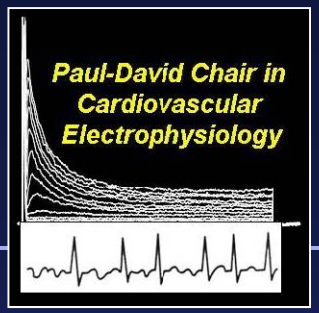


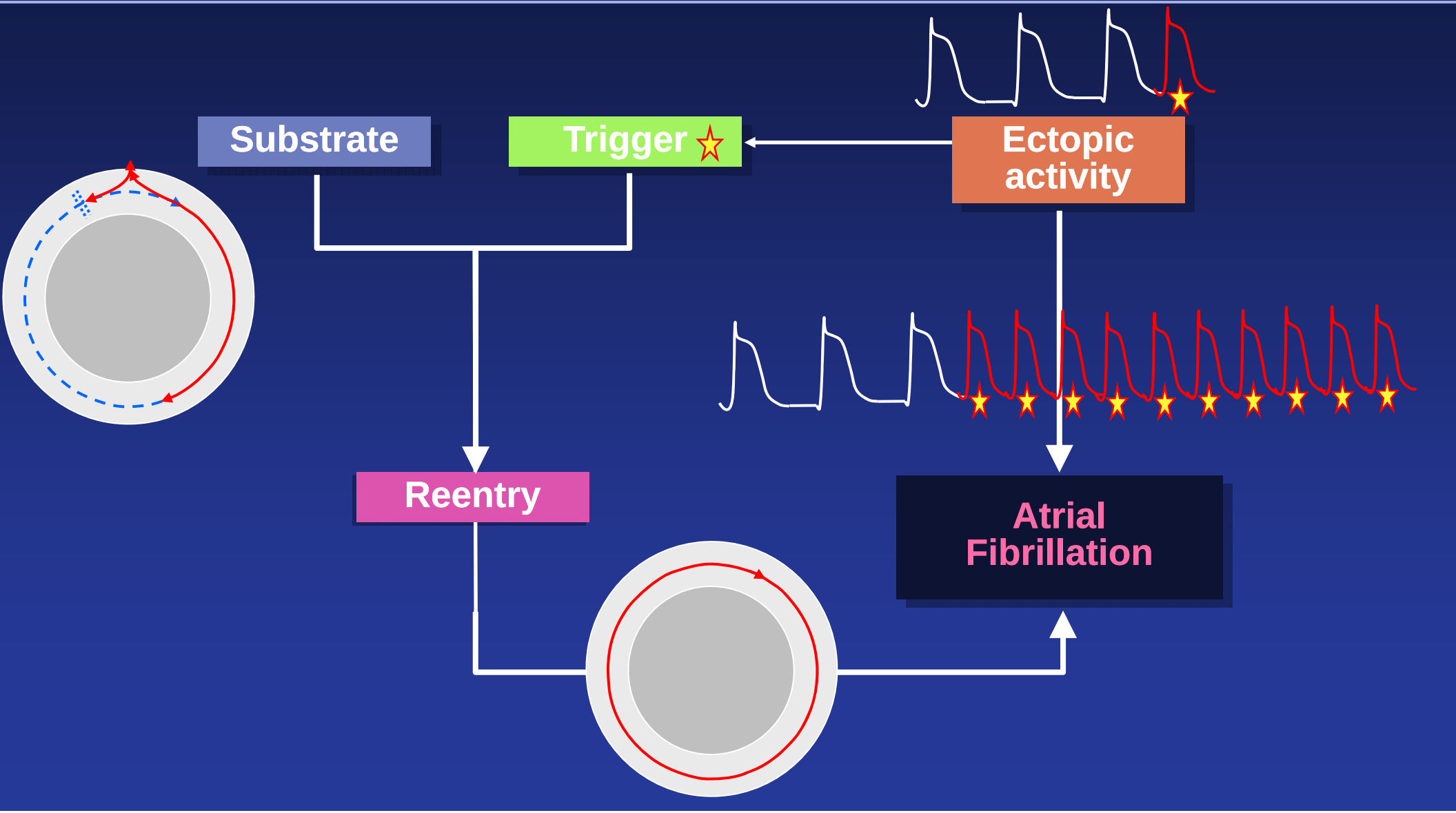
Novel approaches to preventing atrial fibrillation progression: Role of microRNAs

