

ORAL PRESENTATION

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# Chronic beta-adrenergic blockade prevents volume overload-induced re-localization and oxidation of soluble guanylyl cyclase

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## Background

While  $\beta$ -adrenergic blockade is a cornerstone of heart failure therapy, its therapeutic role in chronic mitral regurgitation remains questionable. Animal studies and a small clinical trial have demonstrated cardiac functional improvement with  $\beta_1$ -adrenoceptor blocker metoprolol in chronic mitral regurgitation [1,2]. How  $\beta_1$ AR-blockade halts functional decline of the volume-overloaded, eccentric hypertrophied heart is not well understood; anti-oxidant effects of  $\beta$ -blockade ( $\beta$ B) may play a role. We recently demonstrated that volume-overload cardiac stress induces re-localization and microdomain-specific oxidation of the nitric oxide receptor soluble guanylyl cyclase (sGC) in the failing heart [3,4]. Given that nitric oxide-cyclic guanosine monophosphate (NO-cGMP) modulates cardiac contractility and protects against cardiac hypertrophy, we hypothesized that  $\beta_1$ AR-blockade prevents oxidation of sGC and promotes myocardial NO-cGMP signaling in a microdomain-specific fashion.

## Materials and methods

Volume-overload (VO) was established by chordal rupture-induced mitral regurgitation (MR) in mongrel dogs. Some dogs were treated with metoprolol succinate (100mg orally once daily; MR+  $\beta$ B). Expression, localization, cyclase activity, and redox state of myocardial sGC were assessed in Control, MR, and MR+ $\beta$ B dogs.

## Results

sGC $\alpha_1$  and  $-\beta_1$  subunits were detected within and outside of caveolae-enriched lipid rafts (Cav3<sup>+</sup>LR). In MR,

total sGC $\alpha_1$  expression fell to nearly 50% of Control and re-localized away from Cav3<sup>+</sup>LR to non-lipid raft microdomains (NLR). While overall sGC $\beta_1$  expression was also less in MR+ $\beta$ B, caveolae-localization of sGC $\beta_1$  was preserved. Overall NO-responsiveness of sGC remained intact in MR hearts, irrespective of  $\beta$ B therapy. However, a potentiated response to heme/NO-independent sGC activator BAY 60-2770 suggested that a subset of sGC was heme-oxidized in MR but not in Control or MR+ $\beta$ B. Moreover, differential responses to BAY 60-2770 and NO were noted in Cav3<sup>+</sup>LR and NLR microdomains. In Control hearts, responses to BAY 60-2770 and NO were similar within respective microdomains, suggesting a predominantly reduced form of sGC in both Cav3<sup>+</sup>LR and NLR of Controls. In contrast, BAY 60-2770 response of NLR-localized sGC was potentiated in MR but not in MR+ $\beta$ B hearts, suggesting that  $\beta$ B therapy prevented oxidation of NLR-localized sGC. Moreover, BAY 60-2770 responses of Cav3<sup>+</sup>LR-localized sGC were not potentiated in any hearts, suggesting an anti-oxidation protection associated with caveolae-localization. These changes in caveolae-localization and redox state of sGC were also reflected by microdomain distribution of VASP phosphorylation.

## Conclusion

$\beta_1$ AR blocker mediated cardioprotection in the volume-overloaded heart is associated with enhanced microdomain specific myocardial NO-cGMP signaling, both within and outside of caveolae. Such prevention of volume overload-induced spatial and redox dysregulation of myocardial sGC suggests novel strategies to enhancing cardioprotective NO-cGMP signaling.

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