A Novel Role for Aquaporin 4 Blocker Attenuates the Progression of Atrial Remodeling in Angiotensin II - Induced Atrial Fibrillation Mice Model

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COI Disclosure

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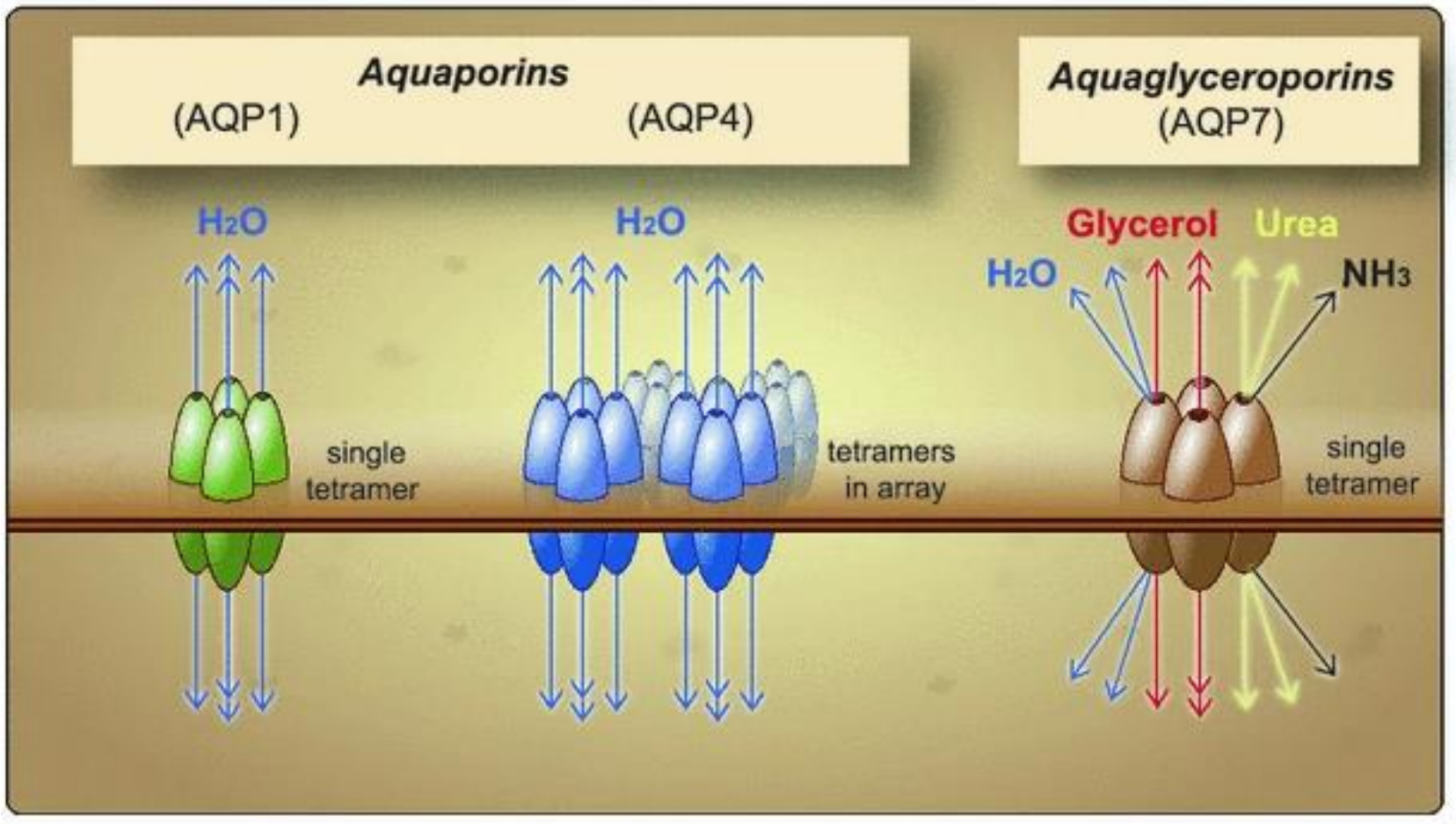
Background

- Aquaporin?
  - Family of small membrane proteins that transport water and have been implicated in human disease such as cancer, cerebral disease, and cardiovascular disease.
  - 13 types of Aquaporin (AQP) have been identified in mammals

Background



Basic Res Cardiol (2013) *108*(6): 1-19.

