

**ENDOTHELIAL CELLS AND NITRIC OXIDE: MALES LIVE FREE AND FEMALES DIE HARD**

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**Objective:** We previously reported that male rodents demonstrate enhanced re-endothelialization following arterial injury; however, after nitric oxide (NO) therapy, females demonstrate greater improvement in re-endothelialization. The purpose of this study is to define the effect of NO on endothelial cell (EC) proliferation and migration between sexes in vitro. We hypothesized that male EC will proliferate and migrate faster, but NO will have a greater stimulatory effect on female EC.

**Methods:** EC harvested from male and female rodents were treated with the NO donor DETA/NO. Proliferation was evaluated by tritiated-thymidine incorporation. Migration was measured using scrape assays. Cell death and cell cycle analysis were performed using flow cytometry.

**Results:** Male EC proliferated faster than females ( $p < 0.05$ ). DETA/NO stimulated EC proliferation at low concentrations and inhibited proliferation at high concentrations in both sexes ( $p < 0.05$ ). With respect to the cell cycle, a similar percent of cells were in G0/G1 for both sexes. However, a greater percent of females were in G2/M, while a greater percent of males were in S ( $p < 0.05$ ). Following NO, both sexes exhibited an increase in G0/G1, decrease in S, and no change in G2/M. Male and female EC migrated at similar rates ( $p = \text{NS}$ ). Low NO concentrations stimulated yet high NO concentrations inhibited migration in both sexes ( $p < 0.05$ ). Female EC exhibited greater cell death than males under basal conditions ( $p < 0.05$ ). A dose-dependent increase in cell death was observed with high NO concentrations in both sexes ( $p < 0.05$ ), but females still exhibited greater cell death than males ( $p < 0.05$ ).

**Conclusions:** Enhanced re-endothelialization following injury in males is attributable to increased EC proliferation in males and increased EC death in females. Improvement in endothelialization following NO treatment in females is not due to enhanced proliferation and migration, but may be attributable to cell cycle differences or bimodal effects of NO at different concentrations.