Stanley Nattel, MD

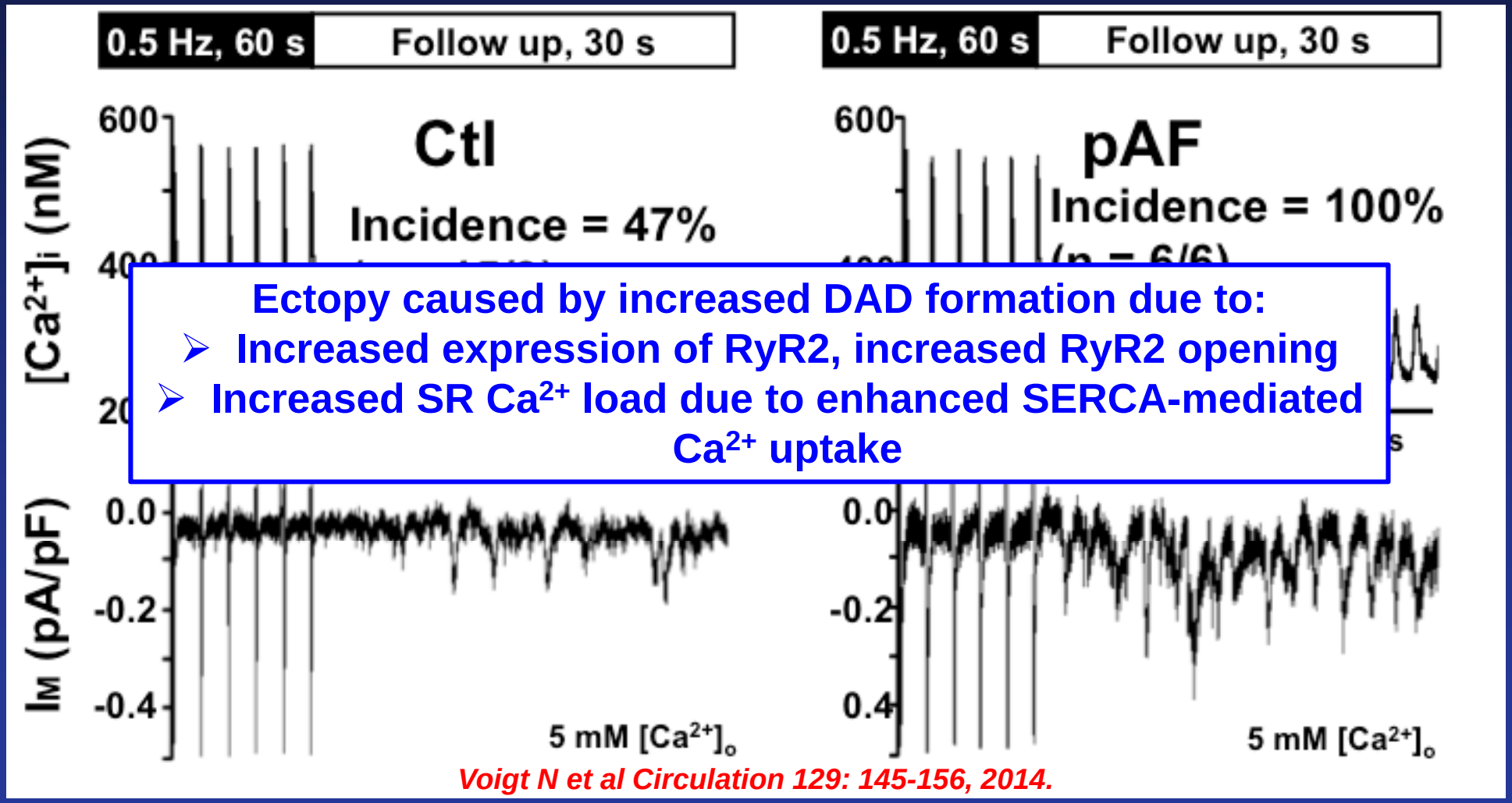
Montreal Heart Institute

University of Montreal

Determinants of Arrhythmia Mechanisms in AF



Mechanism of ectopic activity



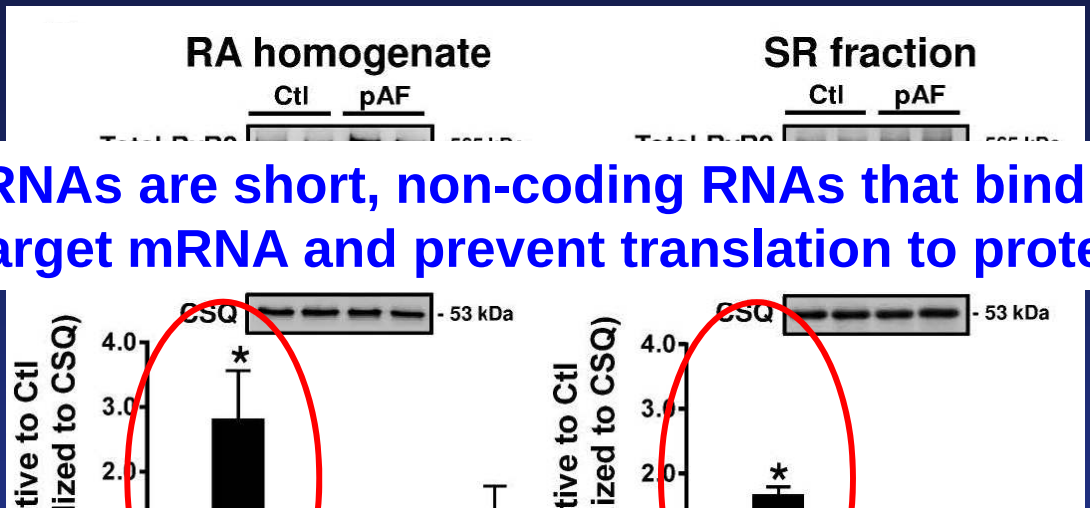
Ectopy caused by increased DAD formation due to:

- **Increased expression of RyR2, increased RyR2 opening**
- **Increased SR Ca^{2+} load due to enhanced SERCA-mediated Ca^{2+} uptake**

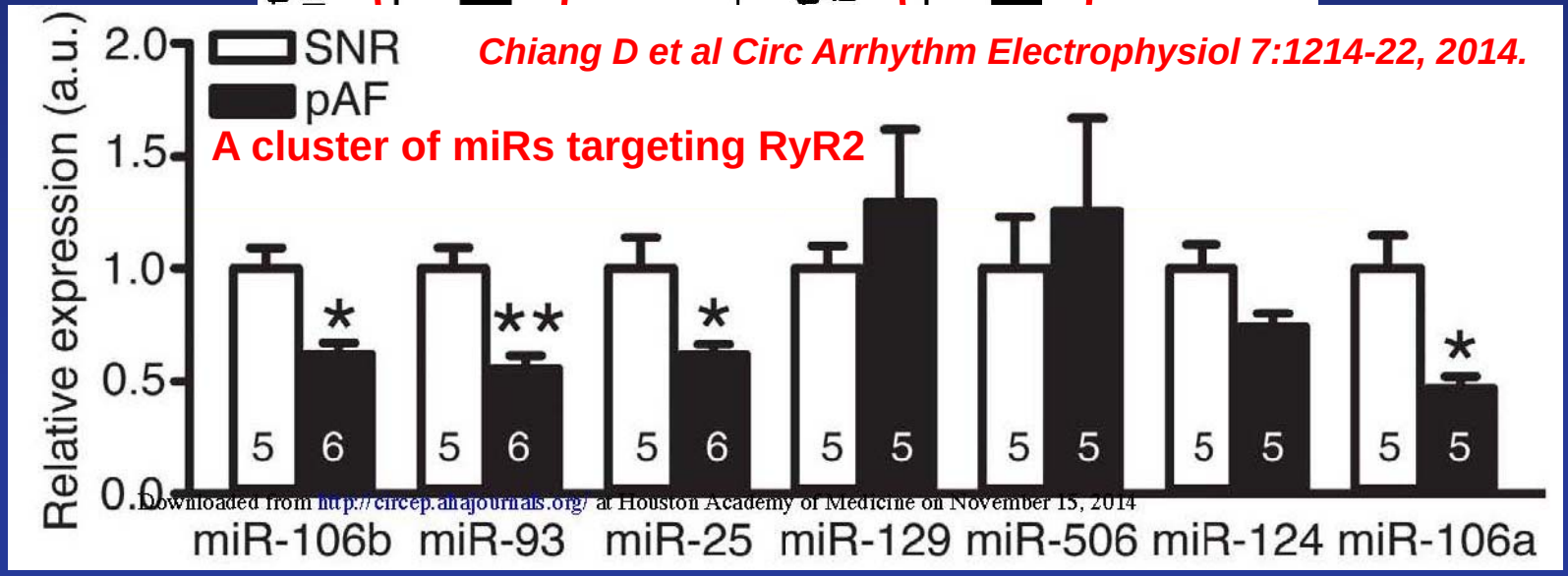
Voigt N et al Circulation 129: 145-156, 2014.

Molecular basis of Ca^{2+} mishandling/DADs in pAF: RyR2 upregulation

MicroRNAs are short, non-coding RNAs that bind to their target mRNA and prevent translation to protein

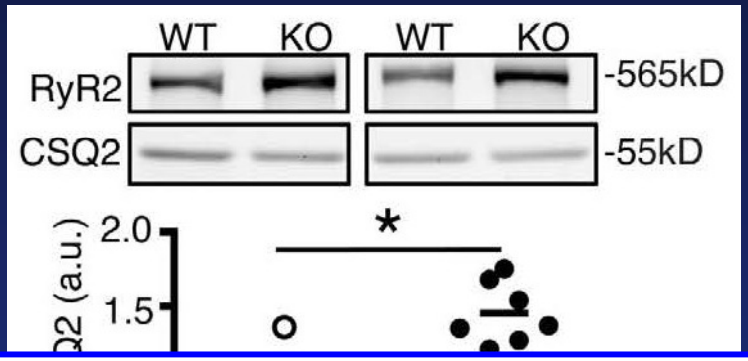


Chiang D et al Circ Arrhythm Electrophysiol 7:1214-22, 2014.