Background

• There was a study that the heart failure with preserved ejection fraction (HFpEF) mouse showed significant increase in cardiac AQP4 expression and ventricle size, suggesting its potential role in cardiac edema.

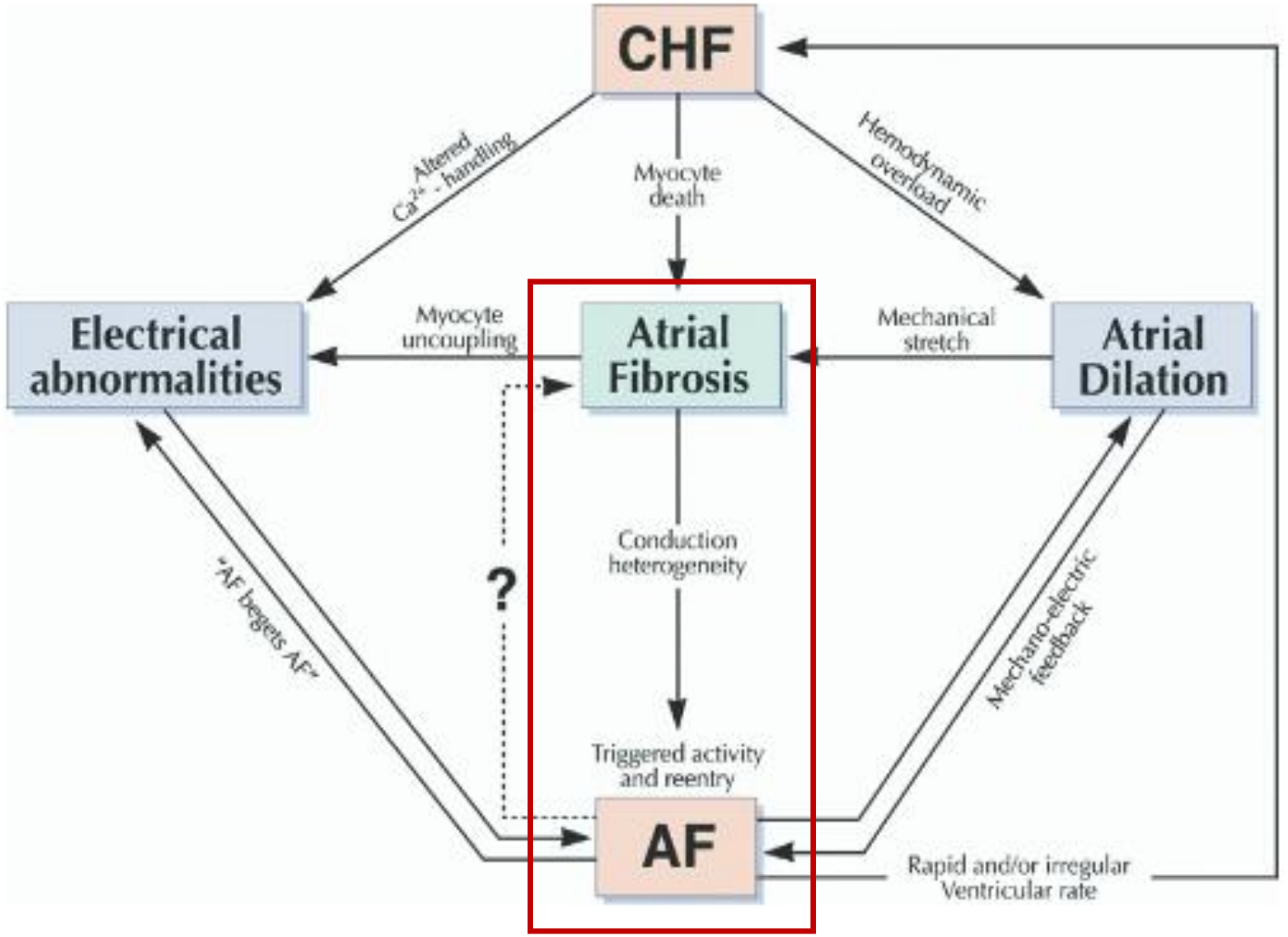
• It has been observed that AQP4 knockout (KO) mice exhibit a reduction in infarct size in the ex vivo ischemia/reperfusion model and the in vivo ischemia without reperfusion model.

