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S100A8/A9 and sRAGE peripheral blood levels in patients with heart failure and an implanted cardioverter/defibrillator: relation with sustained, fast ventricular arrhythmias

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Background: Prediction of sudden cardiac death in heart failure (HF) remains suboptimal. Blood levels of the S100A8/A9 heterodimer protein complex and the soluble receptor of advanced glucation end product (sRAGE) are promising biomarkers in HF, reflecting inflammatory/fibrotic and apoptotic pathways, possibly involved in ventricular arrhythmogenesis. The relation of S100A8/A9 and sRAGE with ventricular arrhythmias and sudden cardiac death risk has not been previously assessed.

Purpose: Purpose of the study was to investigate whether S100A8/A9 and sRAGE serum blood levels of patients (pts) with systolic heart failure are related to the occurrence of life-threatening ventricular tachyarrhythmias.

Patients and methods: We studied 60 pts with clinically stable heart failure due to coronary artery disease (n=37) and dilated cardiomyopathy (n=23), all with a chronically implanted ICD for primary (n=43) or secondary (n=16) sudden death prevention, all in sinus rhythm. Their mean age (±1 SE) was 62±2 years, NYHA class I-II, mean LVEF 28±1%, Nt-pro-BNP 893±85 pg/dl. Blood was drawn at study initiation for S100A8/A9 and sRAGE assessment (ELISA, R&D Systems). They all were systematically followed-up for 4 years regarding the occurrence of fast ventricular tachyarrhythmias (>180 bpm) necessitating antiarrhythmic intervention through the ICD.

Results: S100A8/A9 and sRAGE levels were 16±1.6 ng/ml and 1076±99 pg/ml respectively. S100A8/A9 levels were lower than in normal controls, while sRAGE levels were within normal limits. During the 4-year follow-up period, 39 pts had an uneventful course (Group I), while 16 pts exhibited fast ventricular tachyarrhythmic episodes necessitating ICD activation (anti-tachycardia pacing or shock, Group II). Three pts died of pump failure and 2 pts of non-cardiac causes. No differences were observed between Group I and Group II pts regarding mean NYHA class, Nt-pro-BNP levels. Group II patients had significantly lower LVEF as well as S100A8/A9 serum levels relative to pts without ventricular arrhythmias (LVEF: 30±1.2 vs, 25±1.3%, $p<0.05$, S1OOA8/A9: 18.9±2.2 vs 11.8±1.5 ng/ml, $p<0.05$), while no difference was observed between Groups regarding sRAGE levels 1097±101 1105±239 pg/ml, p:NS). S100A8/A9 levels were not related significantly to LVEF (r:-21, p=0.13).

Conclusion: S100A8/A9 protein levels are reduced in pts with stable HF and an implanted ICD. They are even lower among pts with rapid ventricular tachyarrhythmias occurring during follow-up. This finding implies that S100A8/A9 may constitute a biomarker of increased sudden cardiac death risk in HF, in addition to reduced LVEF.