Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation

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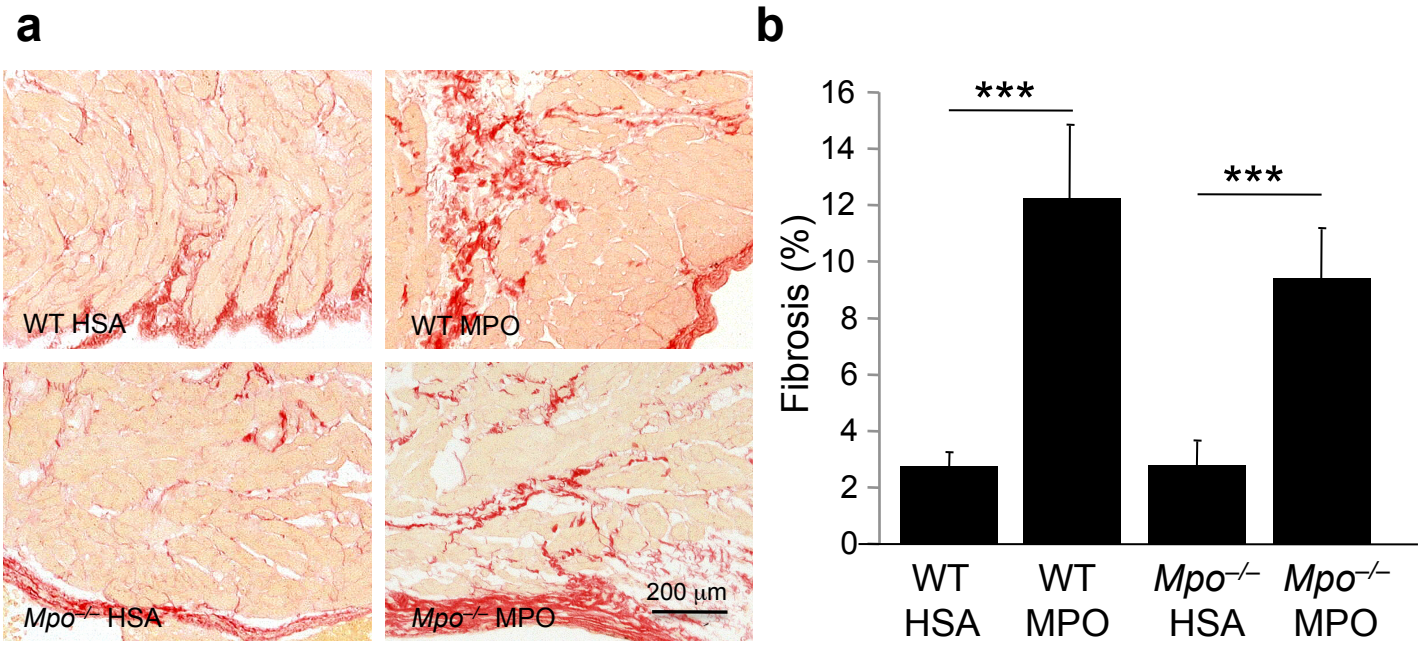
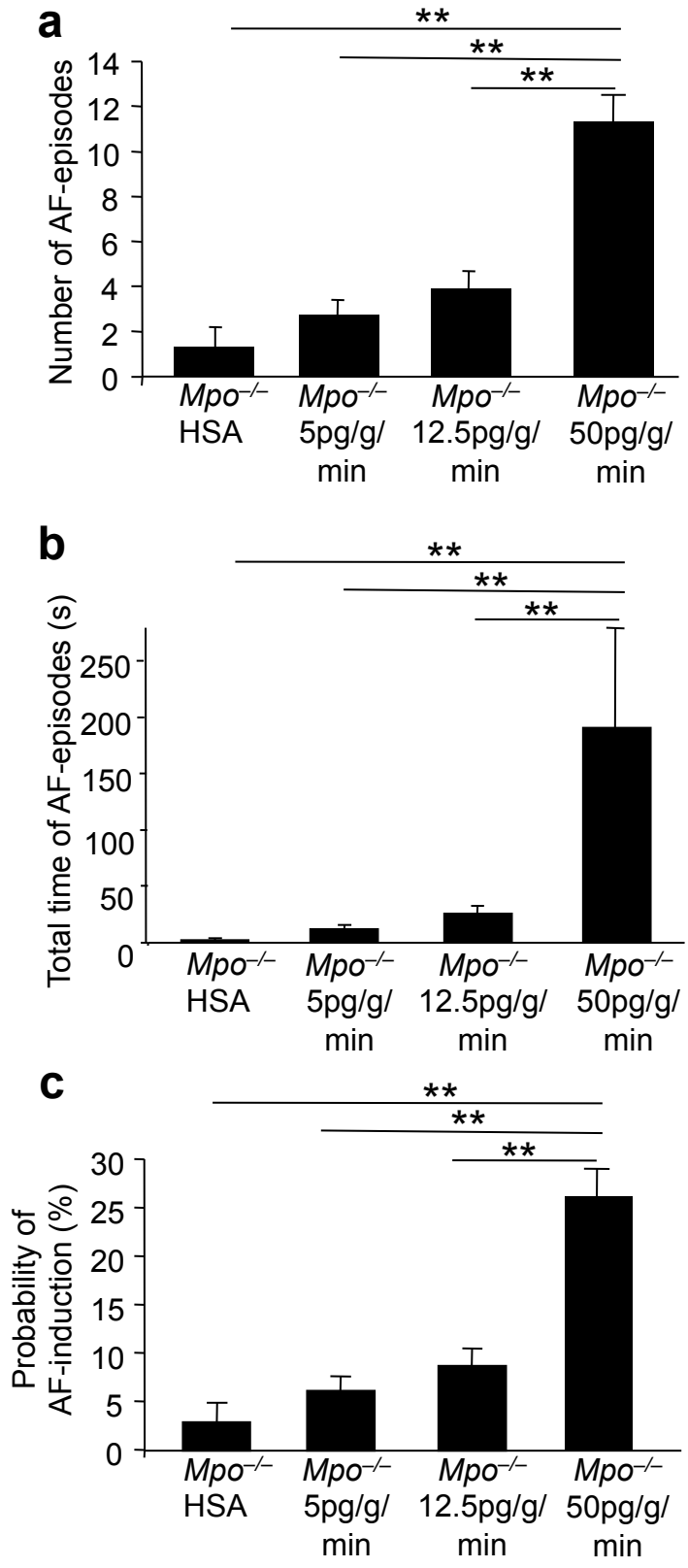
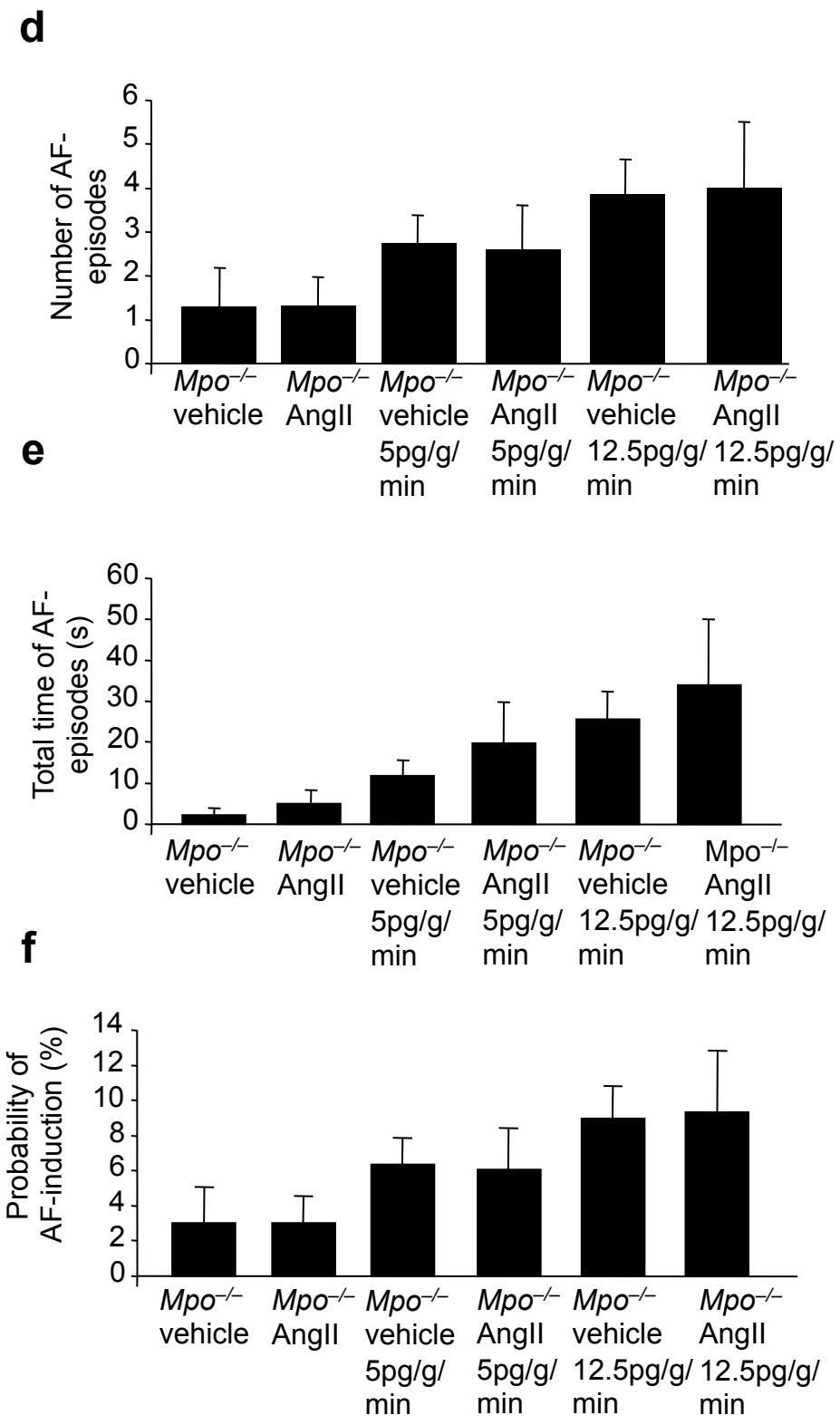