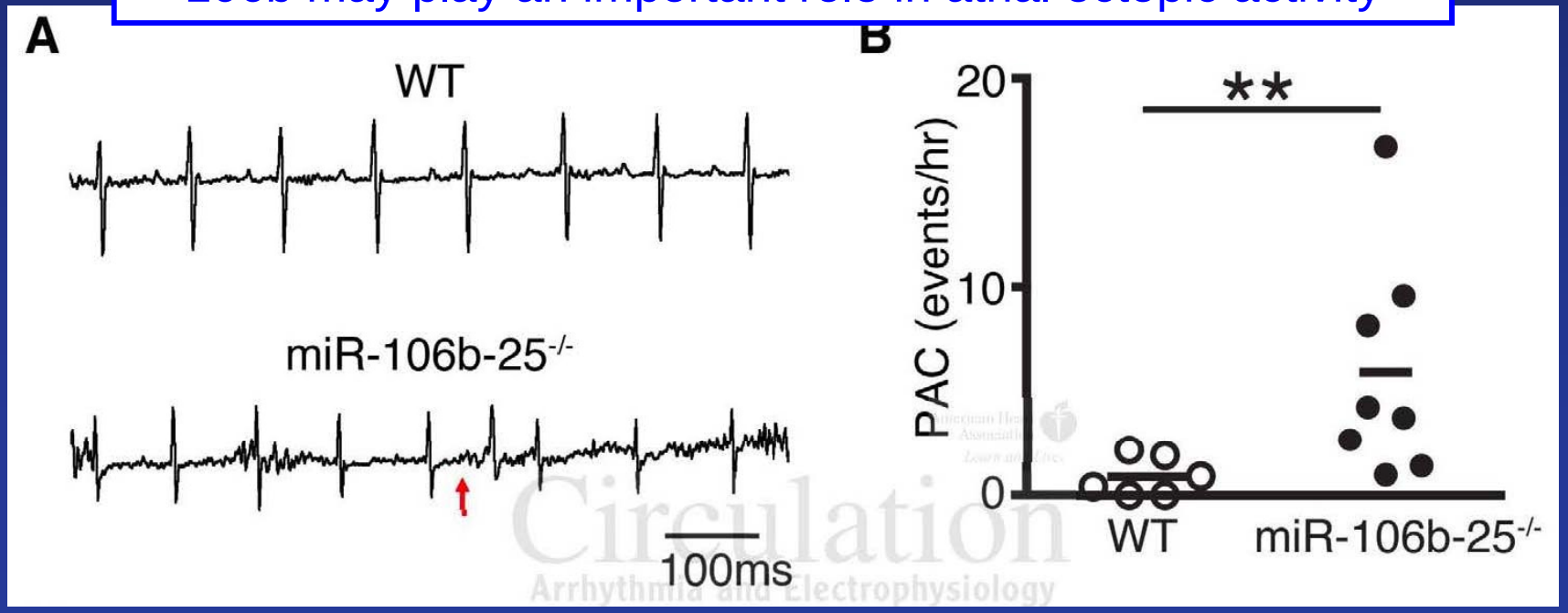


Chiang D et al Circ Arrhythm Electrophysiol 7:1214-22, 2014.

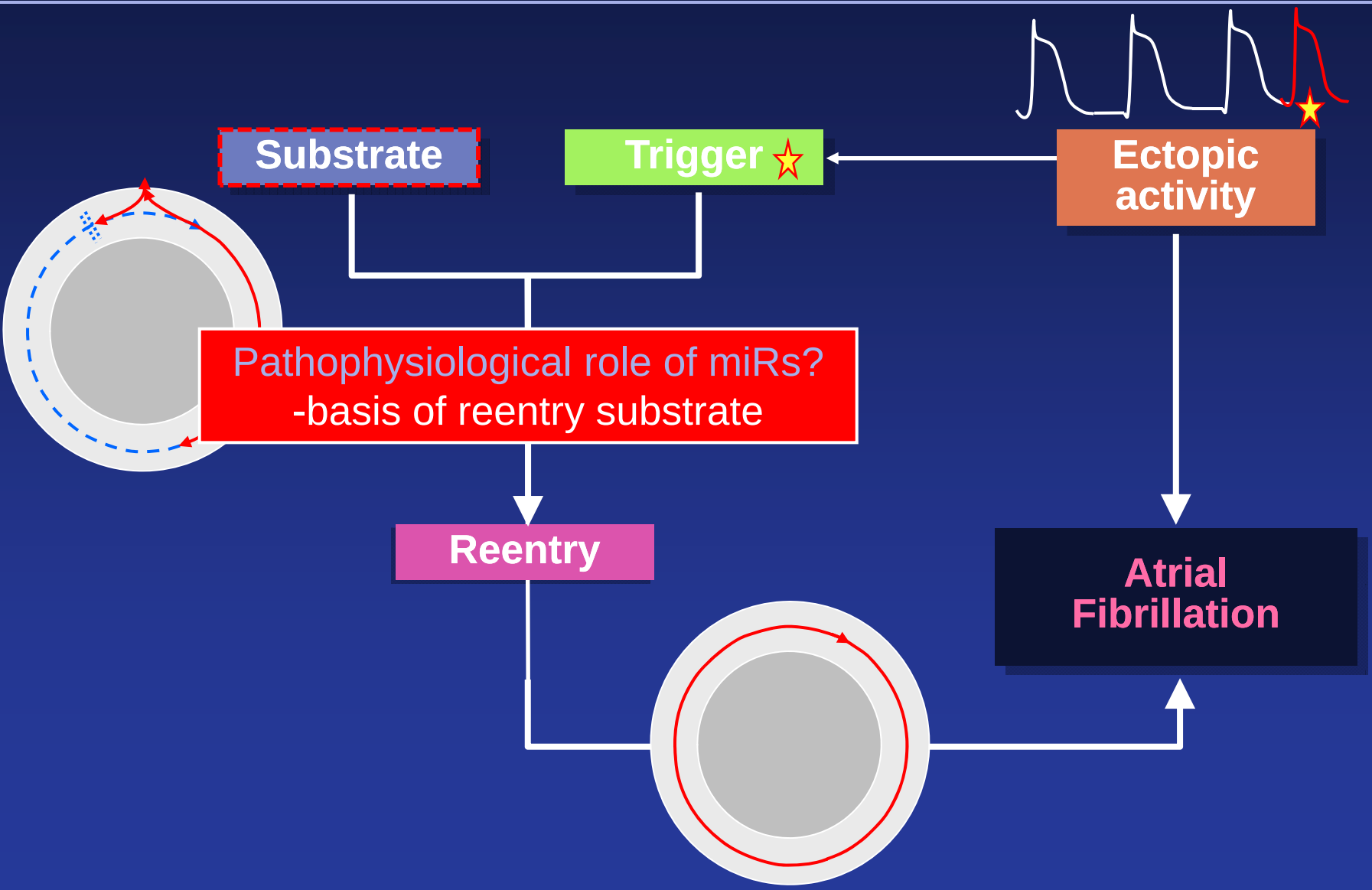
Mechanism of RyR2 dysfunction: Role of miR-106



Therefore, downregulation of microRNAs related to miR-106b may play an important role in atrial ectopic activity

