Contact

Serpina3: A Novel Marker of Anthracycline-Induced Cardiotoxicity: From Bench to Bedside

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inspire European Training Network in Safety Pharmacology

BACKGROUND

Doxorubicin (DOX) is a first-line chemotherapeutic, yet has a high risk to induce cardiotoxicity in patients. In **early cardiotoxicity, endothelial cell dysfunction** is present, which is known to be associated with **diastolic impairment**. Diastolic dysfunction may be an early marker of DOX-induced cardiotoxicity. At present, diagnosis and monitoring of cardiotoxicity in patients is challenging. Therefore, there is an urgent need to improve this issue.

OBJECTIVES

Identification of early functional and molecular markers for cardiotoxicity induced by DOX in both mice (BENCH) and patients (BEDSIDE).

BENCH – MICE STUDY

I. Experimental design

n=8 DOX
n=8 Saline

- Functional and molecular measurements: at week (W) W0, W2 and W6
- Proteomics (liquid chromatography + mass spectrometry) at W2 and W6

II. Functional parameters

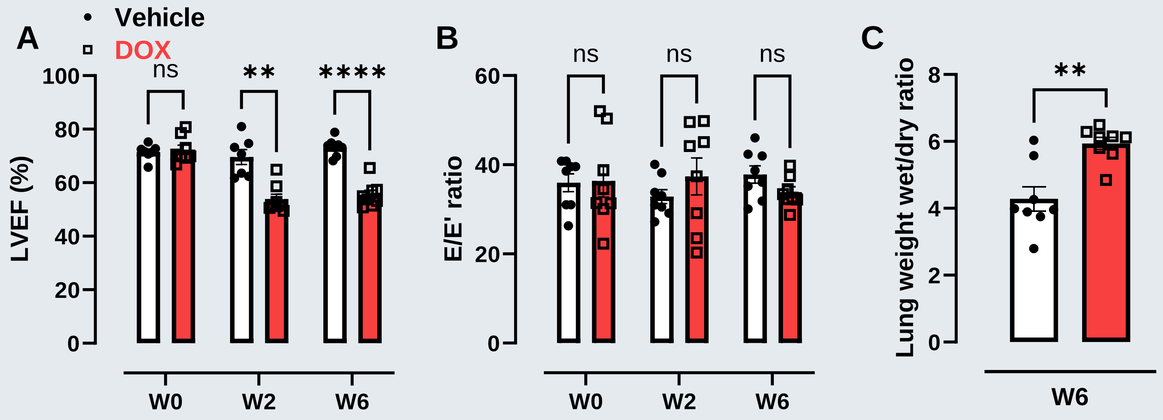

Figure 1: Echocardiography in mice and lung weight. A & B Echocardiography. C: Lung weight (wet/dry) ratio**.**

- **DOX induced consistent cardiotoxicity in all mice** starting from W2
- No alterations of diastolic function via echocardiography.
- **Mice had heart failure symptoms** at W6.

III. Proteomics

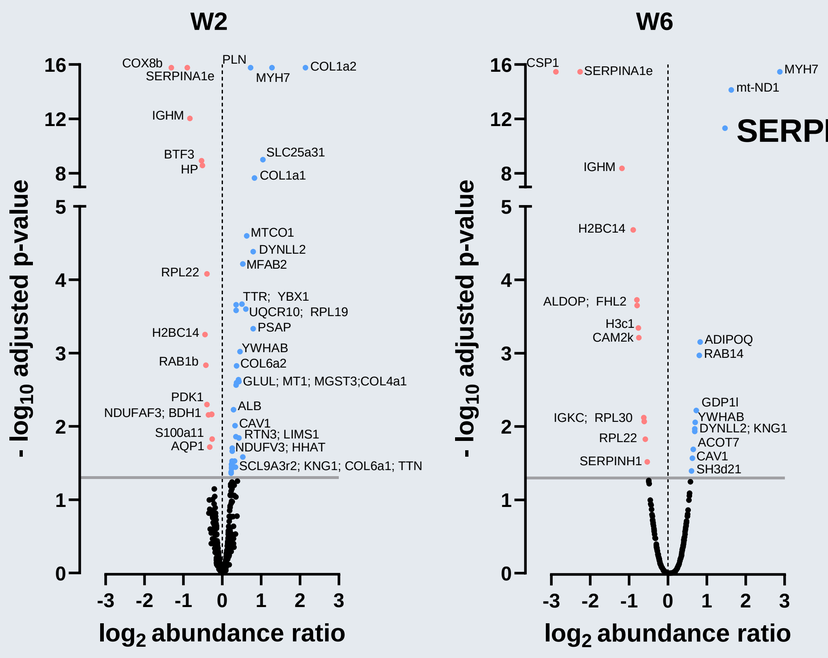

Figure 2: Myocardial proteomics analysis at week 2 and 6. The significance threshold ($p < 0.05$) is represented by a horizontal grey line. Upregulated proteins are highlighted in blue, downregulated proteins are marked in red. Protein expression is compared to vehicle group

