PRO-APOPTOTIC AND PRO-INFLAMMATORY EFFECTS OF PLASMA OF PATIENTS WITH **CARDIORENAL SYNDROME TYPE 1** ON HUMAN RENAL TUBULAR EPITHELIAL CELLS

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INTRODUCTION and AIMS

Cardiorenal Syndrome Type 1 (CRS1) is a specific condition which is characterized by a rapid worsening of cardiac function (most commonly acute decompensated heart failure, ADHF) leading to AKI. The pathophysiology of Cardiorenal Syndrome Type 1 (CRS1) is widely studied, although the mechanisms by which renal tubular epithelial cells (RTCs) cease to proliferate and embark upon terminal differentiation, following the initial insult of heart failure (HF), remain a key target. This study seeks to provide insight into the pathophysiological pathways in CRS1; we evaluated in vitro the effects of CRS1 plasma on RTCs.

METHODS

We enrolled 40 acute HF patients and 15 controls (CTR) without HF or acute kidney injury (AKI). 11/40 HF patients exhibited AKI at the time of admission for HF or developed AKI during hospitalization and were classified as CRS1. In vitro, cell viability, DNA fragmentation and Caspase-3 levels were investigated in RTCs incubated with HF, CRS1, and CTR plasma. We assessed inflammatory cytokines and NGAL expression at gene and protein level.

RESULTS

The mean age of 11 patients with CRS1 was 74.0±13.1 years and 45% of these patients were male.
The median baseline SCr of CRS1 patients was 0.96 mg/dl (IQR 0.88-1.02), the median eGFR was 62 ml/min/1.73m2 (IQR 55-75). The mean age of 29 patients with HF was 73.6±9.5 years and 58% of these patients were male. The median baseline SCr of HF subjects was 0.98 mg/dl (IQR 0.87-1.15), the median eGFR was 67 ml/min/1.73m2 (IQR 53-82).

In vitro, we observed a marked pro-apoptotic activity and a significantly increased in vitro level of apoptosis in RTCs incubated with plasma from CRS1 patients compared to HF and CTR ($p<0.01$) (**Figure 1a**).
The increase of apoptosis was also confirmed by Caspase-3 concentration (**Figure 1b**).
Expression of IL-6, IL18 and NGAL were analyzed by qRT-PCR using mRNAs prepared from RTCs incubated with different plasma (**Figure 2**). In the CRS1 group, mRNA expression of IL-6, IL18 and NGAL resulted significantly higher compared with those incubated with plasma from HF patients and CTR ($p<0.01$).
IL-6, IL-18, NGAL, RANTES levels were significantly higher in RTCs supernatant incubated with CRS1 plasma compared with HF patients and CTR plasma ($p<0.01$) (data not shown).
However, TNF-α and sICAM levels in supernatant were similar in CRS1 and HF groups (data not shown).