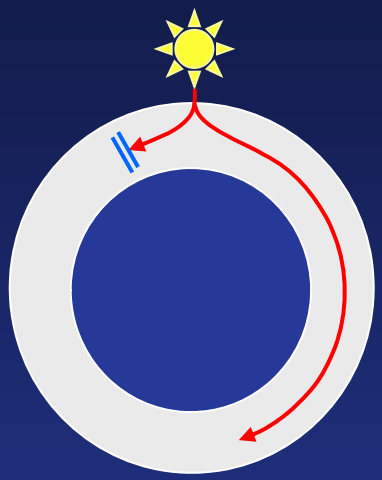


Determinants of Arrhythmia Mechanisms in AF

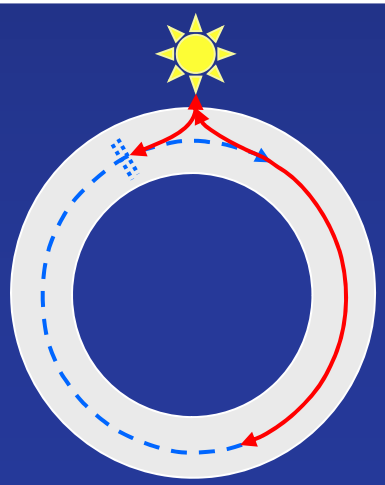


Substrate for Reentry in AF

A



B

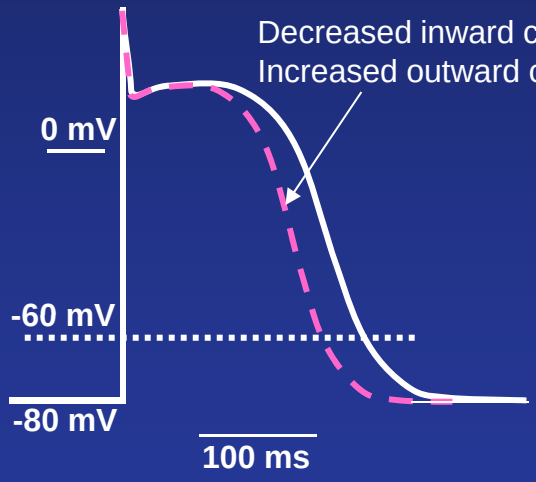


Fundamental determinants of reentry:
-short ERP
-slow conduction velocity

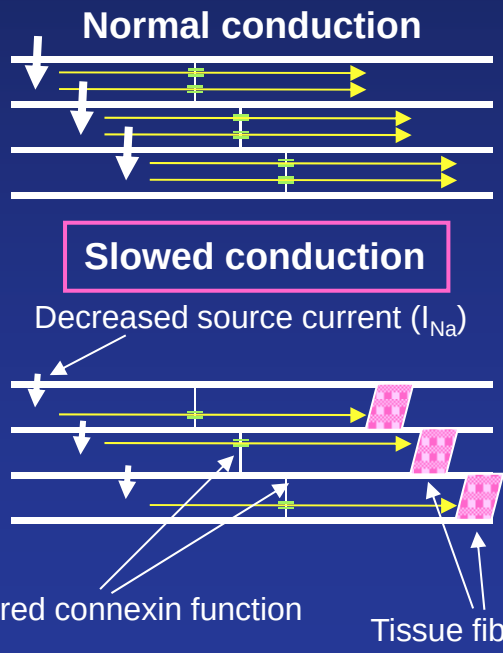
How remodeling promotes reentry

C

Shortened refractory periods

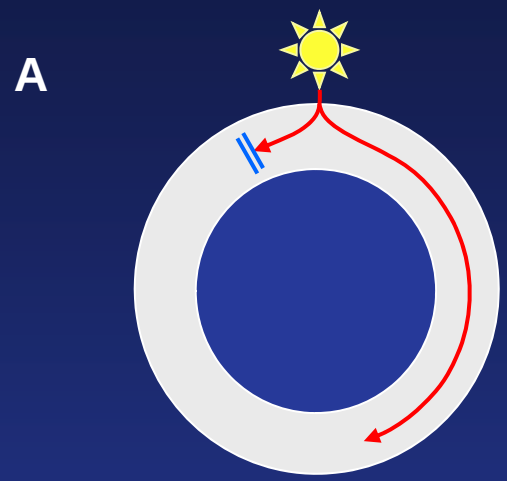


D



Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

Reentry substrate in AF: Changed refractoriness or conduction



Fundamental determinants of reentry:
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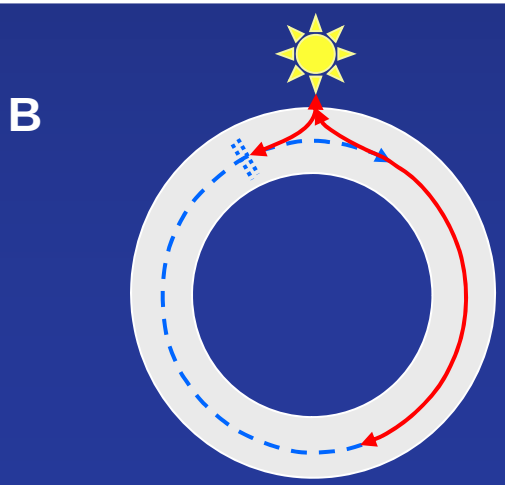
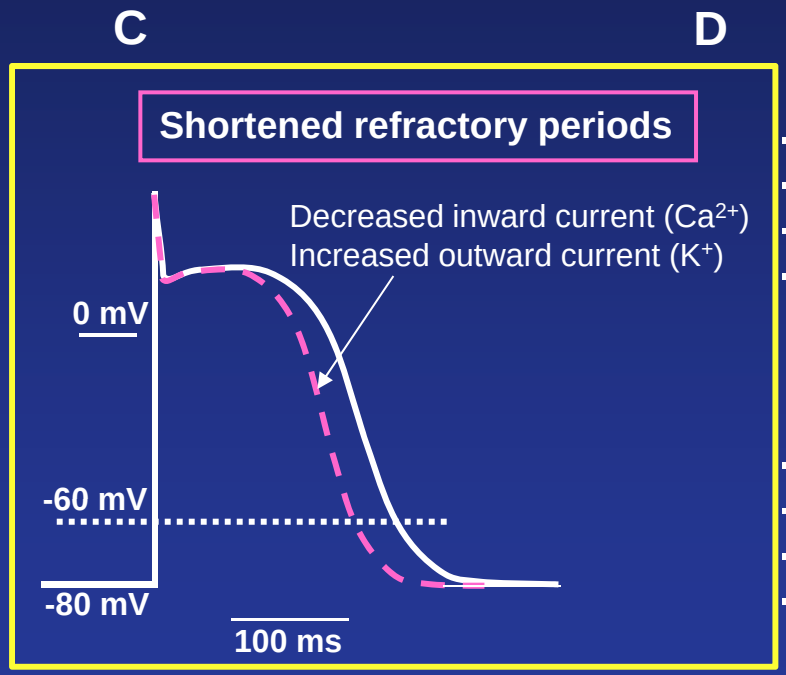
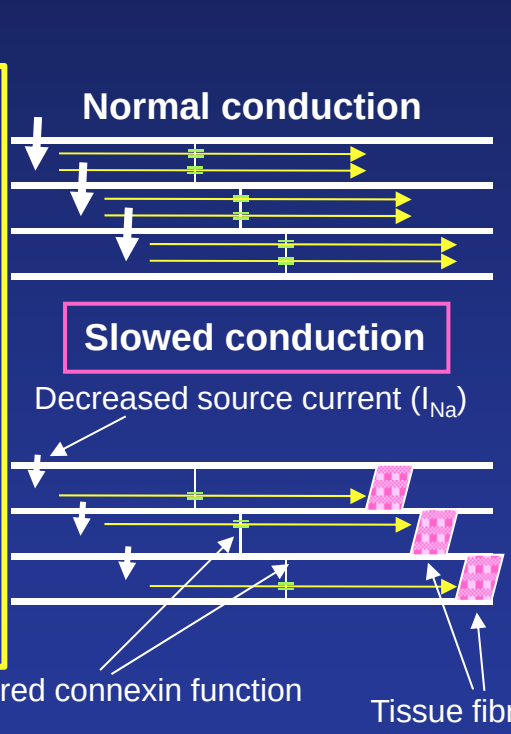


