Early changes in biomarkers of nitrosative stress are associated with doxorubicin and trastuzumab-induced cardiac dysfunction in breast cancer patients

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Background: Oxidative and nitrosative stress are believed to be central to doxorubicin and trastuzumab (Herceptin ®) induced cardiac dysfunction. However, the relations between circulating metabolites of the arginine-nitric oxide (NO) pathway and cancer therapeutics-related cardiac dysfunction (CTRCD) have not been examined.

Methods and Results: In a prospective cohort study of 170 breast cancer participants treated with doxorubicin with or without trastuzumab, we measured six metabolites of the arginine-NO pathway. Arginine, citrulline, ornithine, asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), and N-monomethylarginine (MMA) were quantified at baseline, one month, and two months following doxorubicin initiation. CTRCD was defined as a reduction in left ventricular ejection fraction by ≥10% from baseline to <50%. Determinants of baseline biomarker levels were identified through multivariable linear regression analyses, and changes over time through Wilcoxon signed ranked tests. Individual Cox proportional hazard models defined the associations between baseline biomarker levels, one-, or two-month biomarker changes and risk of first CTRCD event. Age, hypertension, body mass index, and African American race were independently associated with baseline citrulline, ADMA, and SDMA levels. Decreases in arginine and citrulline, and increases in ADMA were observed at one and two months ($p<0.05$). Overall, 32 participants experienced CTRCD. Increases in arginine and MMA at two months were each associated with a two to three-fold increased risk of developing CTRCD ($p<0.05$).

Conclusions: Early increases in arginine-NO metabolites are associated with CTRCD in breast cancer patients undergoing doxorubicin with or without trastuzumab therapy. Our findings highlight the potential mechanistic and translational relevance of this pathway to CTRCD.