- **SERPINA3N was increased at W6 in DOX treated group**

IV. Molecular validation

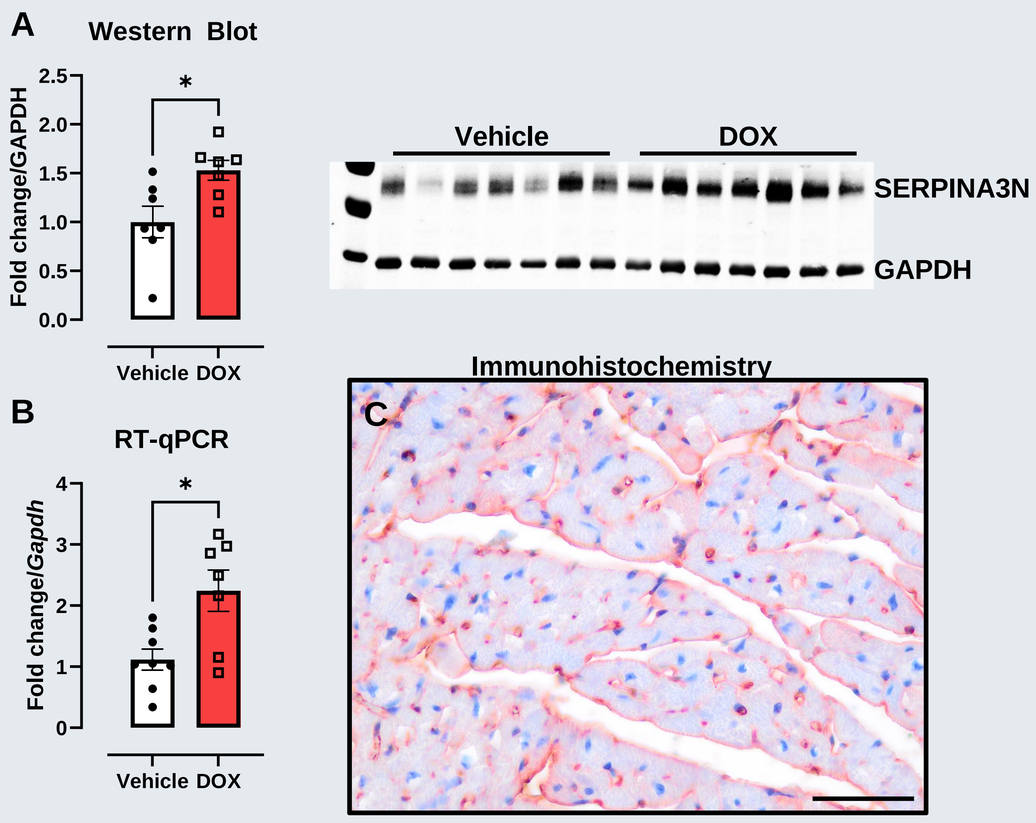

Figure 3: Validation of SERPINA3 location, content and gene expression in the myocardium at W6. A: Image and quantification of western blot. **B:** mRNA level of *Serpina3* (RT-qPCR) **C:** Representative image of mouse myocardium stained for SERPINA3N. Scale Bar: 50 µm.

- **Myocardial protein and mRNA content of SERPINA3N was increased.**
- Histological analysis showed that **SERPINA3N was mostly located in endothelial cells,** especially in the microvasculature of the heart, in cardiomyocytes and was sometimes co-localized with nuclei as well.

BEDSIDE – PATIENT STUDY

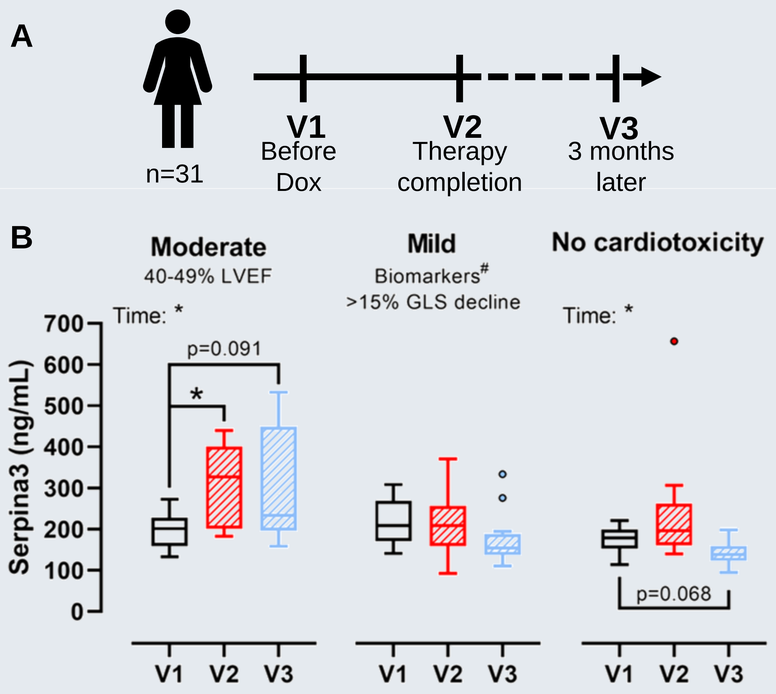

Figure 4: SERPINA3 plasma concentration at 3 different timepoints in patients undergoing DOX based chemotherapy. A: Timeline of treatment and follow-up in 31 female patients **B:** Patients were divided in 3 categories based on the severity of cardiotoxicity.

- **Plasma SERPINA3 was increased in patients** with moderate cardiotoxicity after DOX based chemotherapy.

CONCLUSION

- **DOX induces consistent cardiotoxicity in mice,** evident from lower LVEF and pulmonary edema.
- **Changes in diastolic function were not observed** (E/E`).
- Proteomics revealed **increased myocardial SERPINA3N in mice** with DOX induced cardiotoxicity
- **SERPINA3N was mainly found in the endothelium**, suggesting a potential role for the endothelium in cardiotoxicity.
- We could **confirm increased plasma SERPINA3 in patients** with moderate DOX induced cardiotoxicity.

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