β_1-Blockers enhance inotropy of endogenous catecholamines in chronic heart failure

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Abstract

Background and Purpose: Although β_1-blockers impressively reduce mortality in chronic heart failure (CHF), there are concerns about negative inotropic effects and worsening of hemodynamics in acute decompensated heart failure. May receptor theory dispel these concerns and confirm clinical practice to use β_1-blockers? Experimental Approach: In CHF, concentrations of catecholamines at the β_1-adrenoceptors usually exceed their dissociation constants (K_Ds). The homodimeric β_1-adrenoceptors have a receptor reserve and display negative cooperativity. We considered the binomial distribution of occupied receptor dimers with respect to the interaction of an exogenous β_1-blocker and elevated endogenous agonist concentrations $> [K_D\text{s}]$, corresponding to an elevated sympathetic tone. Key Results: Modeling based on binomial distribution suggests that in the presence of a low concentration of the antagonist, the activation of the dimer receptors is higher than that in its absence. This leads to increased positive inotropic effects of endogenous catecholamines due to a β_1-blocker. Conclusion and Implications: To understand the positive inotropic sequels of β_1-blockers in CHF is clinically relevant. This article may help to eliminate the scepticism of clinicians about the use of β_1-blockers because of their supposed negative inotropic effect, since on the contrary a positive inotropic effect can be expected for receptor-theoretical reasons.

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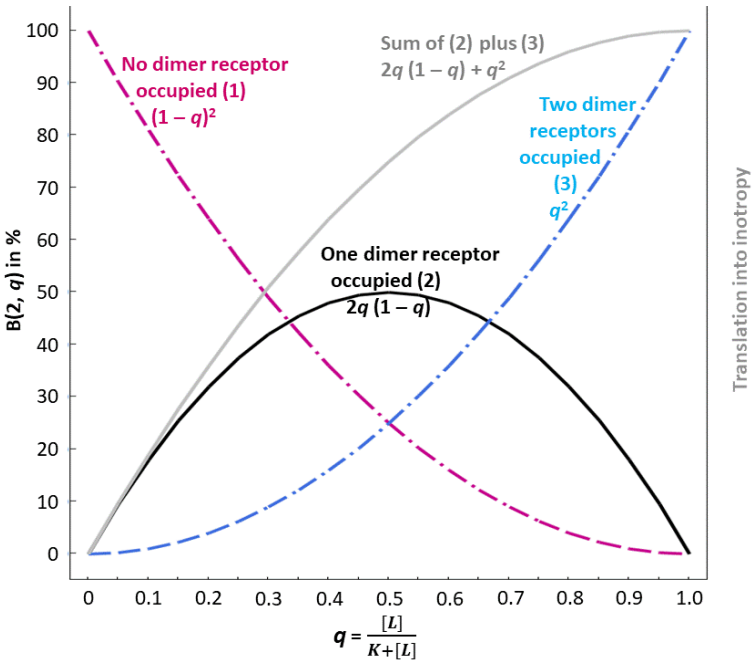

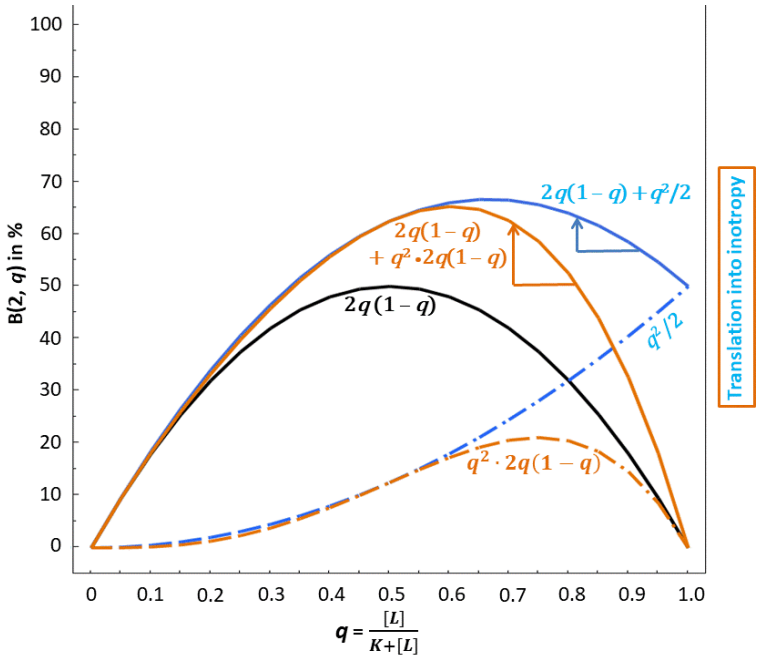

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20-02-24 Table 1.docx available at https://authorea.com/users/300630/articles/430366-%CE%B21-blockers-enhance-inotropy-of-endogenous-catecholamines-in-chronic-heart-failure