How remodeling promotes reentry





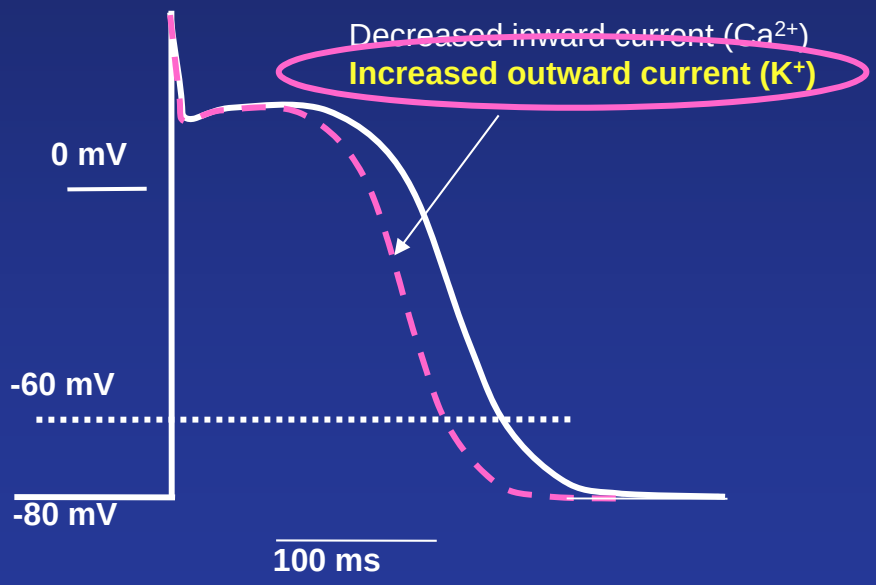
Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

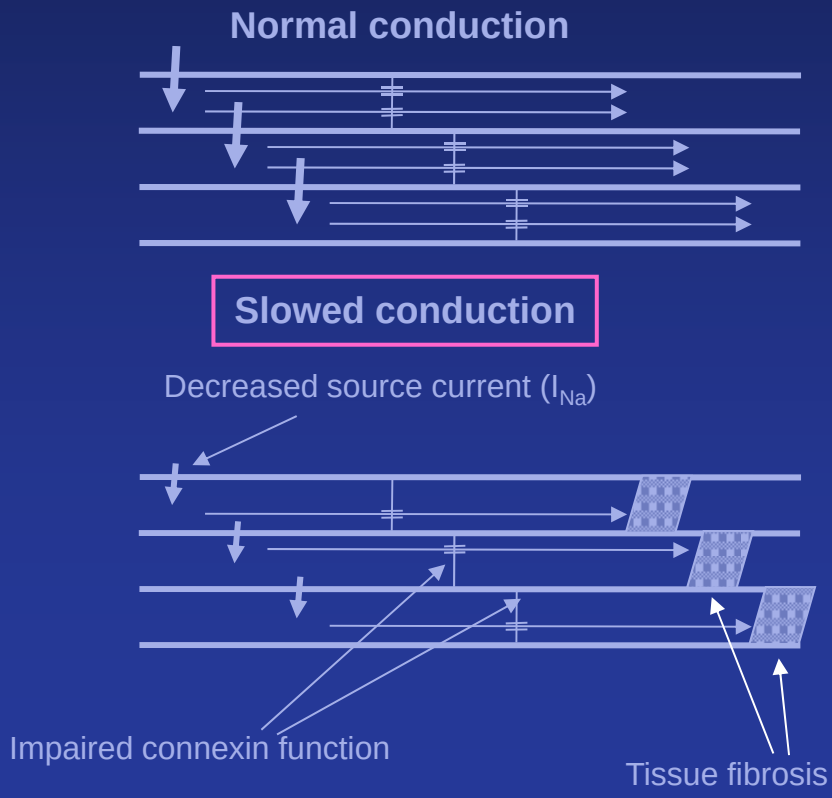
MicroRNAs implicated in AF via remodeling of APD/refractoriness

