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Tolerability of β-Blocker Initiation and Titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)

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Background*:* β-Blockade improves survival when administered over a long period of time to patients with heart failure. However, the time course of any possible deterioration during the titration phase bas not been reported.

Methods and Results: We looked at evidence of clinical deterioration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) by analyzing events and symptoms during the first 90 days. During titration, the Kaplan-Meier curves for the combined end point of all-cause mortality/all-cause hospitalization were similar in all patients randomized, with no significant difference in favor of placebo at any visit or in any of the analyzed subgroups (New York Heart Association class II, III/IV, III/IV, or III/IV with ejection fraction <0.25, heart rate ≤76 bpm, and systolic blood pressure ≤120 mm Hg). The curves started to diverge in favor of β-blockade after 60 days. Low heart rate was the main factor that limited titration. In New York Heart Association class III/IV, 5.9% of the patients receiving placebo discontinued study medicine during the first 90 days compared with 8.1% of those receiving metoprolol CR/XL (P=0.037 unadjusted, P=NS adjusted); corresponding figures in those with New York Heart Association class III/IV and ejection fraction <0.25 were 7.1% and 8.0% (P=NS). From day 90 until the end of the study, more patients in the placebo group discontinued study medicine in all subgroups. There was no change in diuretic or ACE inhibitor dosing with β-blocker titration. Most patients reported no change in symptoms of breathlessness or fatigue during the titration phase.

Conclusions: When carefully titrated, metoprolol CR/XL can be given safely to the overwheiming majority of patients with stable mild to moderate heart failure, with minimal side effects or deterioration.

Key-Words: heart failure, receptors, adrenergic, beta, drugs.

Smoking a Single Cigarette Rapidly Reduces Combined Concentrations of Nitrate and Nitrite and Concentrations of Antioxidants in Plasma

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Background: Cigarette smoking is a well-known risk factor for the development of cardiovascular disease, yet the mechanism of action involved is not completed understood. Because cigarette smoke contains superoxide and other reactive oxygen species, it has been hypothesized that some of the adverse effects of smoking may result from oxidative damage to endothelial cells, which results in nitric oxide (NO) shortage. However, little information is available regarding the acute effects of smoking on plasma concentrations of NO and antioxidants. We measured the changes in the combined plasma concentrations of nitrate and nitrite as an index of NO concentration, as well as changes in concentrations of major serum antioxidants (ascorbic acid, cysteine, methionine, and uric acid) in smokers after smoking a single cigarette.

Methods and Results: A randomized crossover study of the effects of smoking a single cigarette was performed in 20 smokers. Smoking a sham cigarette induced no significant changes in all assayed parameters. However, smoking a single cigarette significantly decreased nitrate and nitrite plasma concentrations by 3.5±1.2 and 3.4±1.1 μmol/L, compared with plasma concentrations at pre-smoking and sham smoking, respectively. The concentrations of ascorbic acid and other antioxidants were also significantly lower after smoking a single cigarette. These parameters returned to pre-experimental levels 60 minutes after smoking cessation.

Conclusion: The present findings indicate that smoking a single cigarette temporarily decreases nitrate, nitrite, and serum antioxidant concentrations in the plasma. These transient changes may partially contribute to coronary vasoconstriction, which is routinely observed after smoking.

Key-Words: smoking, nitric oxide, free radicals, antioxidant, endothelium.