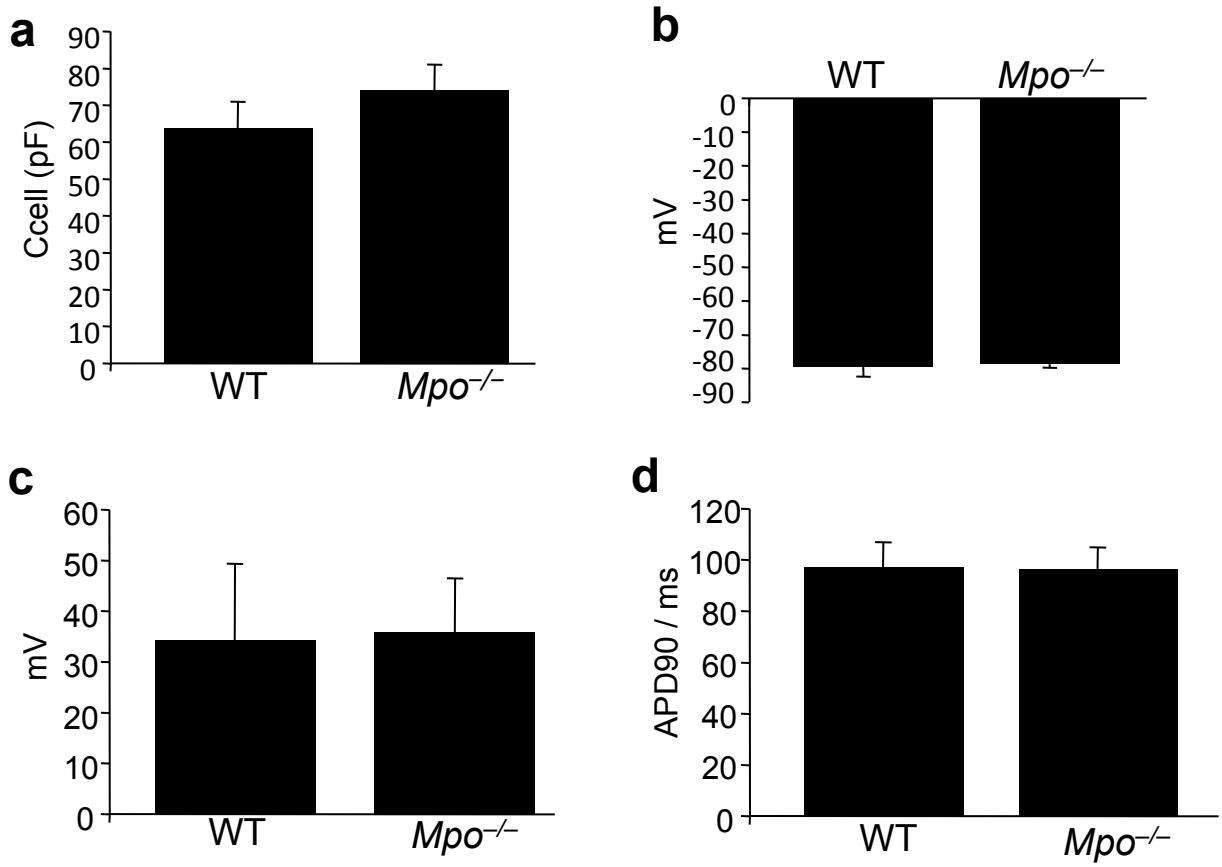
Supplementary Figure 1. Assessment of atrial fibrosis in WT and *Mpo*$^{-/-}$ mice following i.v. HSA or MPO treatment for 7 days. (**a**) Representative picrosirius red stained atria. (**b**) Quantitative analysis. N=6-8, ***P<0.001. ANOVA. All data are expressed as means ± standard deviation.