Substrate for Reentry in AF

How remodeling promotes reentry

Shortened refractory periods

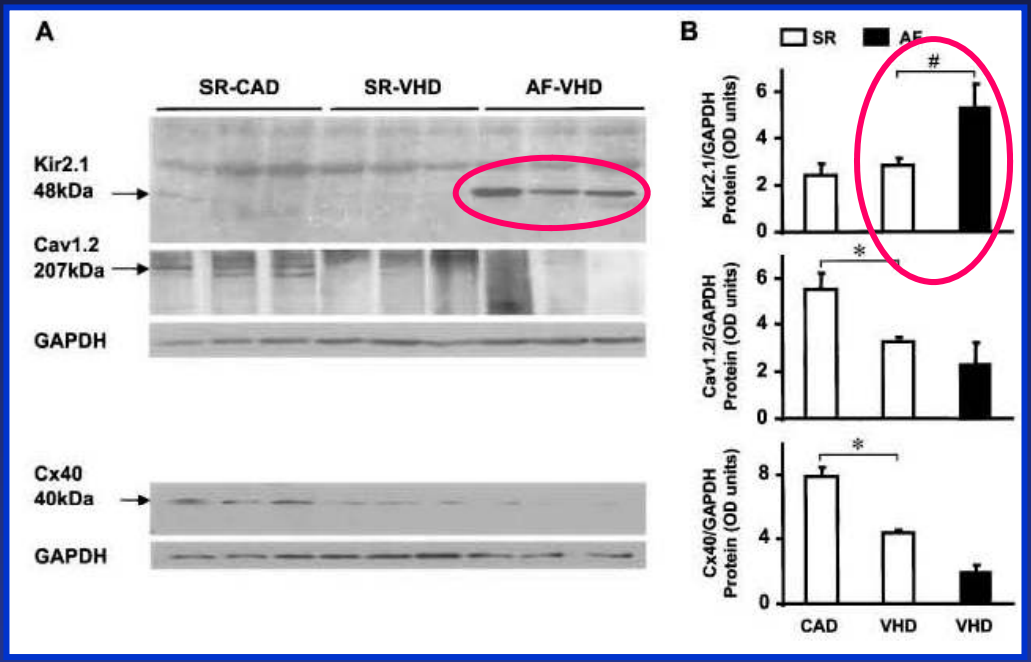




Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

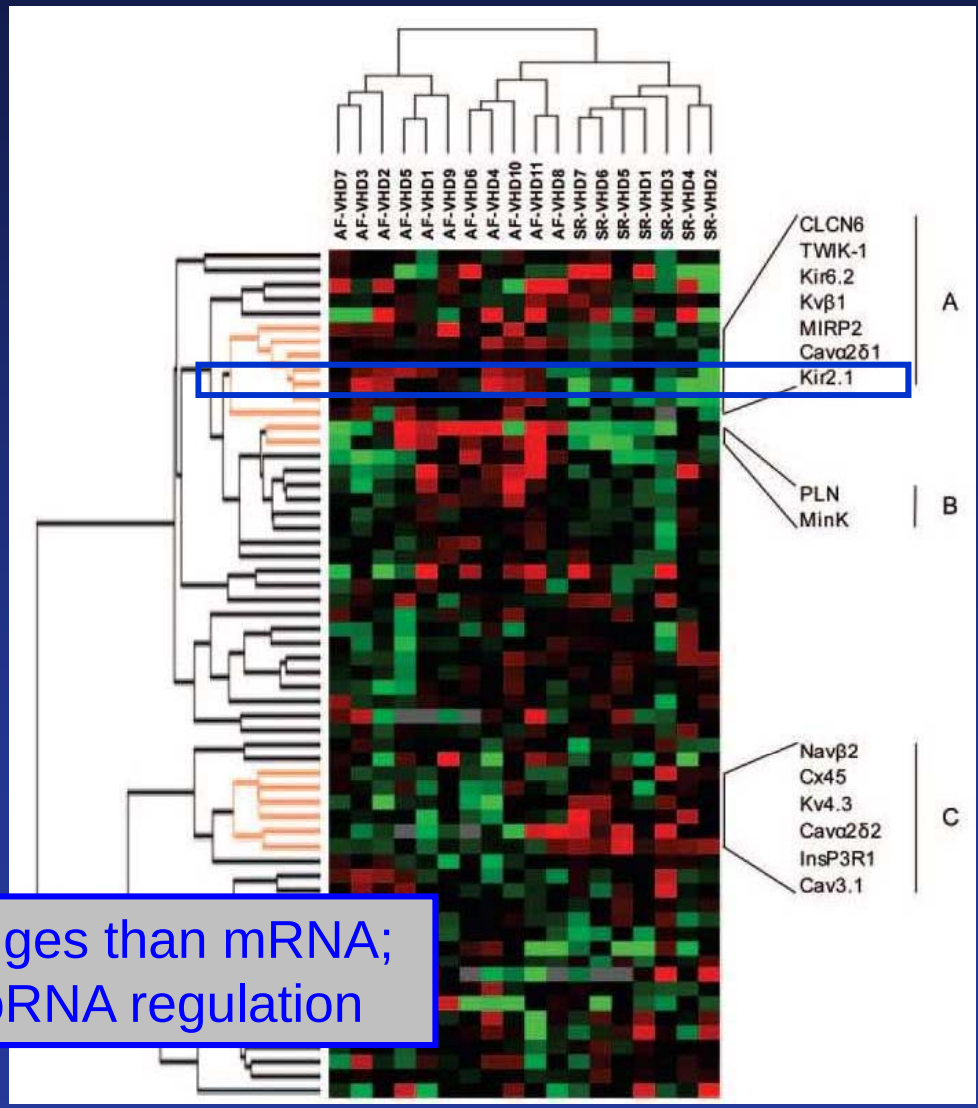
-Kir2.1 mRNA increased about 20-25% in AF

Molecular basis of I_{K1} upregulation?



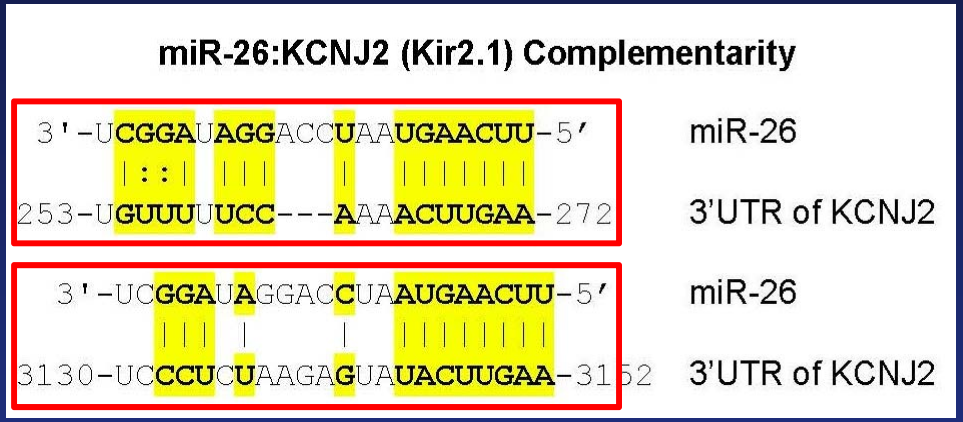
-Kir2.1 protein increased about 100% in AF
-similar change to I_{K1} upregulation

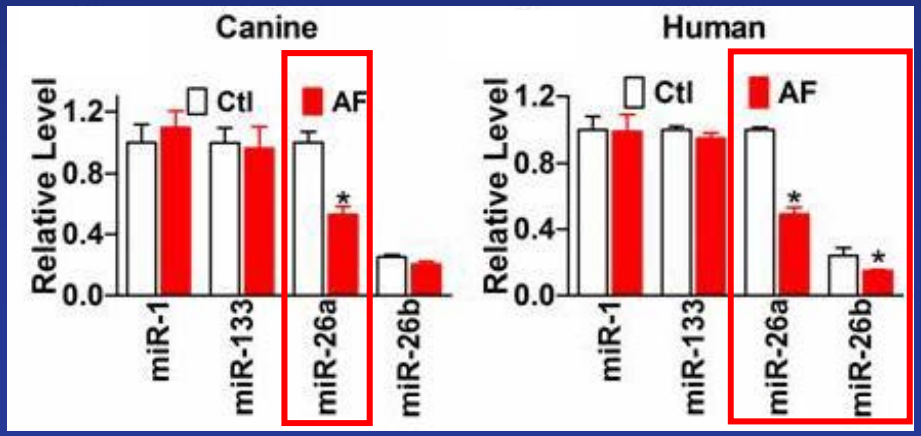
Greater protein changes than mRNA; suggestive of microRNA regulation



GABORIT ET AL, *Circulation. 2005 Jul 26;112(4):471-81.*

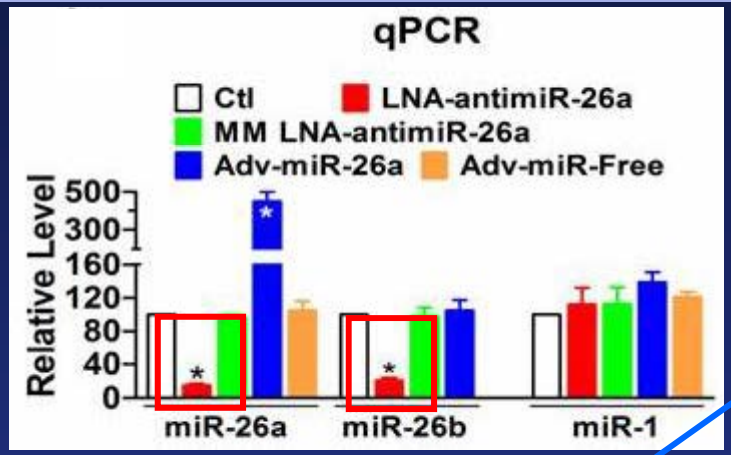
A miRNA potentially involved in I_{K1} upregulation in AF





Luo X et al, J Clin Invest 123:1939-51, 2013

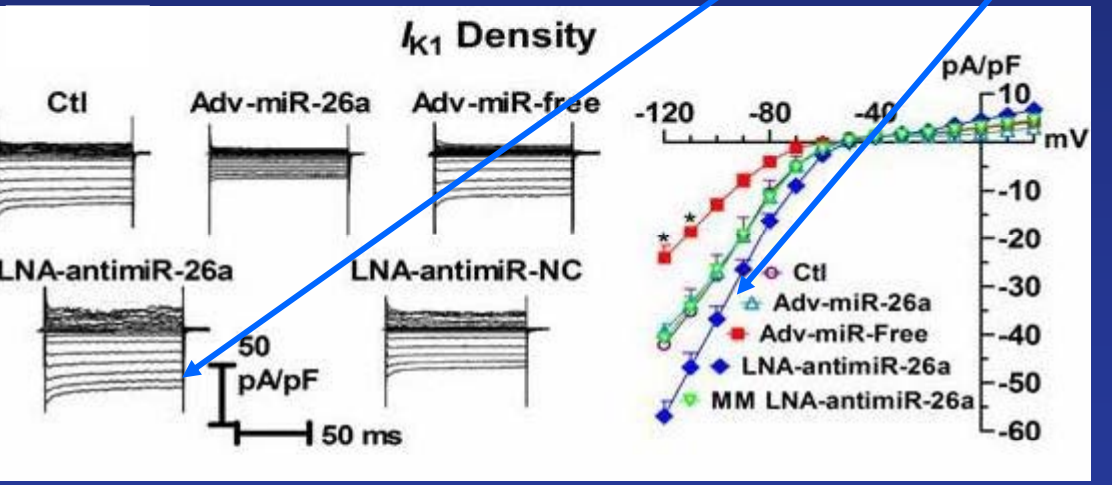
Manipulating miR-26 in vivo changes I_{K1} and profoundly regulates AF susceptibility

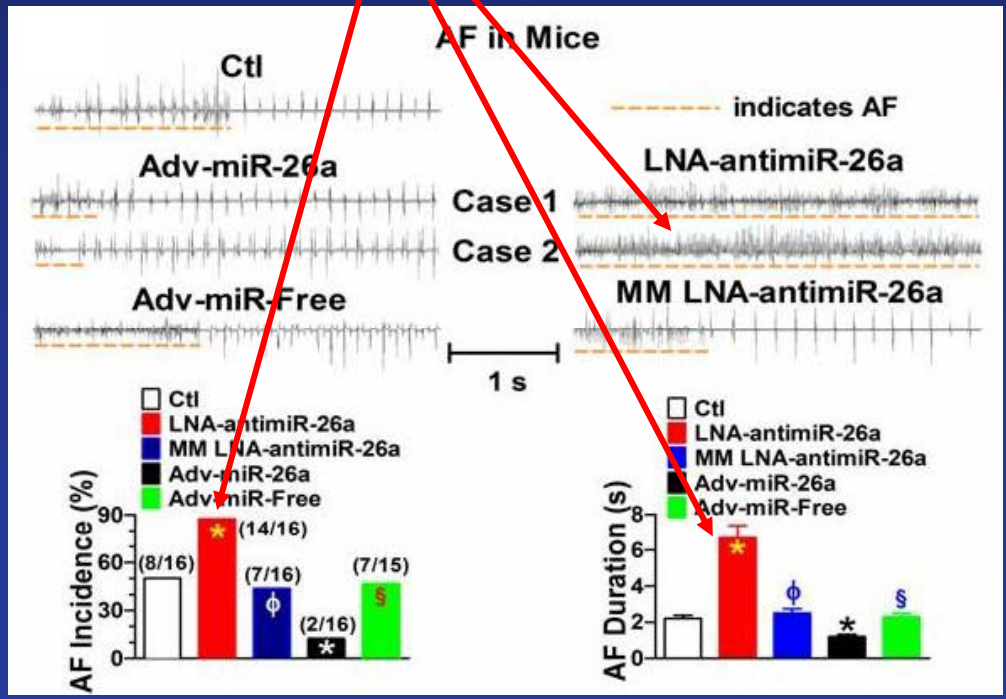


Mimicked AF-related miR-26 downregulation by tail vein injection of antimiR to mice

In vivo miR-26 downregulation upregulated IK1

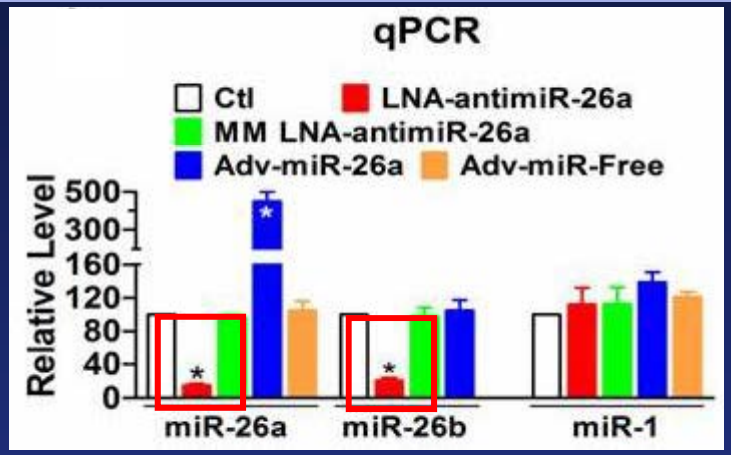
And promoted AF.



