A chronic angiotensin II infusion mouse model of hypertension-induced cardiac fibrosis

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Background & Aim

Development of novel pharmaceutics for hypertension-induced cardiac disease relies upon animal models that reproduce patient phenotypes, including the full spectrum of cardiac fibrosis. Chronic infusion with angiotensin-II (AngII) in mice has become the most widely used translational model and shows hypertension, cardiac fibrosis, cardiomyocyte death, and dilated cardiomyopathy.

Here we present a mouse model of hypertensive cardiac remodelling, left ventricular dysfunction and fibrosis induced by chronic AngII infusion.

Methods

Male C57BL6/N mice were administered saline vehicle (n=10) or AngII (2.5 mg/kg/day, n=12) for 4 weeks using subcutaneous osmotic minipumps (Alzet 2006). Hypertension was confirmed by tail cuff plethysmography on study day -1 (3 days post-implantation). Echocardiography was performed in study week 3. At termination, plasma was collected for biochemistry and the heart was sampled for fibrosis histology.

Conclusion

Chronic AngII infusion:

+ Causes perivascular and interstitial fibrosis
+ Promotes eccentric cardiac hypertrophy
+ Results in systolic and diastolic dysfunction and decreased cardiac output

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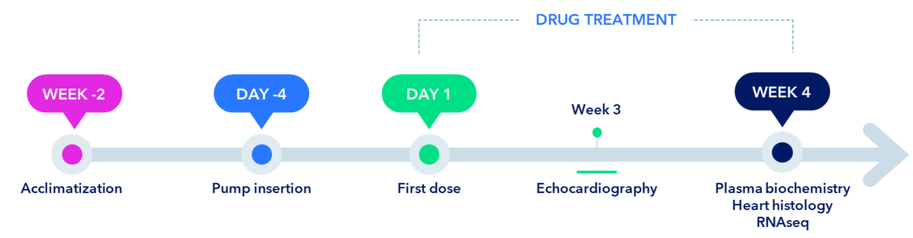
1 Study design and study groups.



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing concentration
1	C57Bl/6N	Male	10	**Vehicle**	Osmotic pump (2006 Alzet)	-
2	C57Bl/6N	Male	10	**Vehicle**	Osmotic pump (2006 Alzet)	**2.5 mg/kg/day**

2 Chronic AngII infusion causes hypertension

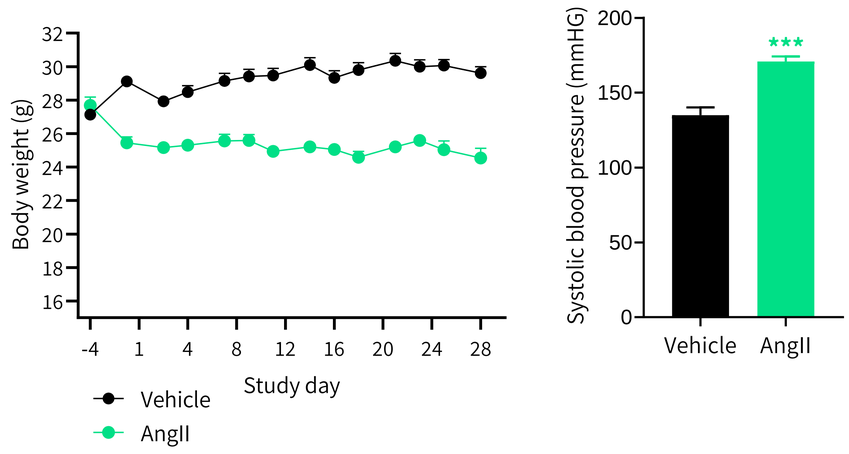
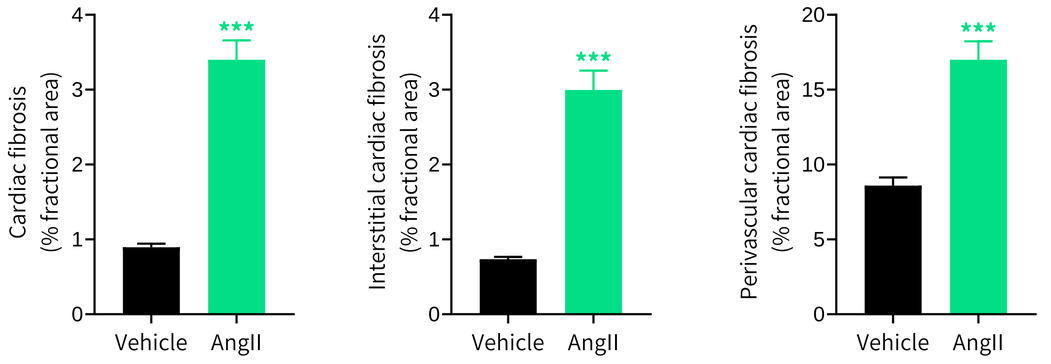


