Telmisartan improves RV function and hypertrophy by modulating processes of fibrosis and autophagy in PA banded rat

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Has documented that I have no financial relationships to disclose or conflicts of Interest (COIs) to resolve.
Introduction

*RV failure is a significant complication in patients with congenital heart disease with right-sided obstructive lesion.

*While ARBs are known to reduce mortality in patients with left side heart failure, their effects for RV failure are unknown.

*Pressure overload stress induces a robust autophagic response and hypertrophic changes in cardiomyocytes.
Objective

To investigate the effect of an ARB, telmisartan, on RV function using a overloaded RV hypertrophy rat model by measuring physiological parameters, histological alterations, and mitochondrial function.
PA banded rat model

A 7-0 suture tied firmly against a 18-gauge needle

Survival rate

Sham n=12
P<0.0001 by log-rank

PAB n=42

PAB; Half-life 17 days

Vivid8
12MHz

Masson
Trichrome

LV
RV

LV
RV

LV
RV

LV
200g SD rat

RT-PCR Pathology

PA banding (n=12)
PA banding with telmisartan (n=24)

4 weeks

Telmisartan 5mg/kg/d or water

PG>80mmHg Severe TR Flat IVS

UCG PV loop

Telmisartan社 1.4F micro cath.
Kaplan Meier Survival Curve

P<0.01
By Log-rank

analysis day
Physiological parameters

RV End Diastolic Pressure

RV Systolic Pressure

PA Banded RV

Ees

Eed

sham

PAB

PAB+T

CO=VTI x HR x CSA

*<0.05

**<0.01
Hypertrophy, a changing of collagen related RNA in stressed RV

![Graphs showing RV/BW ratio and hold changing for sham, PAB, and PAB+tel conditions.](image)

Pro-collagen 3

- **P<0.05**
- **P<0.01

CTGF

- **P<0.05**
- **P<0.01

*Values represent statistical significance compared to the sham group.*
Path-histology in RV

Telmisartan suppressed %fibrosis in RV.
PPARγ activity

Insulin resistant
Hyperlipidemia
inflammation
proliferation
HT
Oxidative stress

Cardio-vascular protection

PPARγ

Representive IHC of PPAR gamma in RV

PAB

PAB+tel

Real time RT-PCR

* P<0.01
Mitochondria and Mitophagy: The Yin and Yang of Cell Death Control
Dietz A. Kashi and Anu B. Gudjonsson

A
Mild Stress

B
Severe Stress

Cell Survival

Cell Death

IMS Protein Release
Electro-Microscopy

Sham operated
PA banded 2wks
PA banded 3wks
PA banded 4wks
LC3, p62 expression in RV

Decreased expressions of LC3A/B and p62 indicated that the reduction of autophagy.
Result

1) Telmisartan improved survival rate in PA banded rat.

2) Telmisartan inhibit cardiac hypertrophy, fibrosis in mRNA level, and inhibited interstitial fibrosis.

3) Telmisartan enhanced expression of PPARγ in the cell nuclear.

4) EM showed that in response to severe afterloaded stress, there was overwhelming mitochondrial damage that autophagy process were unable to efficiently clear.
Conclusion

• Telmisartan had effects to improve RV cardiac output and to decrease mortality without reduction of RV pressure by inhibiting cardiac fibrosis, autophagy and RV hypertrophy in a rat model.
• Telmisartan may be an effective treatment option for RV failure.