# NHE and NBC blockade during ischemia in rat hearts: a $^{23}$Na and $^{31}$P MRS study

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**Introduction -** Blocking the $Na^+/H^+$ exchanger (NHE) during ischemia has been shown to reduce $Na^+$ overload during ischemia and to improve post-ischemic contractile recovery. The effect of ischemic blockade of the $Na^+/HCO_3^-$ co-transporter (NBC) as well as blockade of both, the NHE and the NBC, on ischemic $Na^+_i$ overload is unknown.

**Methods -** Isolated rat hearts were perfused according to Langendorff at a constant pressure of 73.5 mmHg at 37°C with a modified Krebs-Henseleit buffer (pH 7.4). Contractility was assessed with an intraventricular balloon. $[Na^+]_i$, $pH_i$ and HEP's were measured using $^{23}$Na and $^{31}$P NMR spectroscopy, respectively. $^{23}$Na and $^{31}$P were measured simultaneously at frequencies of 105.9 and 162.0 MHz, respectively, on a Bruker Avance DRX400 spectrometer equipped with a dual tuned probe and two digital receivers. To discriminate between intra- and extracellular $Na^+$, the shift reagent $TmDOTP^{5-}$ (3.5 mM) was added to the perfusate, necessitating a lower free $Ca^{2+}$ concentration (0.85 mM). Hearts were subjected to 30 minutes of global ischemia and 30 minutes of reperfusion. Cariporide (3 μM) or bicarbonate free HEPES buffer was used to block the NHE, the NBC or both, respectively.

**Results -** Reduction of ischemic $Na^+_i$ overload (fig. 1) by NHE blockade was 43 %, by NBC blockade 21 % and by combined NHE and NBC blockade 52 %. End-ischemic $pH_i$ (fig. 2) was 6.09 ± 0.06 in bicarbonate perfused, untreated hearts, 5.85 ± 0.02 when the NHE was blocked, 5.81 ± 0.05 when the NBC was blocked and 5.70 ± 0.01 when both the NHE and the NBC were blocked. NHE blockade improved recovery of rate pressure product (heart rate x developed pressure) during reperfusion, NBC blockade and combined blockade did not. Combined blockade of the NHE and the NBC conserved $H^+_i$ load during reperfusion and lead to massive $Na^+$ influx when blockades were raised after 10 minutes of reperfusion. Omission of bicarbonate under conditions of NHE blockade severely and irrevesibly impaired coronary flow, preventing contractile recovery.

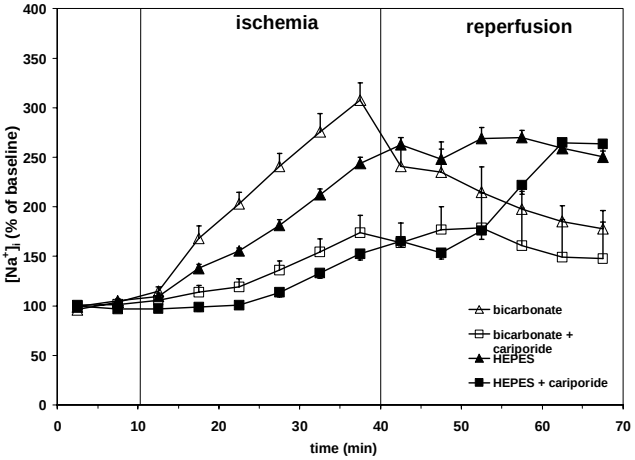


**Figure 1:** $[Na^+]_i$ during ischemia and reperfusion

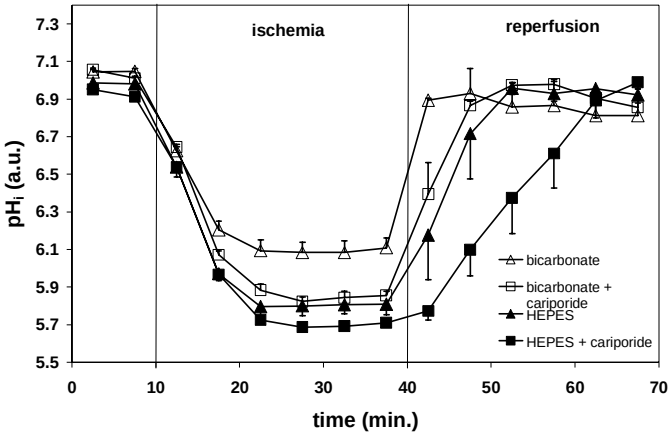


**Figure 2:** $pH_i$ during ischemia and reperfusion

**Conclusion -** Without blockade, both the NHE and the NBC mediate acid equivalent efflux in exchange for $Na^+$ influx during ischemia, the NHE much more than the NBC. Blockade of either one does not affect the other one. Combined blockade of the NHE and the NBC is potentially dangerous due to coronary flow reduction.