusion is shown for the series of simulations examining the effects of varying $pH_e$ (A) and phosphometabolite concentrations (B). Values recorded at the end of preischemia, at the beginning of reperfusion (R0), and once per minute of reperfusion (R1-R10) are shown. The mean RMP during reperfusion for each simulation is shown in (C).

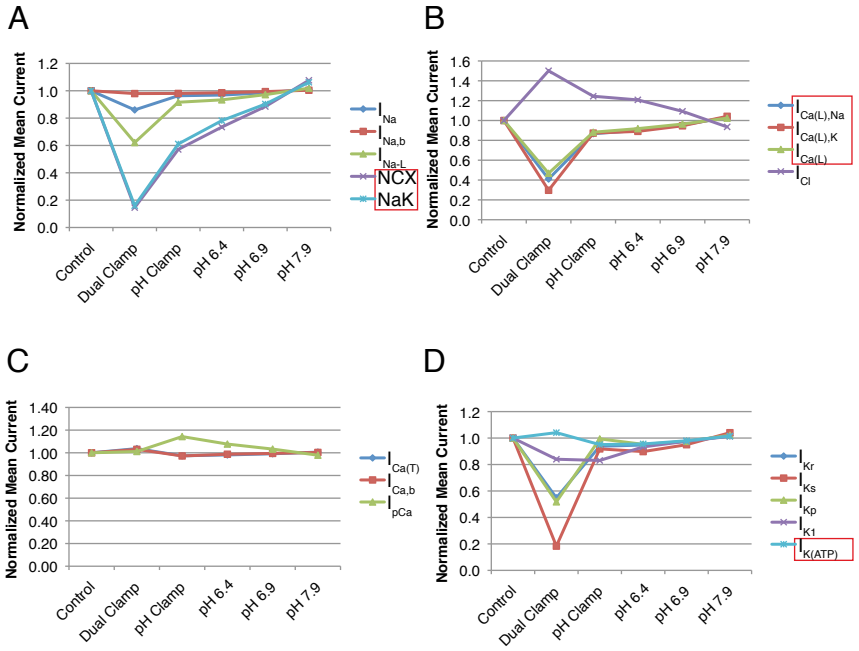


Figure S5: **Normalized mean currents throughout 10 minutes of reperfusion with variable $pH_e$ recovery.** For each of 17 transmembrane currents, mean current in each simulation is normalized to the corresponding control. Currents that are directly modulated by pH and/or phosphometabolite concentrations are shown in red boxes.

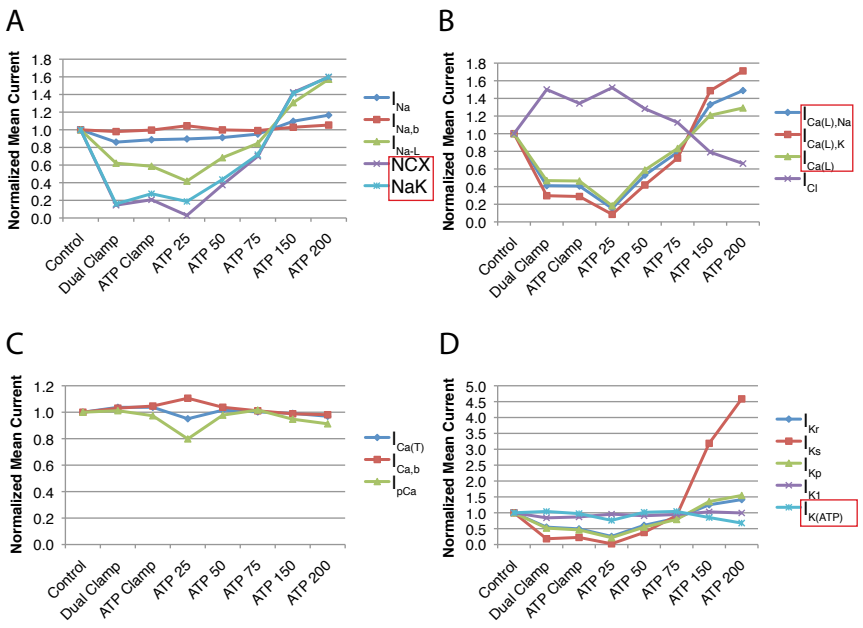


Figure S6: **Normalized mean currents throughout 10 minutes of reperfusion with variable phosphometabolite end-reperfusion target concentrations.** For each of 17 transmembrane currents, mean current in each simulation is normalized to the corresponding control. Currents that are directly modulated by pH and/or phosphometabolite concentrations are shown in red boxes.