Background

• Atrial fibrillation (AF) is the most common persistent arrhythmia in clinical practice.

• It is already well known that fibrosis plays an important role in structural remodeling

Background



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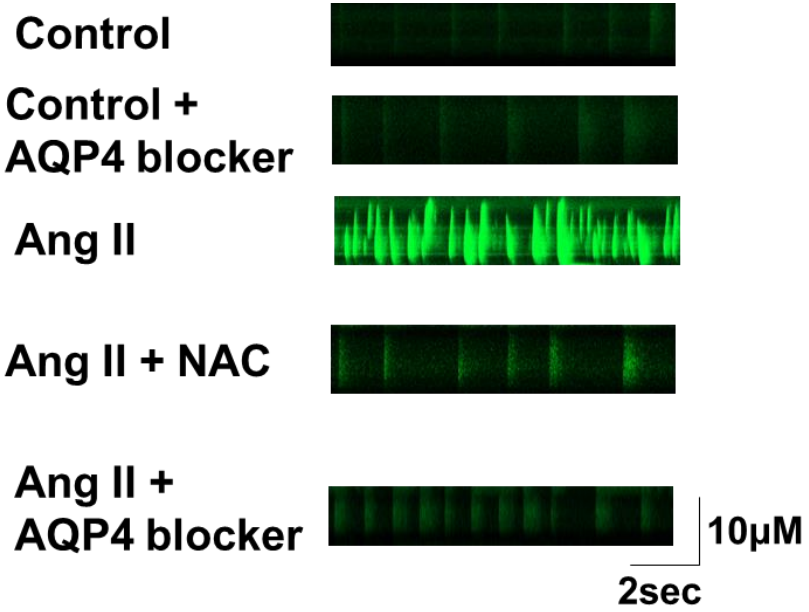
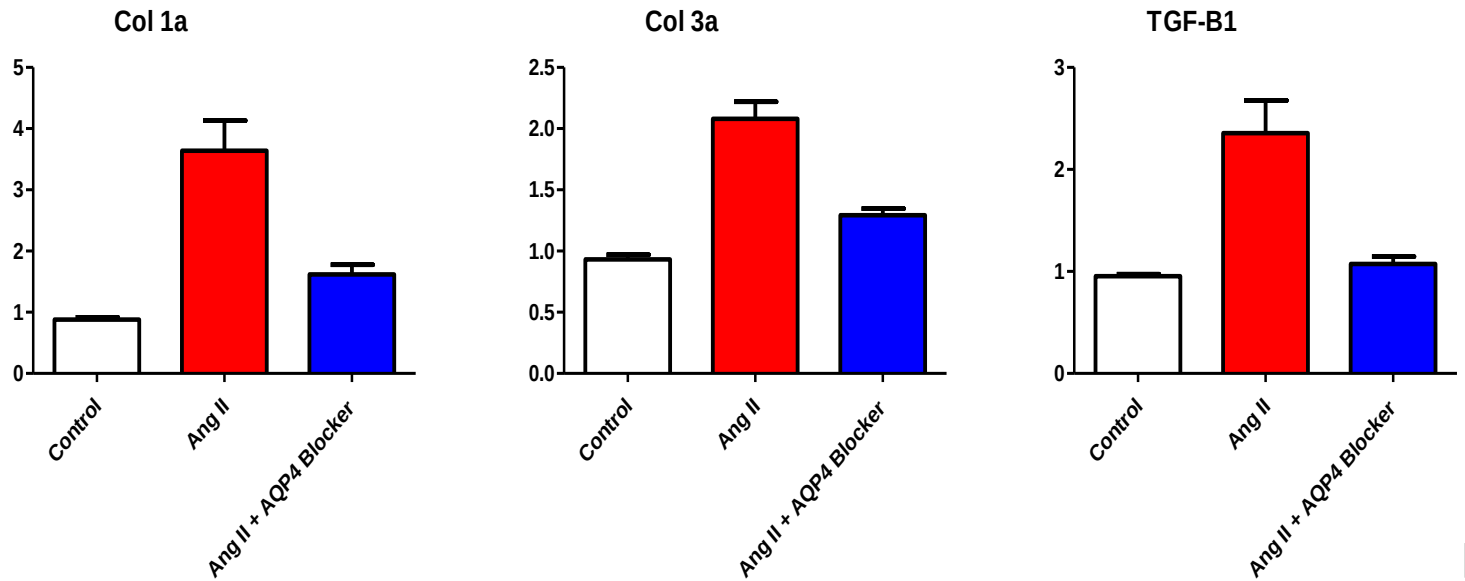
Background

