

GW23-e1501

**ACTIVATION OF SECRETORY ACID SPHINGOMYELINASE AND ELEVATION OF CERAMIDE IN PLASMA IS ASSOCIATED WITH CHRONIC HEART FAILURE**

doi:10.1136/heartjnl-2012-302920b.21

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**Objectives** The sphingolipid pathway generates bioactive molecules that are crucial to the regulation of a variety of physiological and pathological processes. Recent studies indicate that plasma secretory acid sphingomyelinase (S-SMase) activity correlates with inflammatory cytokines and the severity of chronic heart failure (CHF). However, the roles of sphingomyelin (SPM) and ceramide (Cer) remain unclear in the heart failure process.

**Methods** To investigate sphingolipids and sphingolipid signalling in patients with left ventricular dysfunction, we measured plasma S-SMase activity, SPM, Cer, N-terminal pro-B-type natriuretic peptide (BNP), high sensitivity C-reactive protein (hsCRP), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), soluble Fas, soluble Fas ligand and hemodynamic parameters in 423 patients with CHF and in 104 healthy subjects.

**Results** Plasma Cer levels increased stepwise with New York Heart Association (NYHA) functional classification (I,  $5.32 \pm 1.98$ ; II,  $5.81$

$\pm 1.63$ ; III,  $6.14 \pm 2.14$ ; IV,  $6.66 \pm 2.61$ ,  $p < 0.001$ ). Cer levels further correlated with S-SMase activity ( $R = 0.235$ ,  $p < 0.001$ ), BNP ( $R = 0.624$ ,  $p < 0.001$ ), hsCRP ( $R = 0.257$ ,  $p = 0.017$ ), TNF- $\alpha$  ( $R = 0.593$ ,  $p < 0.001$ ) and sFas levels ( $R = 0.645$ ,  $p < 0.001$ ), as well as with LV ( $R = 0.172$ ,  $p < 0.001$ ) and LVEF ( $R = -0.250$ ,  $p < 0.001$ ). Plasma SPM levels increased significantly in proportion to the plasma cholesterol levels.

**Conclusions** Elevated plasma Cer levels correlated with the severity of CHE. The accumulation of ceramide was associated with the hemodynamic status, BNP levels, circulating pro-inflammatory cytokines TNF- $\alpha$  and hsCRP, as well as with the soluble apoptosis receptor Fas, suggesting that the sphingolipid signalling pathway is involved in the persistent immune activation and apoptosis associated with CHE, and may contribute to the pathophysiology.