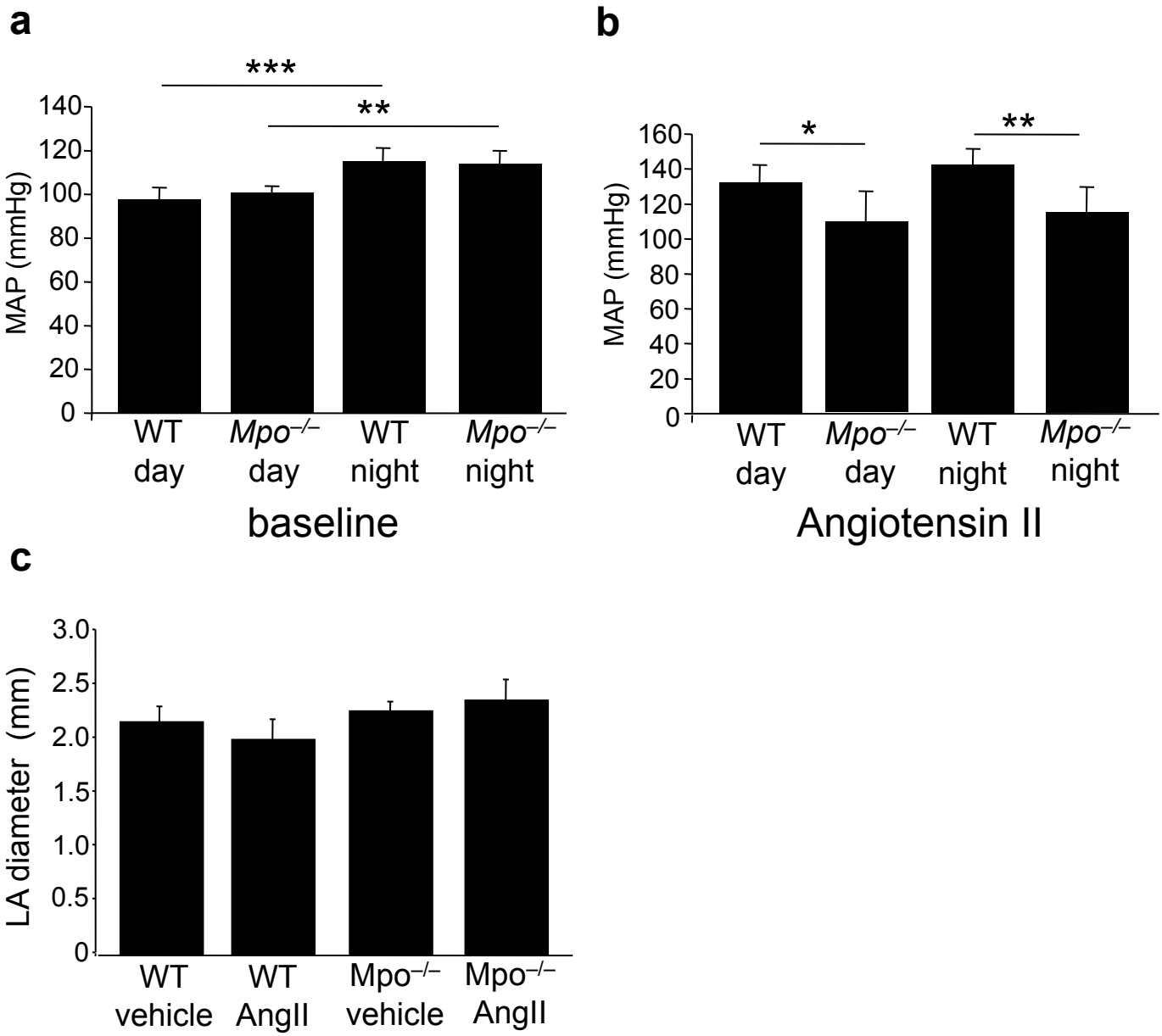
Supplementary Figure 2. see next page for figure legend.