- In vitro model using HL-1 cells suggests the potential rolet of cardiac AQP4 in cardiac remodeling caused by AF.





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Background

- To establish a more definitive understanding of the relationship between cardiac remodeling in AF and AQP4, further precise evidence is required.

- Our hypothesis is that regulation of the AQP4 channel may have a protective effect in AF. To investigate this, we conducted an in vivo experiment.

Method

- A total of 40 mice were divided into 4 groups
  - a control group,
  - an Angiotensin II (AngII) group as AF induced model
  - an AngII + AQP4 blocker (TGN-020) group
  - a negative control group with AngII + phosphate-buffered saline (PBS).
- After 4 weeks of pretreatment, an intracardiac catheter was inserted to perform rapid atrial pacing.

Method

- Baseline intracardiac EKG
- EKG after burst pacing
- MMP2, MMP9, Col1α, and Col3α were confirmed by quantitative real-time PCR.

Result

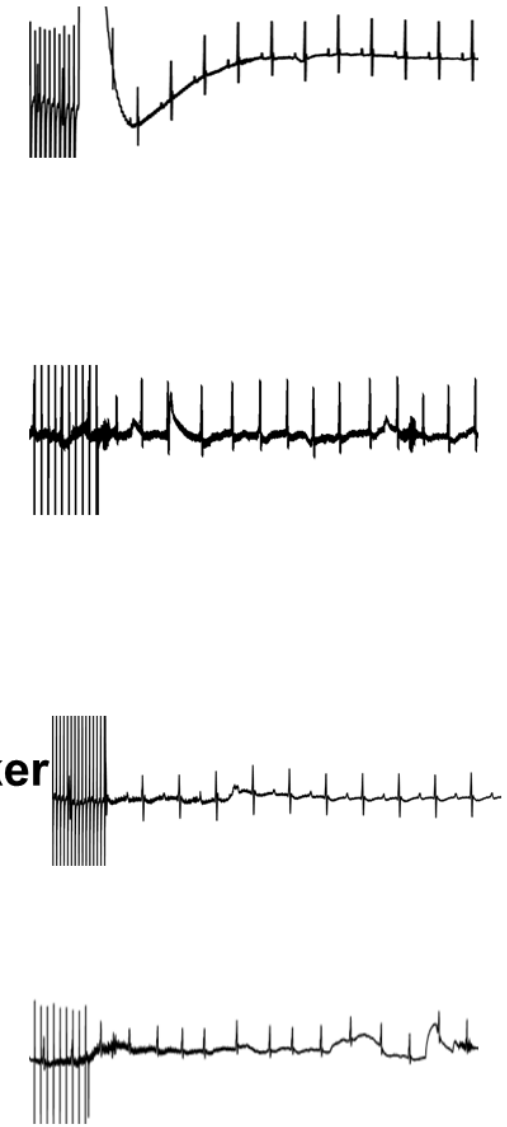
A

Control
– 60ms

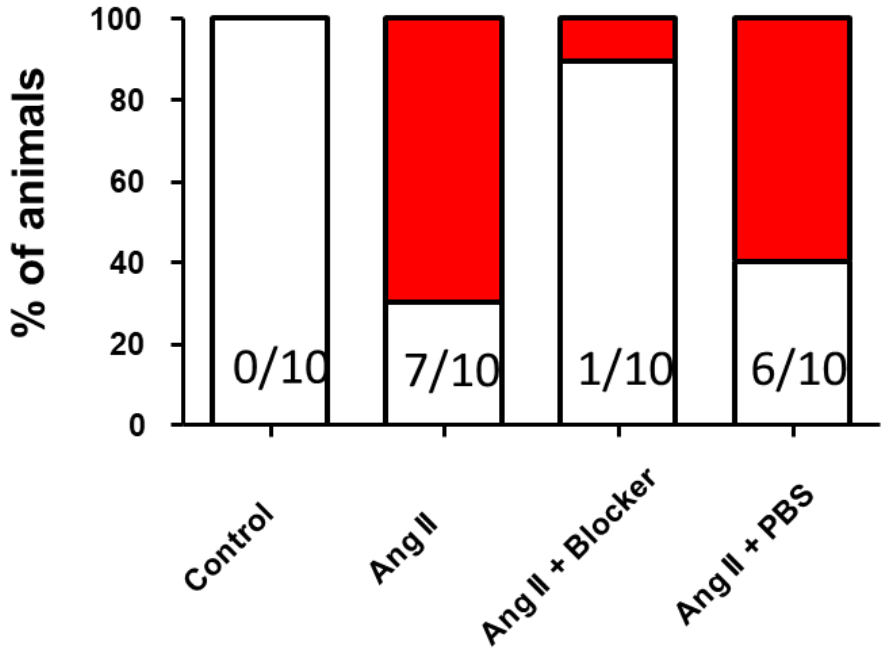
Ang II
– 60ms

Ang II + Blocker
– 30ms

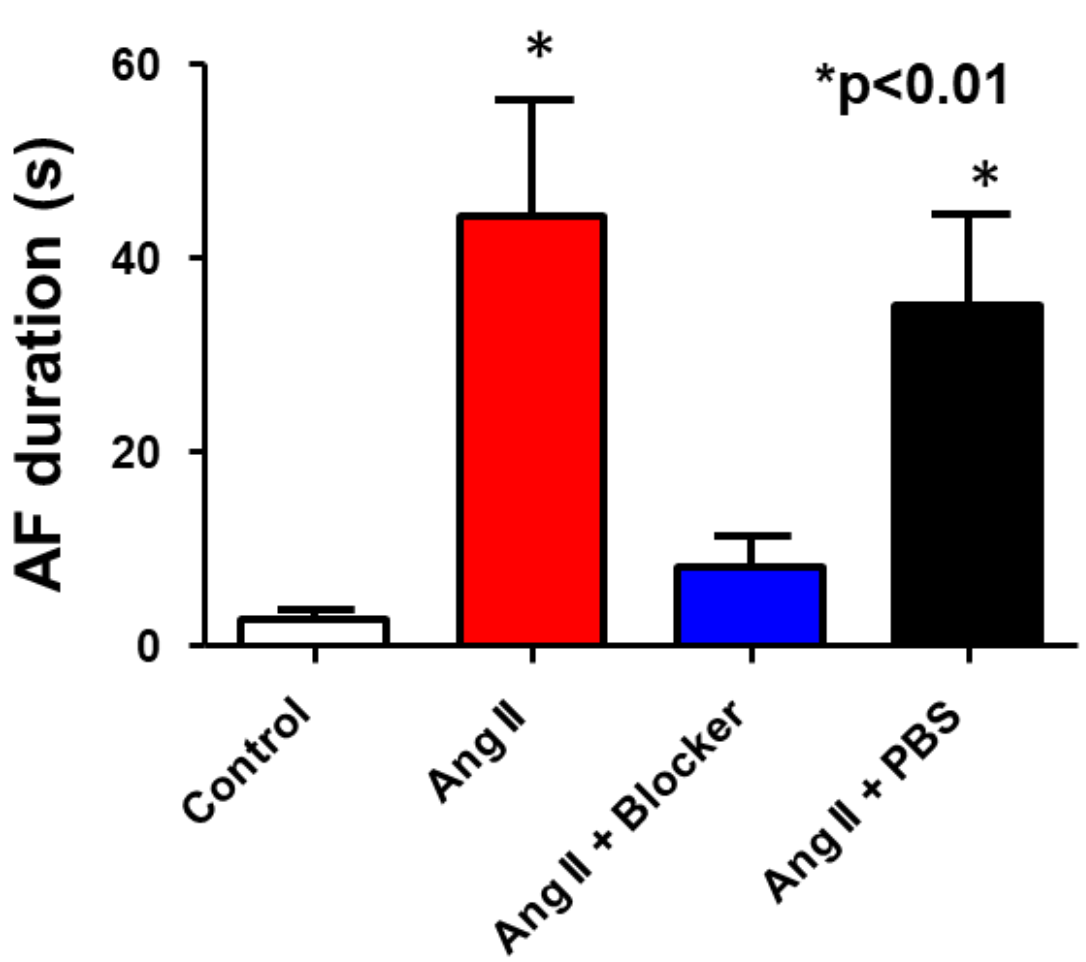
Ang II +PBS
– 60ms



B



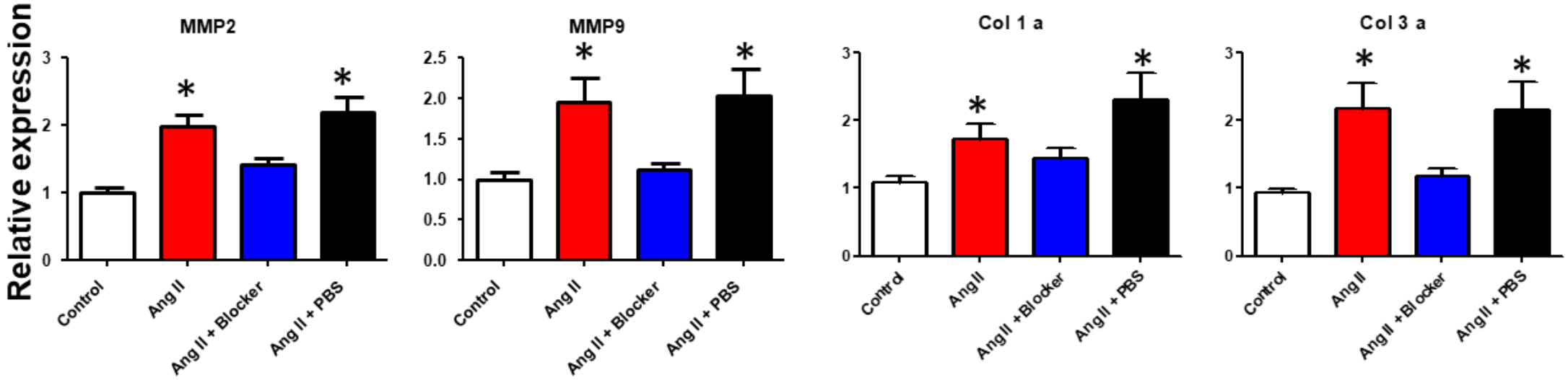
Result



The duration of induced AF showed significant differences ($p<0.01$); Control group (1 ± 0 seconds); AngII group (44.4 ± 13.2 seconds); AngII + AQP4 blocker group (6.8 ± 3.2 seconds); AngII + PBS group (37.5 ± 10.2 seconds).

Result

D



Fibrosis marker, MMP2, MMP9, Col1α, and Col3α, showed significantly higher in AngII group and negative control group compared with control group or AngII + AQP4 blocker group. ($p<0.01$)

Discussion

- AF and HFpEF can mutually cause or worsen one another through various mechanisms.
- Since HFpEF was observed in the group of mice treated with Ang II, there might have been a tendency for it to progress into AF, but the progression towards AF could potentially be inhibited by suppressing the advancement of HFpEF through the use of an AQP4 blocker.
- However, a limitation of this study is the lack of clear identification regarding the role of AQP4 in the interrelationship between these two diseases.

Conclusion

- This study provides evidence that treating with AQP4 blocker at the in vivo level has a protective effect on AF progression.

- This indicates that regulation of the AQP4 channel may be associated with AF progression.

Thank you for your attention