Figure 1. Body weight and systolic blood pressure. Osmotic minipumps were inserted on study day -4. **(A)** Absolute body weight (g) throughout the study. **(B)** Systolic blood pressure measured on study day -1. Mean + S.E.M. ***p<0.001 vs. Vehicle (Dunnett's test one-factor linear model).

3 Chronic AngII infusion induces cardiac fibrosis



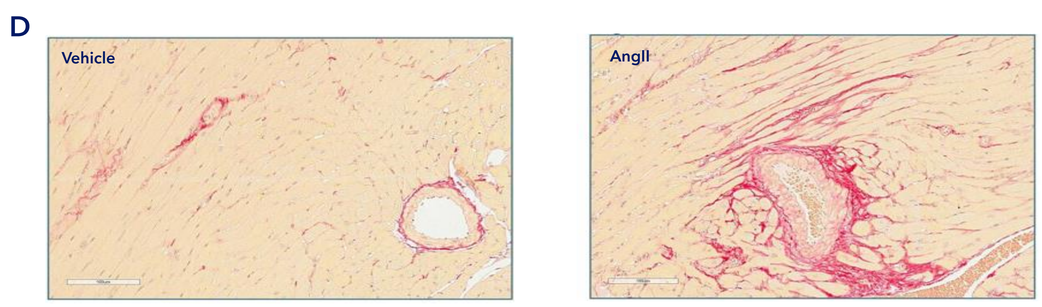
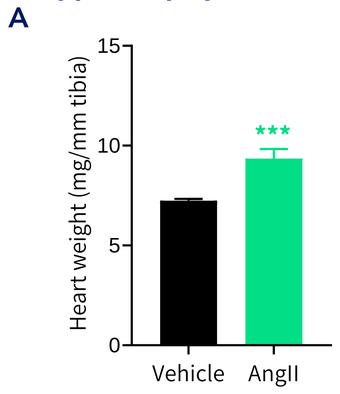


Figure 2. Histomorphometrics. (A) Whole-heart, **(B)** interstitial and **(C)** perivascular fibrosis. **(D)** Representative images of left ventricular sections stained with Picro Sirius red (PSR). Mean + S.E.M., ***p<0.001 vs. Vehicle (Dunnett's test one-factor linear model).