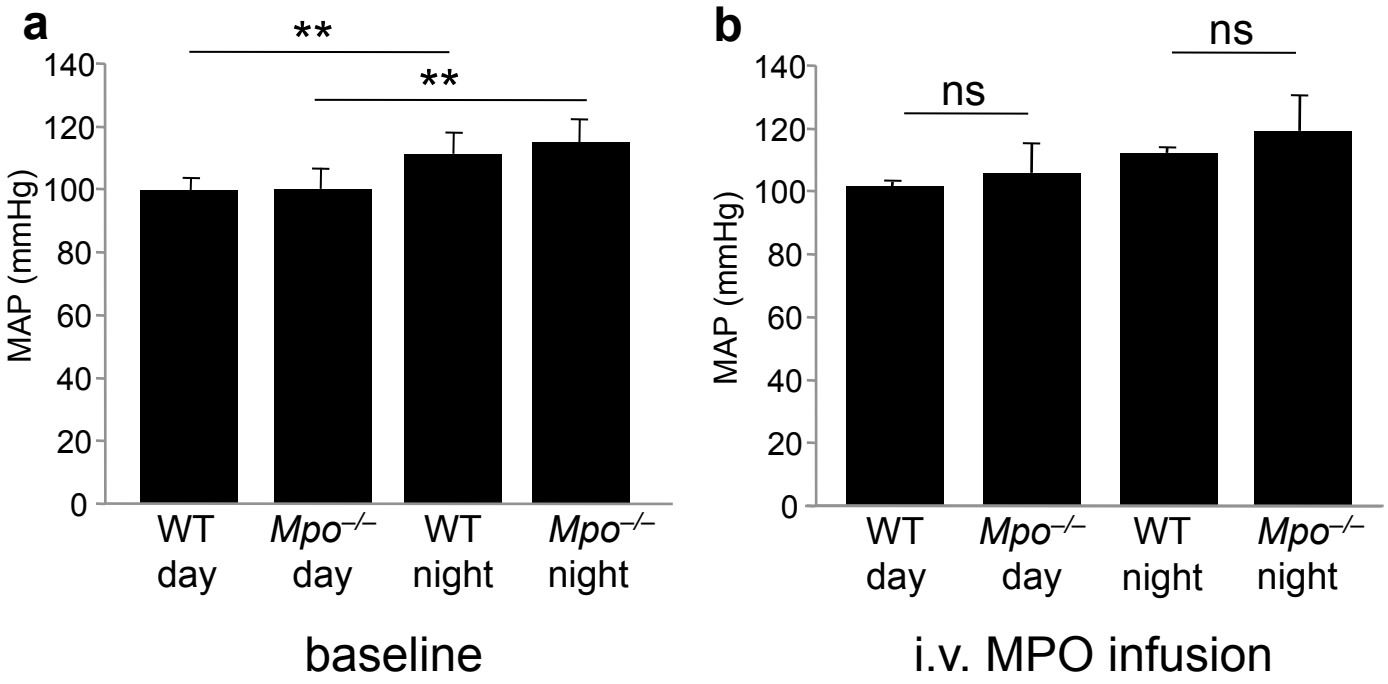
Supplementary Figure 2. Analysis of AF inducibility in Mpo$^{-/-}$ mice following 7 days of continuous i.v. MPO treatment in-vivo. MPO dose is given as pg/g body weight/min (n=10-15 per group). (**a**) Quantification of number of AF-episodes. **P<0.001. P for trend: <0.001 (**b**) Total time of AF-episodes. **P<0.001. P for trend: <0.001 (**c**) Probability of induction of AF. **P<0.001. P for trend: <0.001. (**d-f**) No effect of Ang II on number of AF-episodes (**d**), total time of AF-episodes (**e**) and probability of AF-induction (**f**) also at lower doses of MPO. All data are means ± standard deviation. ANOVA followed by Bonferroni post hoc test.



