

# CHRONIC KIDNEY DISEASE IMPAIRS MYOCARDIAL PERFUSION AND DISTURBS CARDIAC CALCIUM HANDLING

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## Introduction

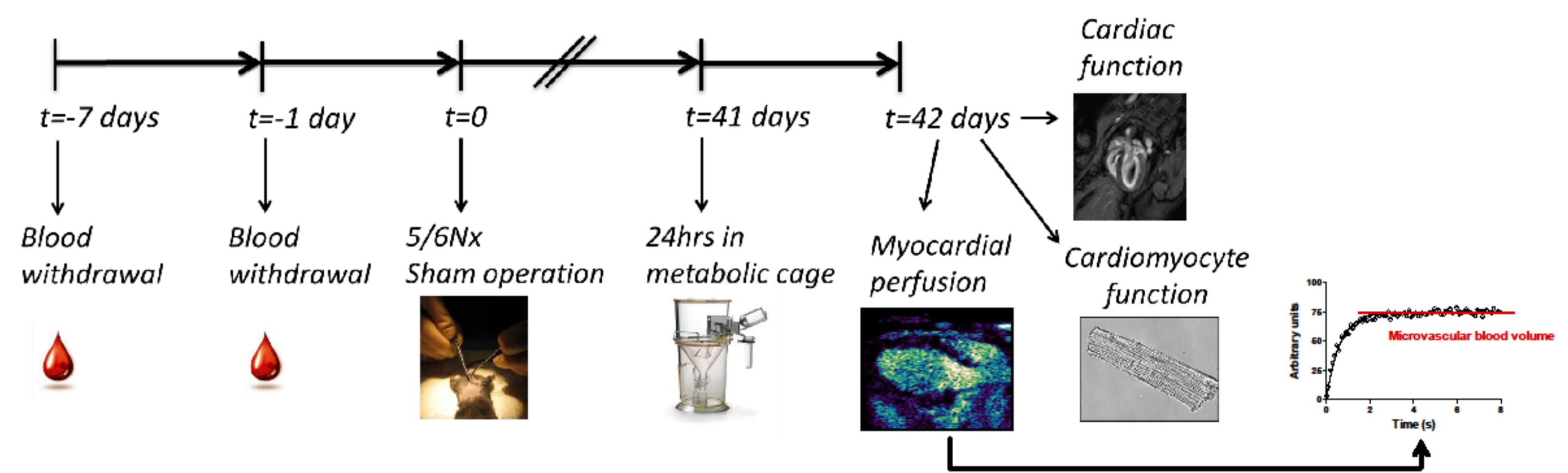
- Chronic kidney disease is associated with increased cardiovascular mortality.
- 60-85% of CKD patients have diastolic dysfunction and sudden cardiac death accounts for 60% of cardiovascular mortality in ESRD patients.
- In heart failure calcium (Ca<sup>2+</sup>) cycling across the sarcoplasmic reticulum (SR) is profoundly altered.

## Aim

We hypothesized that CKD directly impairs myocardial perfusion and impairs cardiac function due to disturbed calcium handling.

## Methods

Eight week old male wild type C57Bl/6J mice were subjected to partial nephrectomy (5/6Nx) or sham-surgery, and after 6 weeks mice were placed into a metabolic cage and subjected to myocardial contrast echocardiography (MCE) to test myocardial perfusion. Cardiac function was assessed using MRI. Single intact cardiomyocytes were isolated from Langendorff-perfused hearts and diastolic and systolic function, as well as intracellular calcium transients were measured by fura-2 loaded cardiomyocytes. Calcium channel expression in these cells was determined by Western blot.



## Results

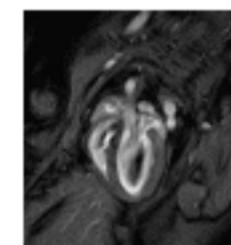
Table 1. Parameters 6 weeks after surgery.



	Sham	5/6Nx	p-value
Plasma urea (mmol/L)	12.72 ± 0.34	22.10 ± 1.05	<0.001
Plasma creatinine (µmol/L)	15.00 ± 1.50	28.32 ± 1.59	<0.001
Urinary creatinine (µmol/24h)	2.62 ± 0.23	3.33 ± 0.15	0.021
Creatinine clearance (µl/min)	137.10 ± 20.40	92.81 ± 5.97	0.060
Plasma Pi (mmol/L)	3.37 ± 0.19	2.93 ± 0.12	0.088
Urinary Pi (µmol/24h)	19.20 ± 2.80	114.95 ± 18.39	<0.001
Fractional excretion phosphate (FEP) (%)	2.95 ± 0.92	17.01 ± 2.87	0.003
FGF23 (pg/ml)	210.2 ± 13.1	315.2 ± 27.6	0.002
KLOTHO/HPRT mRNA expression (fold change) in kidney	1.01 ± 0.04	0.69 ± 0.06	<0.001
Plasma Ca <sup>2+</sup> (mmol/L)	2.00 ± 0.02	2.17 ± 0.03	0.001
Urinary Ca <sup>2+</sup> (µmol/24h)	1.07 ± 0.21	3.55 ± 0.31	<0.001
Plasma 1,25-dihydroxyvitamin D <sub>3</sub> (pmol/L)	226.8 ± 10.2	252.6 ± 23.5	0.317
CYP27B1/HPRT mRNA expression (fold change) in kidney	3.62 ± 0.66	8.07 ± 1.67	0.111
CYP24A1/HPRT mRNA expression (fold change) in kidney	1.87 ± 0.29	0.71 ± 0.12	<0.001

Data are Mean ± SEM

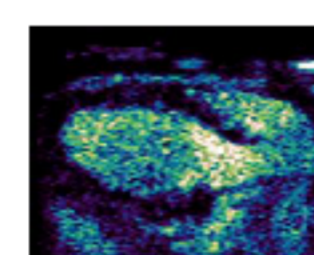
Table 2. No difference in cardiac parameters between groups 6 weeks after surgery.



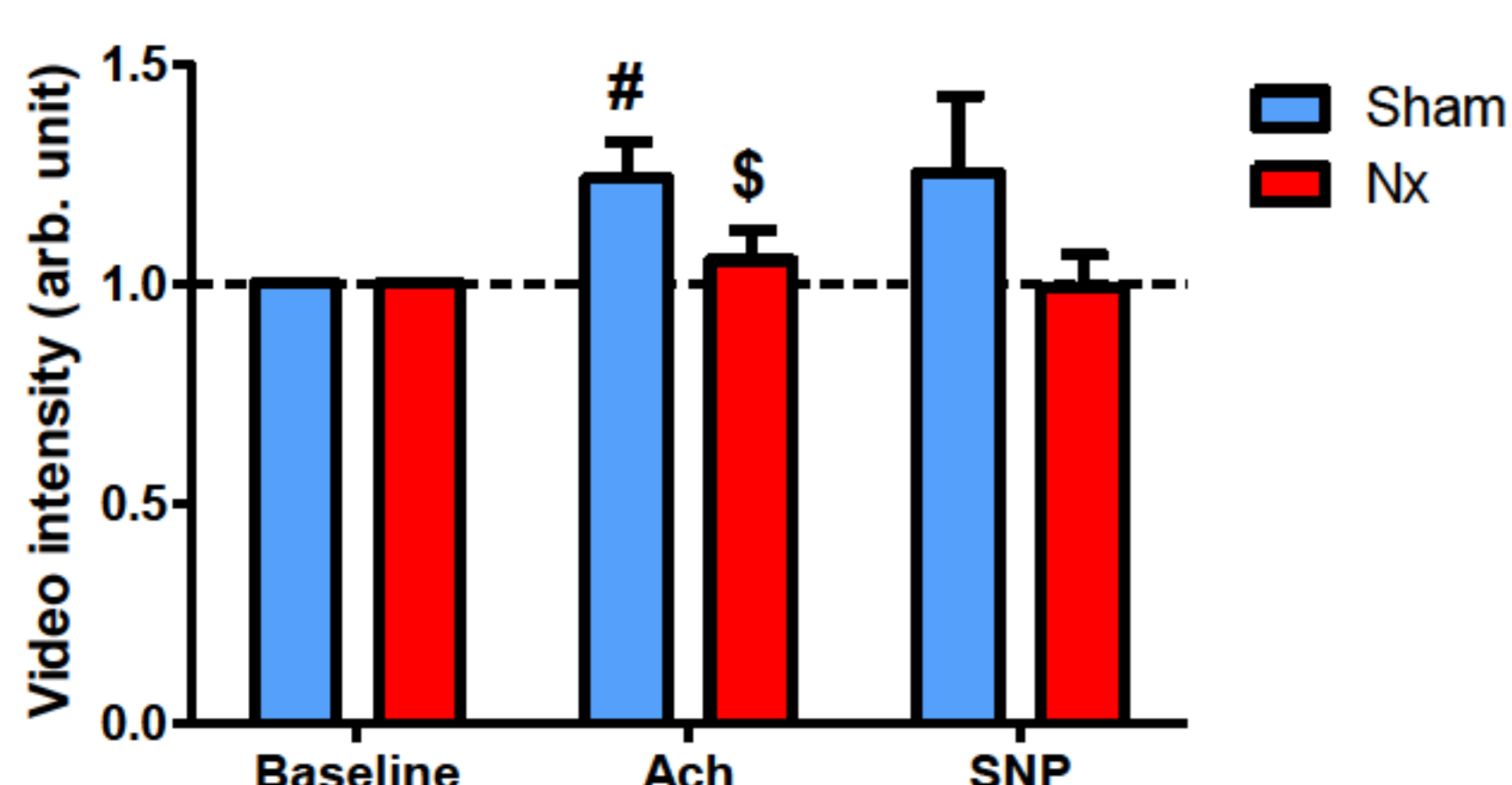
	Sham	5/6Nx	p-value
Cardiac output (L/min)	4.80 ± 0.39	4.76 ± 0.25	0.886
Ejection fraction (%)	73.3 ± 1.6	72.4 ± 0.9	0.886
Stroke volume (µl)	43.9 ± 2.6	43.5 ± 1.9	0.631
End diastolic volume (µl)	60.2 ± 4.6	60.2 ± 2.9	0.886
End systolic volume (µl)	16.4 ± 2.1	16.7 ± 1.1	0.886
E/A ratio	1.39 ± 0.26	1.79 ± 0.20	0.182
Heart weight:tibia length (mg:cm)	61.8 ± 1.0	62.8 ± 0.9	0.269

