The calcimimetic R568 does not improve microvascular function in in myocardium and peripheral arteries experimental renal failure

M Verkaik[1,2], WG Richards[3], EC Eringa[2], MG Vervloet[1]
On behalf of the NIGRAM consortium
[1]Dept. of Nephrology and [2]Dept. of Physiology, Institute Cardiovascular Research VU (ICaR-VU), VU University Medical Center, Amsterdam, The Netherlands, [3]Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States.

Introduction

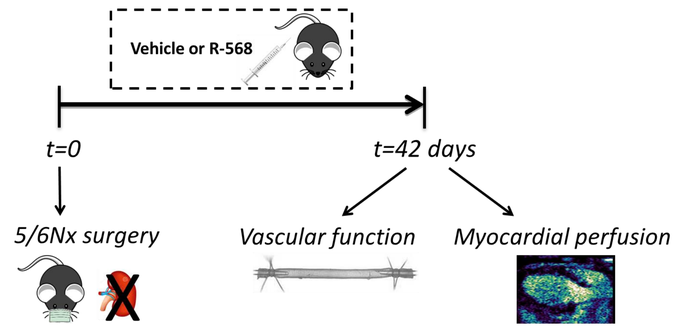
- Cardiovascular causes account for approximately 50% of mortality in patients with chronic kidney disease (CKD). FGF23 is suggested to contribute to this risk.
- Calcimimetics are originally used to treat secondary hyperparathyroidism, but also showed to decrease FGF23 concentrations in patients on dialysis. This decline was associated with improved clinical outcome.

Hypothesis

- **Here we tested the hypothesis that treatment with the calcimimetic R568 in experimental CKD improves microvascular function by lowering FGF23 in experimental CKD.**

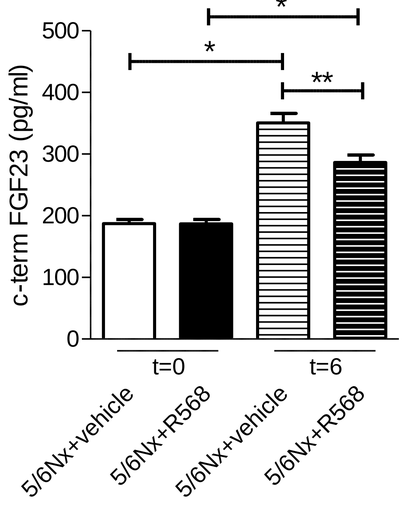
Methods

- Eight week-old male C57Bl/6 mice were subjected to partial nephrectomy (5/6Nx) and injected with vehicle or R568 (30 mg/kg/day).
- After 6 weeks of renal failure, *ex vivo* vascular function was assessed in resistance arteries using pressure myography.
- Microvascular myocardial perfusion was assessed *in vivo* using myocardial contrast echocardiography (MCE).



Results

Figure 1. R568 treatment in 5/6Nx mice decreases plasma FGF23 concentrations.



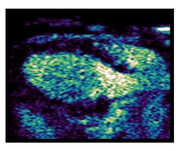
Data are mean ± SEM.
N=5 for t=0 and n=13-15 for t=6.

Table 1. Pooled plasma samples of 5/6Nx mice with vehicle or R568 treatment.

	5/6Nx + vehicle t=0	5/6Nx + vehicle t=6	5/6Nx + R568 t=0	5/6Nx + R568 t=6
Phosphate (mmol/L)	2.04	1.59	1.98	1.65
Creatinine (µmol/L)	12	23	13	24
Urea (mmol/L)	7.7	27.0	7.7	27.9

N=16-17 for t=0 and n=13-15 for t=6.

Figure 2. R568 treatment in 5/6Nx mice does not alter myocardial perfusion during acetylcholine infusion.