Supplementary Figure 3. Electrophysiological investigations in isolated cardiomyocytes. (**a**) Cell capacity (Ccell) in cardiomyocytes isolated from untreated WT and Mpo$^{-/-}$ mice. (**b**) Quantification of resting membrane potential. (**c**) Overshoot in WT and Mpo$^{-/-}$ mice. (**d**) Duration of action potential at 90% repolarization (APD90). All data are expressed as means ± standard deviation. Unpaired Stundent‘s t-test.



Supplementary Figure 4. (a) Continuous radiotelemetric blood pressure measurements in WT and *Mpo*$^{-/-}$ mice at baseline and (**b**) following AngII treatment. n=6-7, *P<0.05, **P<0.01, ***P<0.001. ANOVA. (**c**) Echocardiographic assessment of left atrial diameter in WT and *Mpo*$^{-/-}$ mice following saline (vehicle) or AngII treatment. n=8, P=non-significant. ANOVA for intergroup comparisons. Paired student‘s t-test for day to night difference. All data are expressed as means ± standard deviation.



Supplementary Figure 5. (a) Continuous radiotelemetric blood pressure measurements in WT and *Mpo*$^{-/-}$ mice at baseline and (**b**) following continous i.v. MPO treatment for 7 days. N=5-6. **P<0.01. ns P>0.05. ANOVA for intergroup comparisons. Paired student‘s t-test for day to night difference. All data are expressed as means ± standard deviation.

Supplementary Table 1

Rodent electrophysiological parameters.

	WT vehicle (n=13)	**WT AngII (n=16)**	***Mpo*$^{-/-}$ vehicle (n=10)**	***Mpo*$^{-/-}$ AngII (n=10)**
Surface ECG				
Heart rate, min-1	540.8 ± 41.0	526.3 ± 57.1	504.1 ± 43.9	531.2 ± 55.13
P, ms	10.8 ± 1.0	14.1 ± 1.2[1,2]	10.4 ± 0.8	11.2 ± 1.3[3]
PQ, ms	41.2 ± 3.4	40.7 ± 5.7	38.6 ± 2.6	36.7 ± 3.0
Intracardiac ECG				
AH, ms	33.1 ± 3.5	35.2 ± 6.3	33.8 ± 8.9	28.7 ± 3.5
AV, ms	40.7 ± 4.5	43.0 ± 7.7	41.8 ± 10.4	37.4 ± 3.8
EP stimulation				
SNRT, ms (S_1S_1 100 ms)	154.0 ± 32.8	169.6 ± 44.3	178.8 ± 32.7	168.3 ± 46.1
ARP, ms (S_1S_1 100 ms)	19.2 ± 4.4	19.3 ± 7.5	17.0 ± 2.7	15.5 ± 6.9
	WT HSA (n=7)	**WT MPO (n=9)**	***Mpo*$^{-/-}$ HSA (n=6)**	***Mpo*$^{-/-}$ MPO (n=7)**
Surface ECG				
Heart rate, min-1	486.9 ± 46.6	496.2 ± 31.1	519.2 ± 57.4	545.8 ± 34.5
P, ms	10.3 ± 1.0	13.8 ± 1.9[4,5]	11.0 ± 0.85	12.6 ± 1.3[6]
PQ, ms	39.3 ± 4.2	41.8 ± 5.4	39.2 ± 3.3	39.4 ± 4.2
Intracardiac ECG				
AH, ms	34.0 ± 5.3	36.6 ± 6.3	31.8 ± 2.5	29.7 ± 3.8
AV, ms	41.0 ± 6.3	44.1 ± 7.3	38.8 ± 2.5	37.1 ± 3.8
EP stimulation				
SNRT, ms (S_1S_1 100 ms)	180.5 ± 55.5	154.3 ± 30.3	147.8 ± 16.3	143.1 ± 19.7
ARP, ms (S_1S_1 100 ms)	19.2 ± 2.0	18.9 ± 3.3	16.7 ± 2.9	16.4 ± 6.3