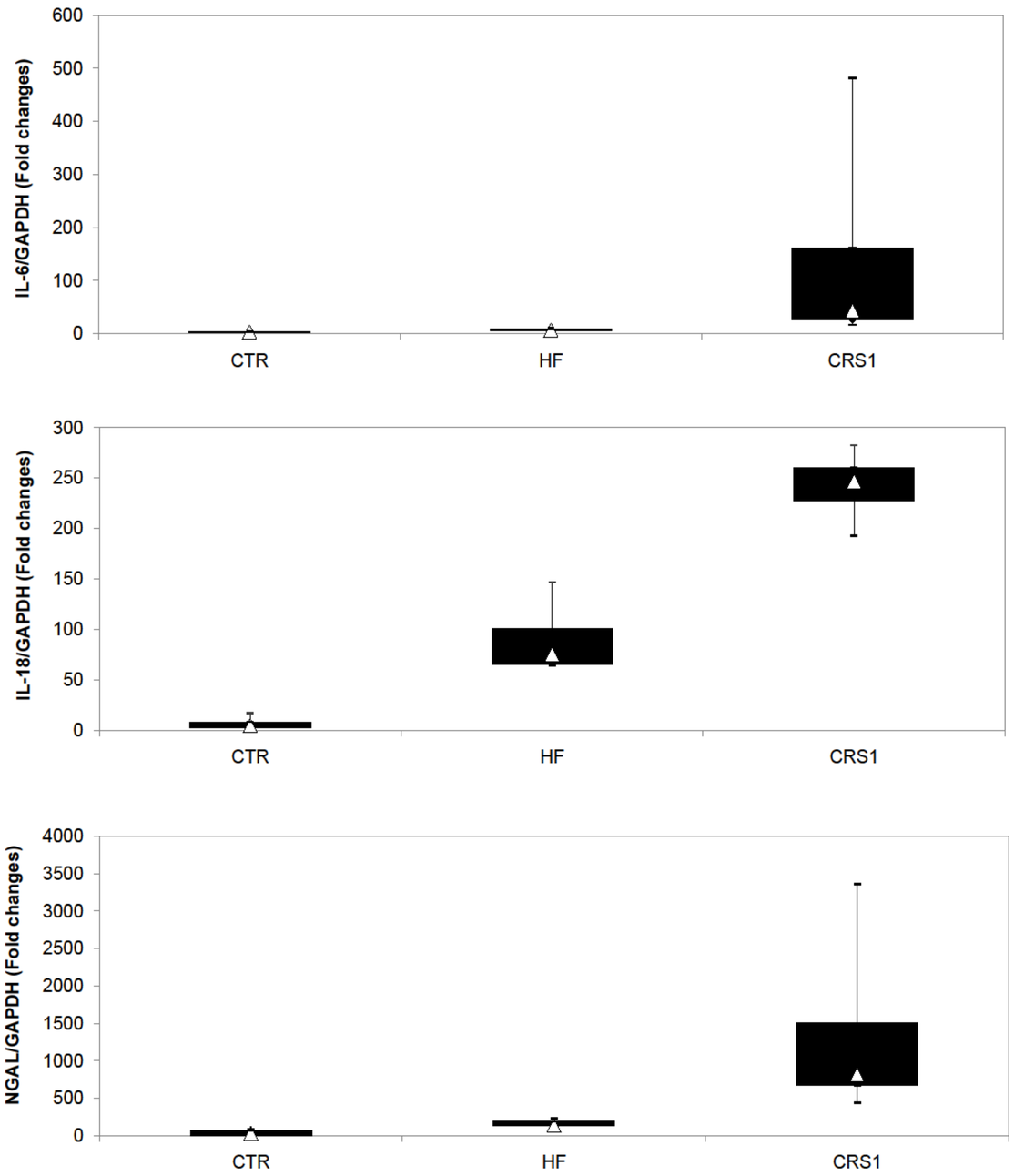

Figure 2: Cytokines mRNA Expression in RTCs treated by CRS1, HF and CTR plasma.
The mRNA expression of IL-6, IL-18 and NGAL resulted significantly higher in RTCs incubated with CRS1 plama compared with those incubated with plasma from HF patients and CTR ($p<0.01$).

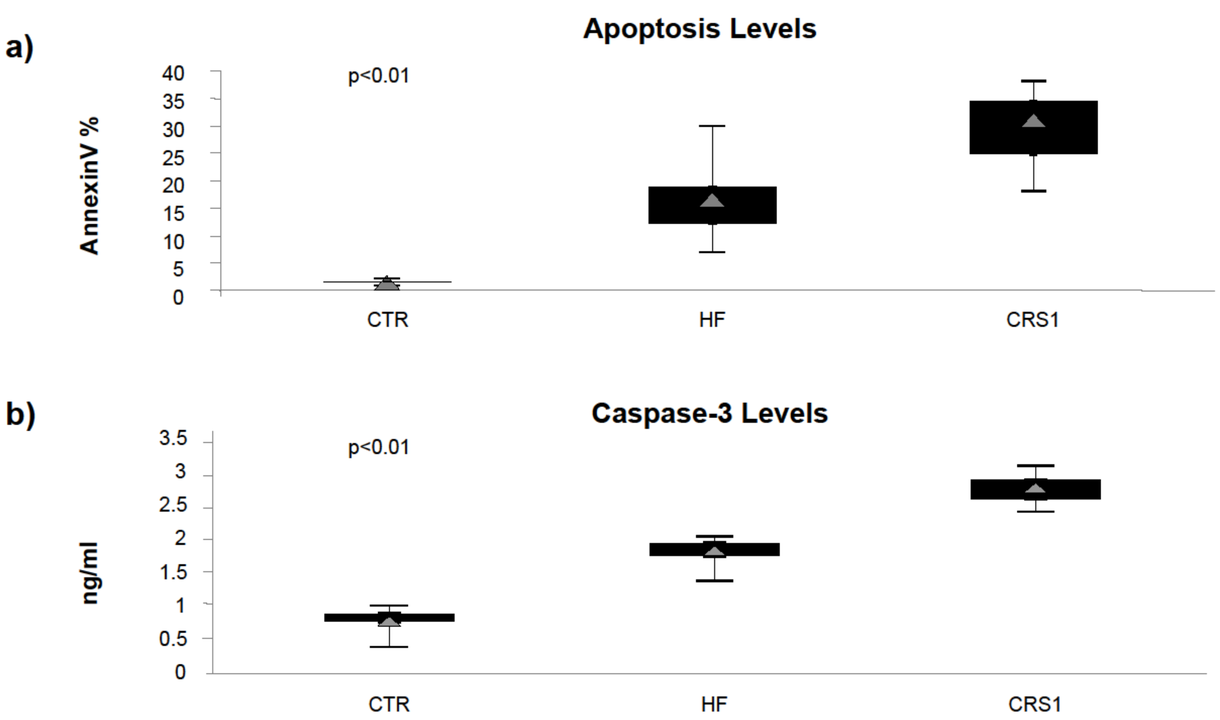

Figure 1: Quantitative Analysis of Apoptosis in RTCs
In a quantitative analysis of apoptosis RTCs incubated with plasma from CRS1 patients showed significantly higher apoptosis rates compared with those incubated with plasma from HF patients and CTR (**a**). In concordance with the apoptosis rate, RTCs incubated with plasma from CRS1 patients demonstrated a significantly higher Caspase-3 concentration (**b**).

CONCLUSIONS

In vitro exposure to plasma from CRS1 patients altered the expression profile of RTCs characterized by increases in pro-inflammatory mediators, release of tubular damage markers, and apoptosis.

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