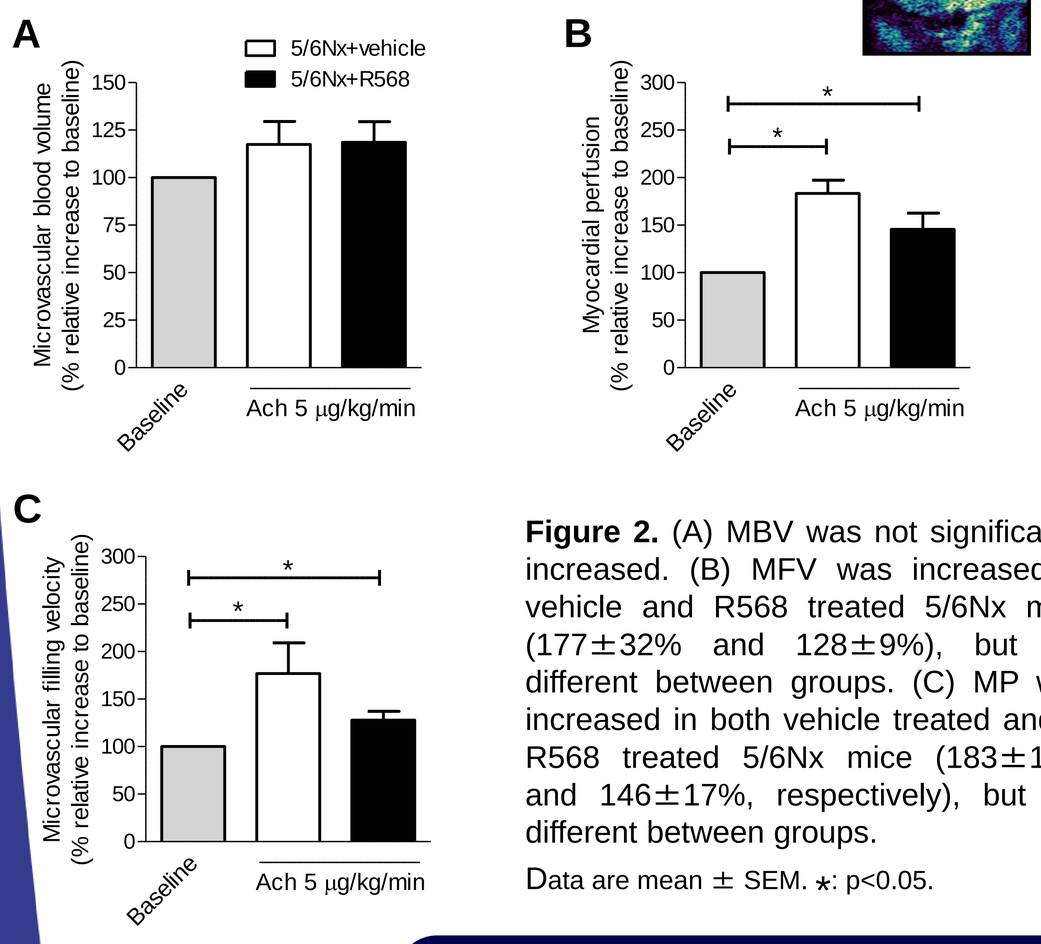


Figure 2. (A) MBV was not significantly increased. (B) MFV was increased in vehicle and R568 treated 5/6Nx mice (177±32% and 128±9%), but not different between groups. (C) MP was increased in both vehicle treated and in R568 treated 5/6Nx mice (183±14% and 146±17%, respectively), but not different between groups.

Data are mean ± SEM. *: p<0.05.

Figure 3. R568 treatment in 5/6Nx mice does not alter vascular function.