All data presented are mean ± standard deviation. EP, electrophysiological; SNRT, sinus node recovery time; ARP, atrial refractory period. [1]P<0.001 vs. WT vehicle, [2]P<0.001 vs. *Mpo*$^{-/-}$ vehicle, [3]P<0.05 vs. WT Ang II, [4]P<0.01 vs. WT HSA, [5]P<0.05 vs. *Mpo*$^{-/-}$ HSA, [6]P<0.05 vs. *Mpo*$^{-/-}$ HSA.

Supplementary Table 2

Patients' characteristics, analysis of plasma

	No AF (n=18)	**AF** (n=24)	**p**
Females	5(27.8)	8(33.3)	0.70
Age	68.5±8.3	70.1±6.8	0.50
BMI	24.2±7.0	24.0±5.4	0.94
Hypertension	15(83.3)	21(87.5)	0.40
Hypercholesterolemia	10(55.5)	10(41.7)	0.28
Diabetes mellitus	2(11.1)	3(12.5)	0.89
Smoking	0(0.0)	0(0.0)	
Family history	13(72.2)	13(54.2)	0.19
ASA	7(38.9)	3(12.5)	0.05
Oral Anticoagulation	6(33.3)	19(79.2)	<0.05
Betablocker	6(33.3)	12(50.0)	0.28
ACE Inhibitor	12(66.6)	10(41.7)	0.11
AT1 Inhibitor	0(0.0)	2(8.3)	0.21
Statin	7(38.9)	8(33.3)	0.71
Hemoglobin, g/dL	14.4±0.9	14.0±1.3	0.22
Leukocyte count, 1000/μl	5.8±1.1	5.8±1.4	0.99
Thrombocyte count 1000/μl	284.2±50.1	257.9±61.5	0.15
Creatinine, mg/dL	1.0±0.5	1.1±0.2	0.41
Total cholesterol, mg/dL	211.3±27.6	193.8±38.7	0.11
LDL cholesterol, mg/dL	110.7±19.9	102.9±30.1	0.35
HDL cholesterol, mg/dL	71.0±15.6	63.0±16.8	0.12
Ejection fraction, %	51.9±9.0	49.3±8.7	0.38
Mitral Regurgitation, I	9(50.0)	12(50.0)	0.43
II	2(11.1)	6(25.0)	
Left atrial diameter, mm	44.2±4.3	44.4±4.8	0.91
Pacemaker intervention rate, min^{-1}	57.5±15.7	57.5±13.6	1.00

Values are given as n(%) or mean ± standard deviation. ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; AT1, angiotensin II type 1; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein.

Supplementary Table 3

Patients' characteristics, analysis of atrial tissue

	No AF (n=17)	AF (n=10)	P
Females	4(23.5)	4(40)	0.37
Age, years	68.6±13.8	71.0±6.5	0.60
Hypertension	10(58.8)	7(70.0)	0.69
Hypercholesterolemia	6(35.3)	3(30.0)	0.78
Diabetes mellitus	3(17.6)	2(20.0)	0.89
Smoking	5(29.4)	1(10.0)	0.36
ASA	14(82.4)	1(10.0)	<0.05
Betablocker	12(70.6)	4(40.0)	0.22
ACE Inhibitor	10(58.8)	6(60.0)	0.95
Statin	13(76.5)	5(50.0)	0.22
Hemoglobin, g/dL	13.6±1.9	13.0±1.2	0.41
Leukocyte count, 1000/ml	7.59±1.98	7.58±2.1	0.99
Creatinine, mg/dL	1.16±0.36	1.14±0.41	0.86

Values are given as n(%) or mean ± standard deviation. ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme.