

Serum neprilysin levels in patients with Marfan syndrome are associated with ascending aortic diameter

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Background

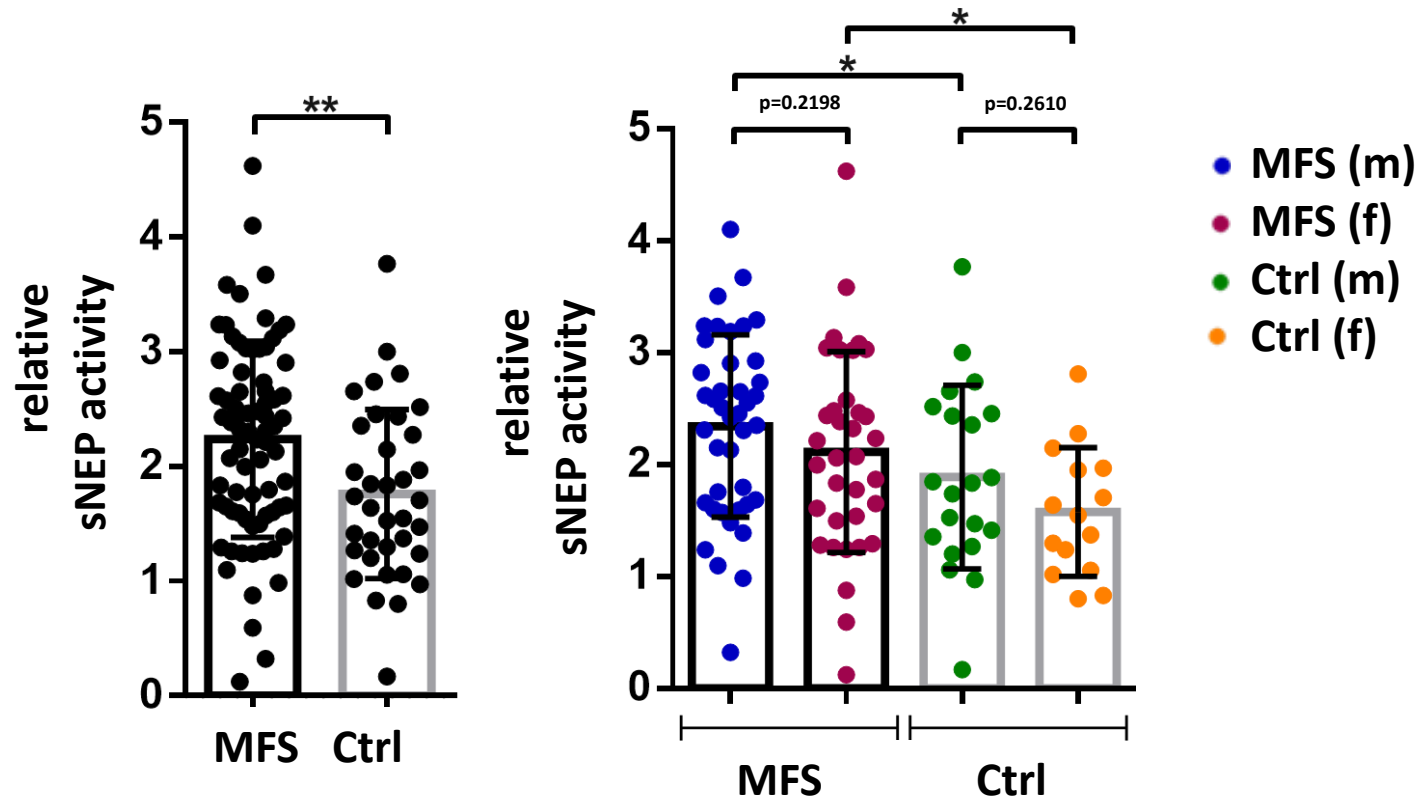
- Marfan syndrome (MFS) is the most common hereditary disorder causing lethal aortic syndrome by degradation of the aortic wall.
- Recently, neprilysin (NEP)/angiotensin II receptor blockers sacubitril/valsartan have been shown to improve cardiac function in heart failure and positively affect the aortic wall in mouse models of MFS.
- NEP degrades and inactivates apelin peptides, which have been reported to be protective in terms of aortic aneurysm formation
- Here, we aimed to investigate possible correlations between NEP and MFS in aortic specimens and serum of patients with MFS.

Methods

- We collected serum and aortic specimens from patients with MFS (age 19-64 years) in the outpatient MFS centre and resected tissue from patients with MFS undergoing valve sparing aortic root replacement.
- Control samples were collected from the aortic tissue of patients undergoing routine coronary artery bypass grafting.
- Enzyme-linked immunosorbent assay (ELISA) was used to analyze blood serum soluble NEP (sNEP) levels.
- sNEP activity in the serum was assessed using a fluorogenic peptide substrate.
- Aortic tissue was examined using immunofluorescence microscopy.