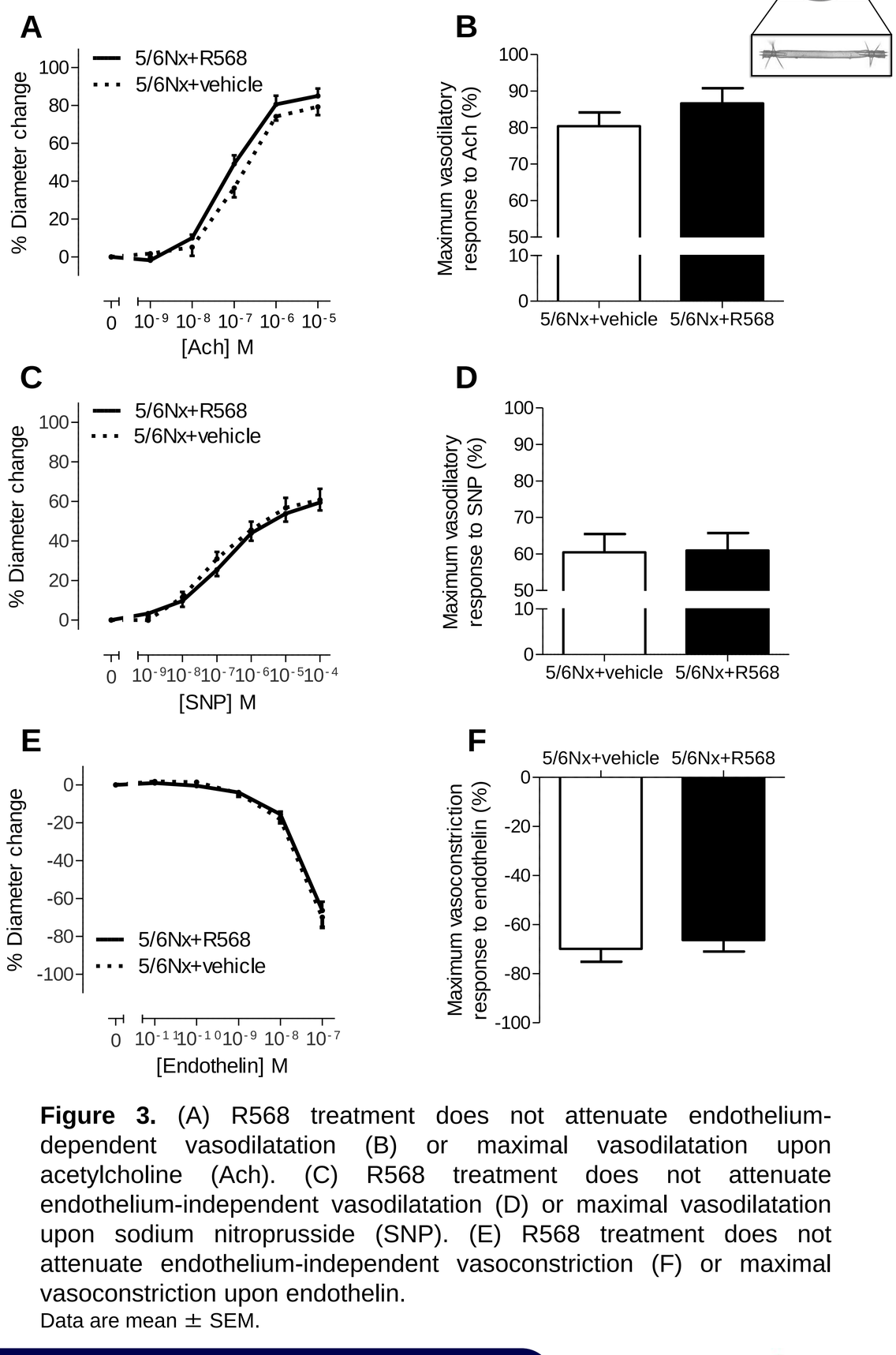


Figure 3. (A) R568 treatment does not attenuate endothelium-dependent vasodilatation (B) or maximal vasodilatation upon acetylcholine (Ach). (C) R568 treatment does not attenuate endothelium-independent vasodilatation (D) or maximal vasodilatation upon sodium nitroprusside (SNP). (E) R568 treatment does not attenuate endothelium-independent vasoconstriction (F) or maximal vasoconstriction upon endothelin.
Data are mean ± SEM.

Conclusions

- R568 treatment in experimental CKD decreases plasma FGF23 concentrations.
- Endothelial function is not improved after R568 treatment.
- R568 treatment does not improve myocardial perfusion in experimental CKD.

54 ERA
378--SP
CKD - MBD
Melissa Verkaik
DOI: 10.3252/pso.eu.54ERA.2017
ePosters supported by F. Hoffmann- La Roche Ltd.