4 Chronic AngII infusion promotes cardiac hypertrophy



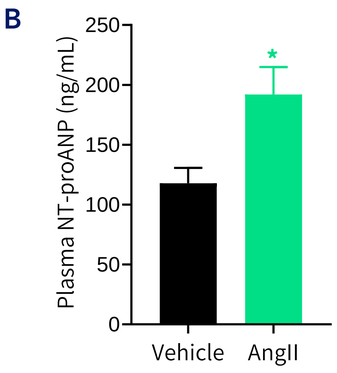
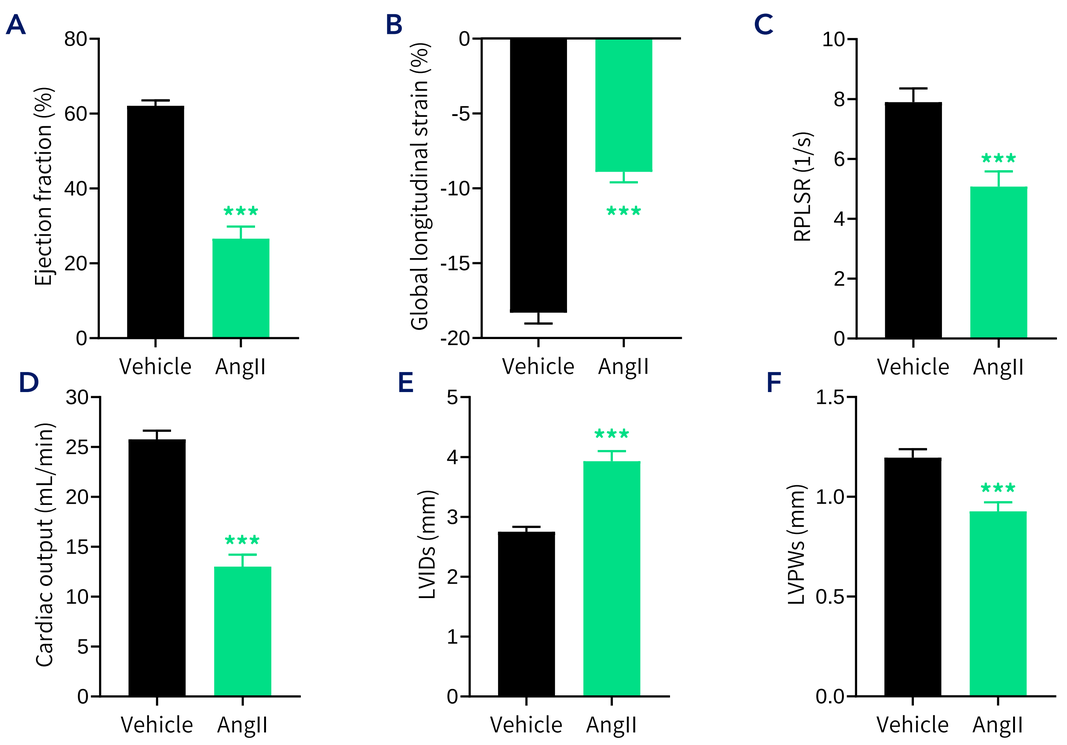


Figure 3. Heart weight and plasma NT-proANP. Measured at termination on study day 29 **(A)** Heart weight relative to tibial length at termination. **(B)** Plasma N-terminal pro-atrial natriuretic peptide (NT-proANP) levels at termination. Mean + S.E.M. *p<0.05, ***p<0.001 vs. Vehicle (Dunnett's test one-factor linear model).

5 Chronic AngII infusion causes LV dilation and cardiac dysfunction



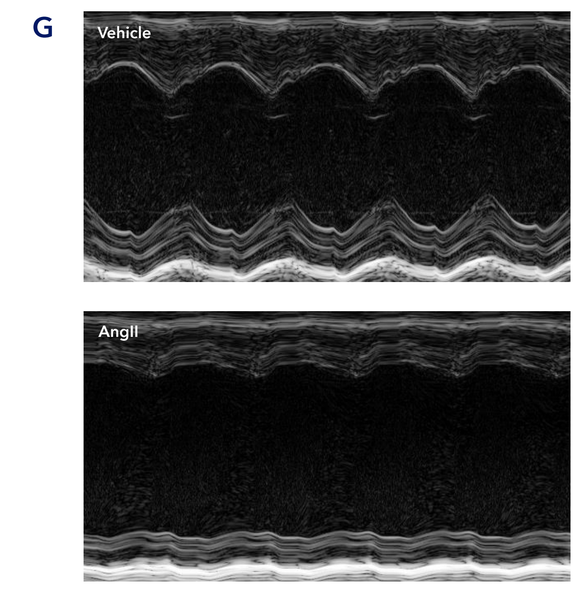


Figure 4. Echocardiography.
Echocardiography was performed on study day 21-25 **(A)** Ejection fraction. **(B)** Global longitudinal strain (GLS). **(C)** Reverse peak longitudinal strain rate (RPLSR). **(D)** Cardiac output, **(E)** Left ventricular **(**LV) systolic diameter (LVIDs). **(F)** LV posterior wall thickness in systole (LVPWs), **(G)** Representative M-mode images of the LV in short axis view from vehicle- and AngII-treated animals. Mean + S.E.M. ***p<0.001 vs. Vehicle (Dunnett's test one-factor linear model).