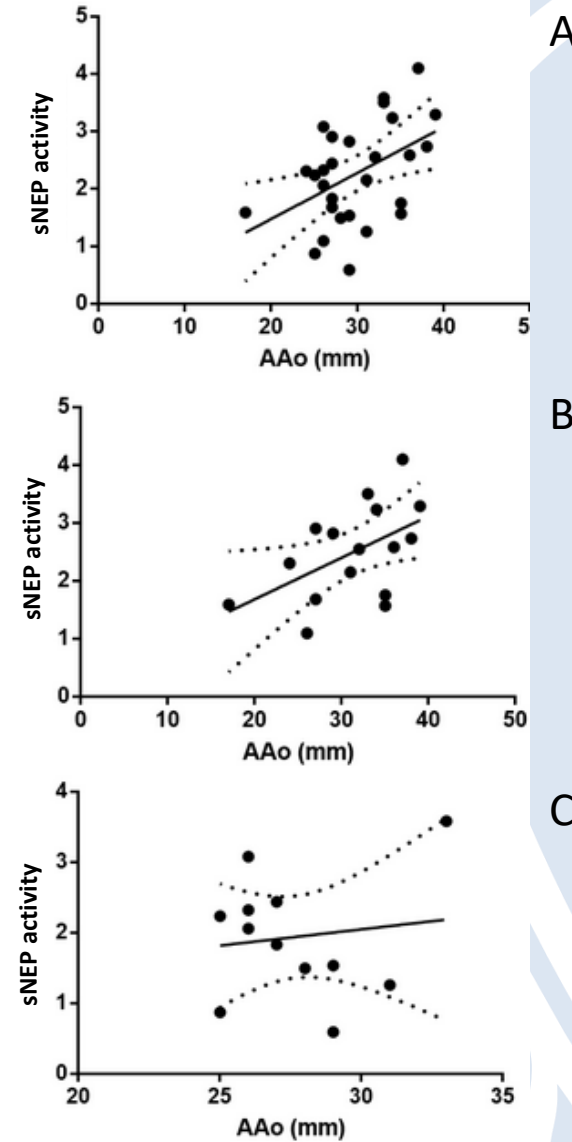
Results I

- Soluble neprilysin activity was significantly higher in patients with MFS than in control individuals without a connective tissue disorder diagnosis (n=36-76, p=0.0047**). The difference could also be seen after dividing the groups by gender: male MFS patients compared to control (p=0.0403*), and also for female patients (p=0.0361*).



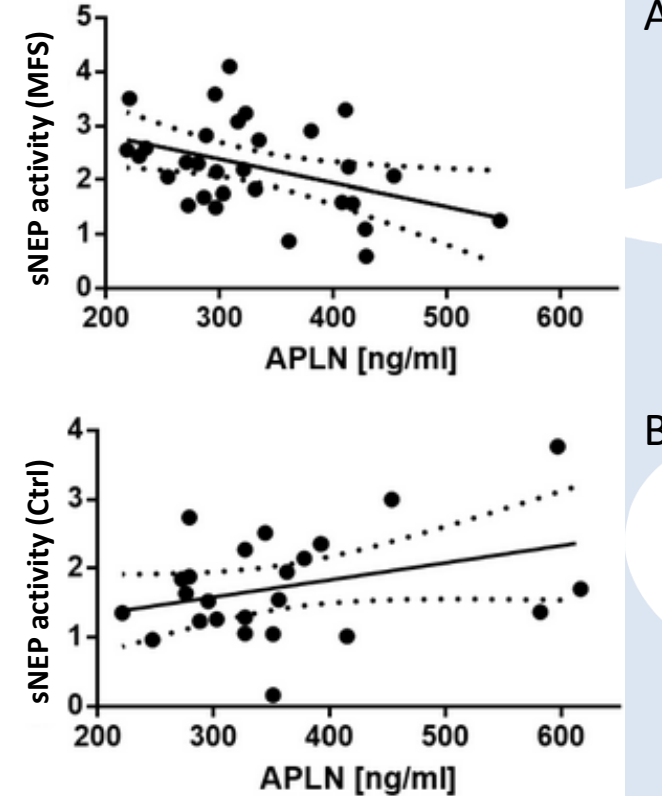
Results II

- We observed a positive correlation between aortic root diameter and sNEP activity (A; $r=0.46$, $p=0.0137$), predominantly driven by male gender (B; $r=0.5178$, $p=0.0399$), whereas it was not relevant in female patients with MFS (C).
- Exemplary NEP immunofluorescent staining of aortic tissue derived from MFS patients ($n=2$) revealed a 47% higher NEP protein abundance in the AAo media than in control individuals ($n=2$). However, in MFS patients, sNEP plasma levels were 78% higher ($p=0.004$, $n=24-29$), independent of gender, age, aortic diameter, and clinical data such as pre-/ post-surgery.



Results III

- Elevated sNEP levels correlated negatively with apelin concentration in patients with MFS (A; $r=0.4083$, $p=0.0251$) compared to control individuals (B; $r=0.3417$, $p=0.1023$).



Conclusions

- **Elevated serum neprilysin levels may play a pivotal role in developing and progressing aortic aneurysm formation in patients with MFS.**
- **The addition of neprilysin receptor blockers may influence the progression of aneurysm formation in patients with MFS, reducing the need for early aortic replacement surgery.**