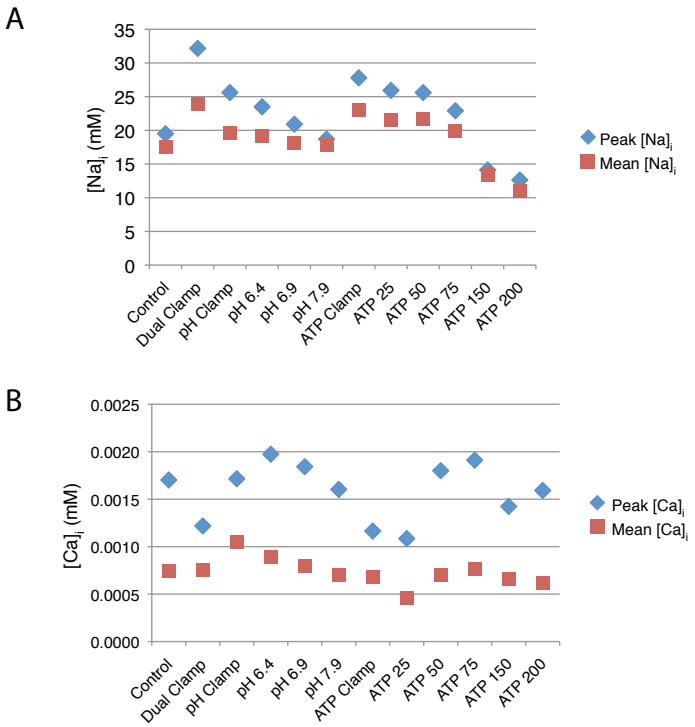


Figure S7: **Sodium and Calcium Concentrations During Simulated Reperfusion.** Peak (blue diamonds) and mean (red squares) intracellular sodium (A) and calcium (B) concentrations.

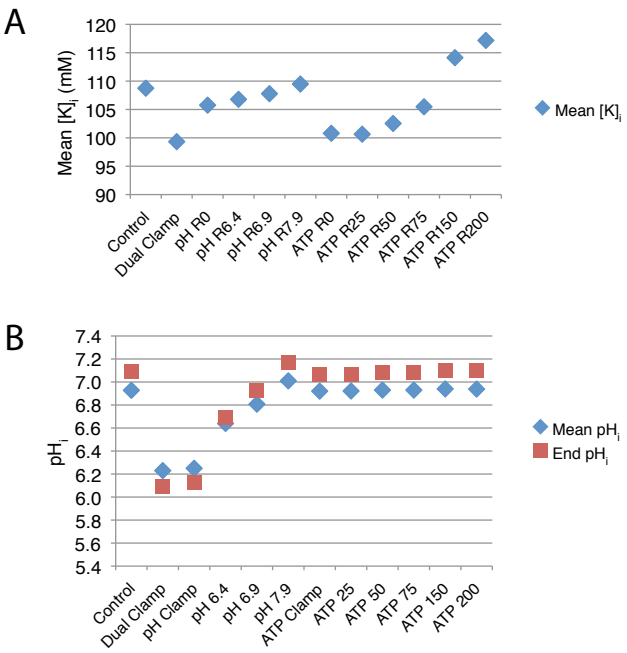


Figure S8: **Intracellular pH and Potassium Concentrations During Simulated Reperfusion.** (A) Mean intracellular potassium concentrations. (B) Mean intracellular pH (blue diamonds) and pH after 10 minutes of reperfusion (red squares).