Data are Mean ± SEM

Figure 1. Experimental renal failure impairs myocardial perfusion reserve.

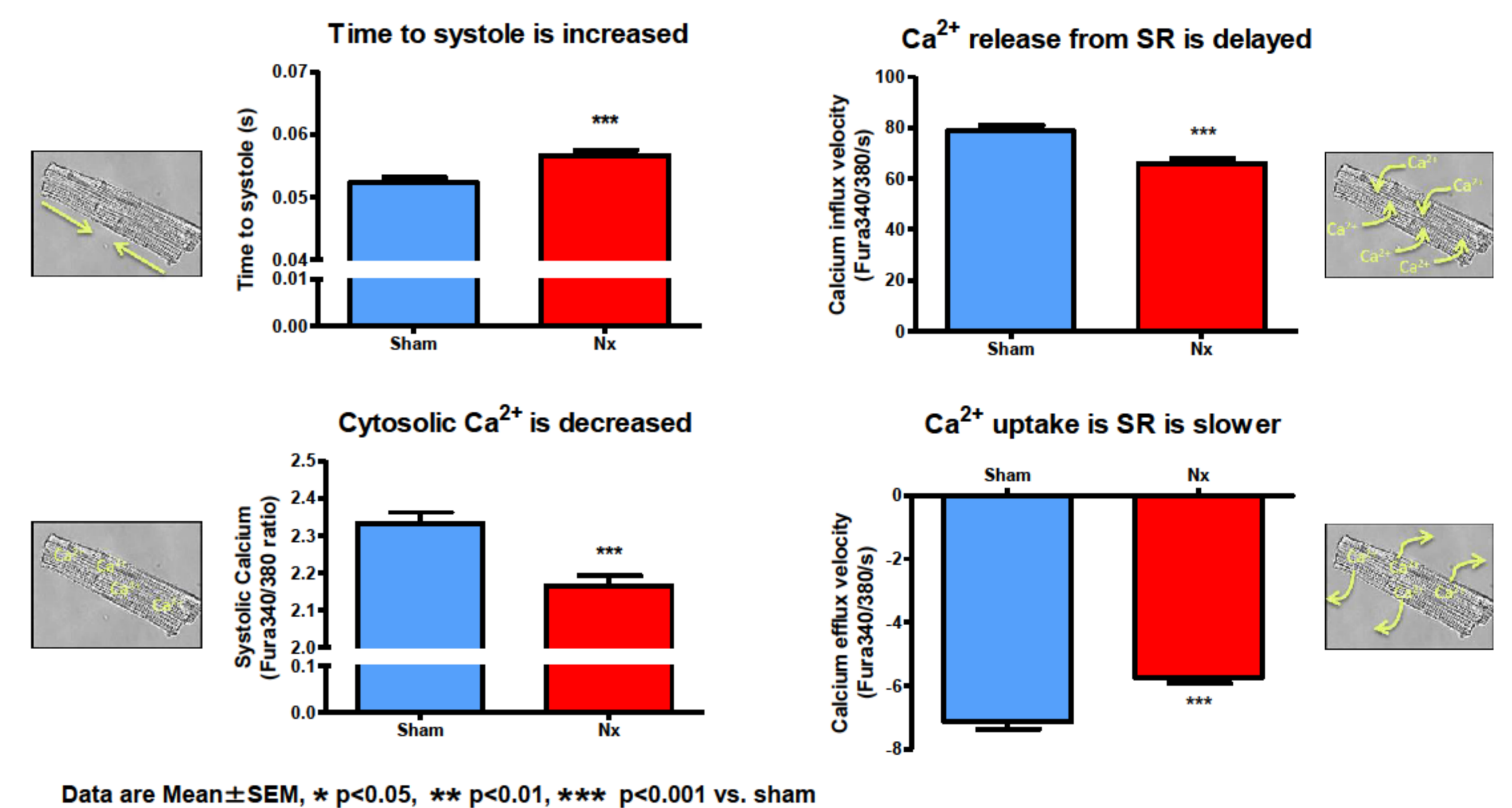


### Microvascular blood volume



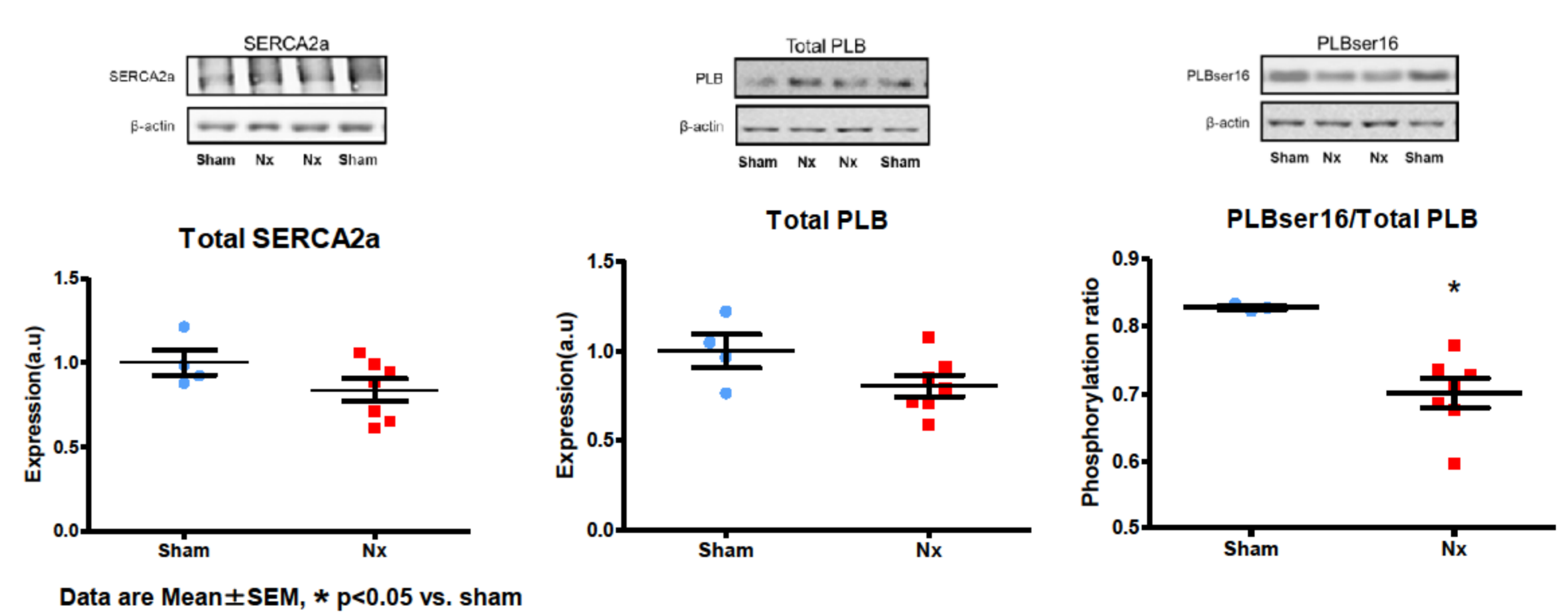
Data are Mean ± SEM, # p<0.05 vs. baseline, \$ p<0.05 vs. sham

Figure 2. Calcium entry and removal velocity is reduced in CKD.



Data are Mean ± SEM, \* p<0.05, \*\* p<0.01, \*\*\* p<0.001 vs. sham

Figure 3. Phosphorylated phospholamban (PLB) is reduced in CKD, resulting in reduced activity of the calcium pump SERCA that pumps calcium back into the sarcoplasmic reticulum (SR).



Data are Mean ± SEM, \* p<0.05 vs. sham

## Conclusion

- CKD compromises myocardial microvascular perfusion reserve.
- CKD reduces Ca<sup>2+</sup> fluxes in cardiomyocytes.
- CKD reduces phosphorylated phospholamban expression, resulting in slower calcium removal.

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