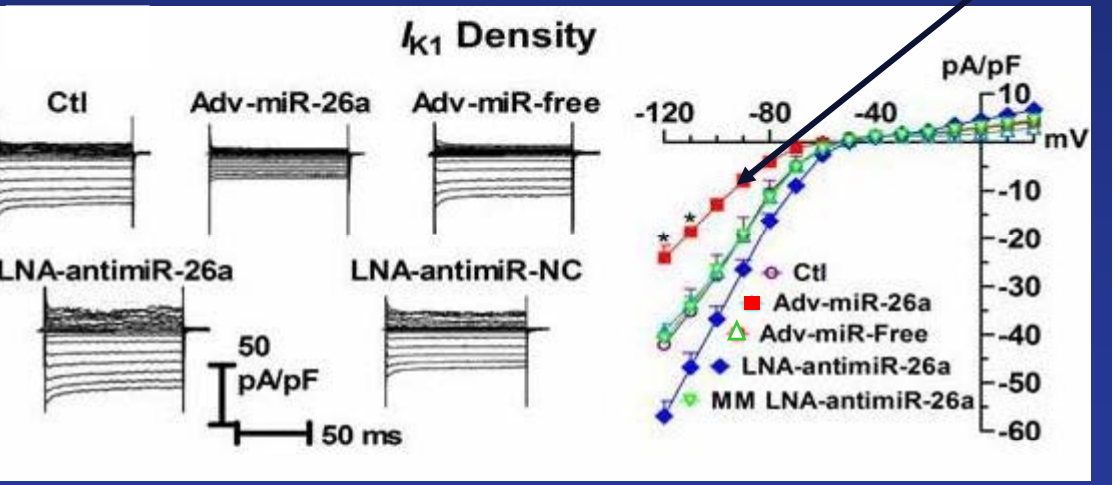


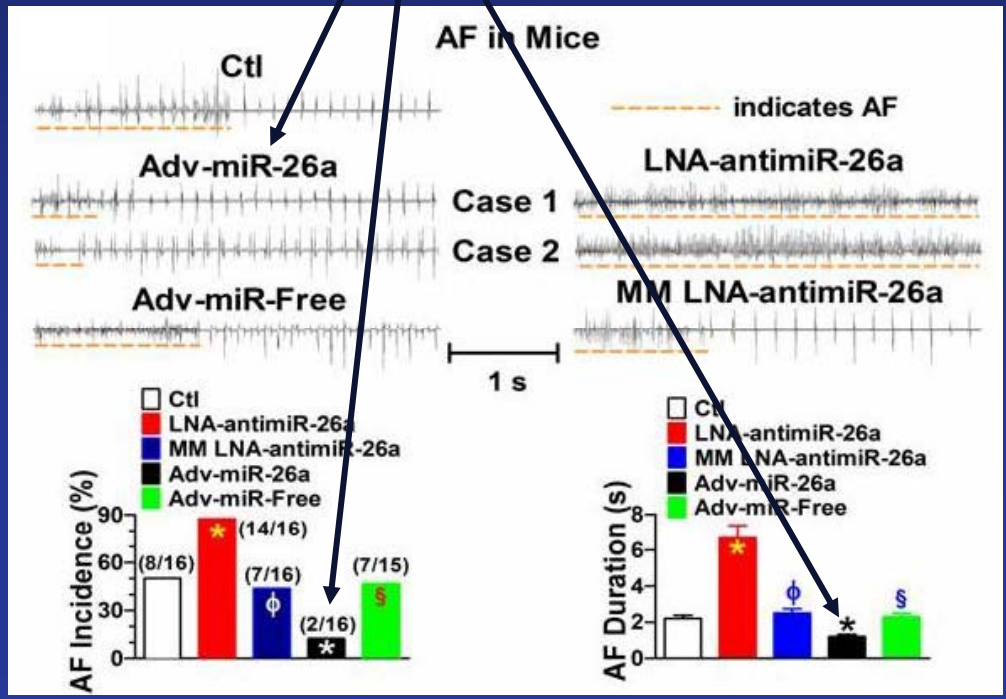
Luo X et al, JCI, J Clin Invest 123: 1939-1951, 2013 .

Manipulating miR-26 in vivo changes I_{K1} and profoundly regulates AF susceptibility



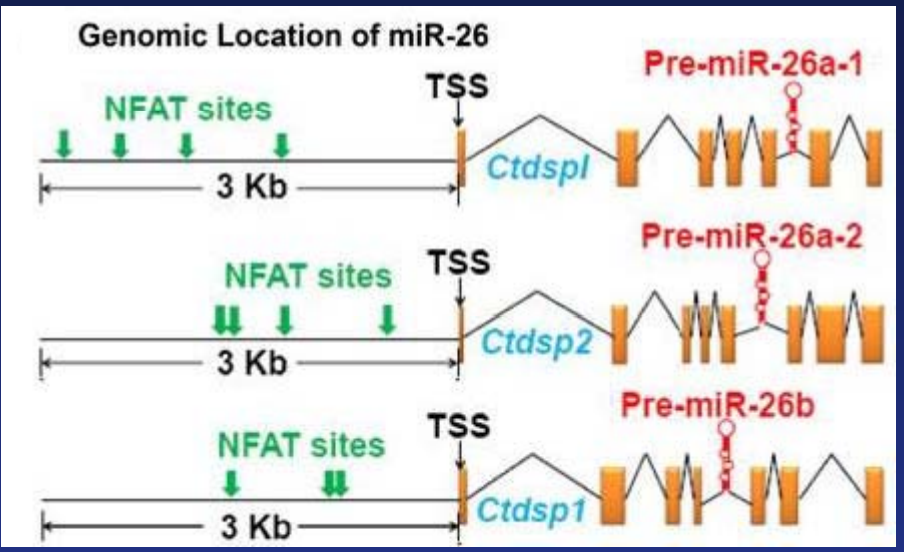
In vivo miR-26 overexpresssion reduced I_{K1} and suppressed AF.





Luo X et al, *JCI, J Clin Invest 123: 1939-1951, 2013 .*

Relating miR-26 and I_{K1} changes back to AF related remodeling: what downregulates miR-26?



NFAT

Kir2.1 ⊣ miR-26

Luo X et al, J Clin Invest 123:1939-51, 2013

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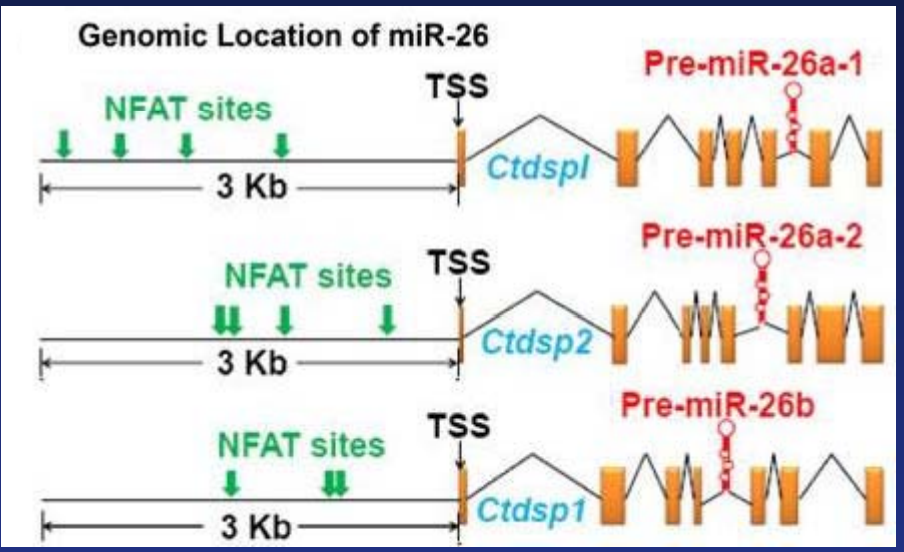
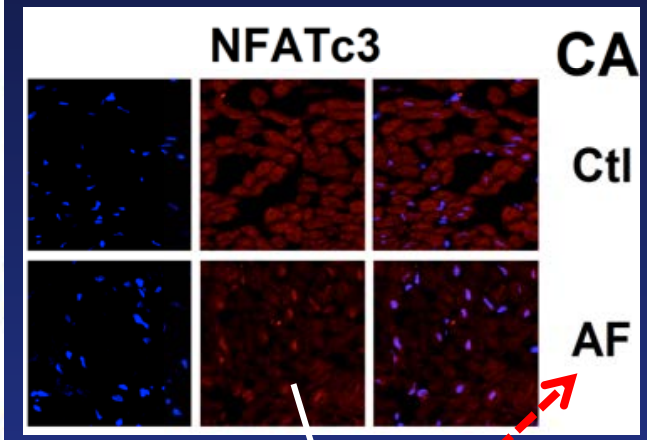
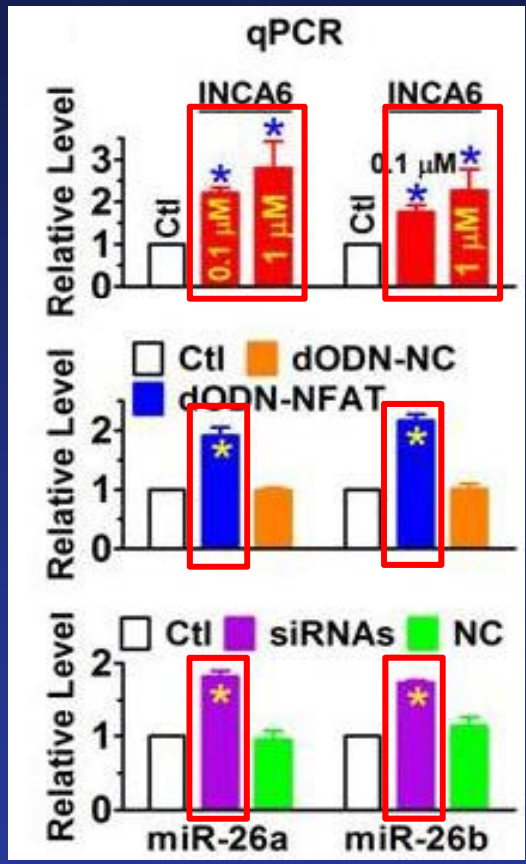
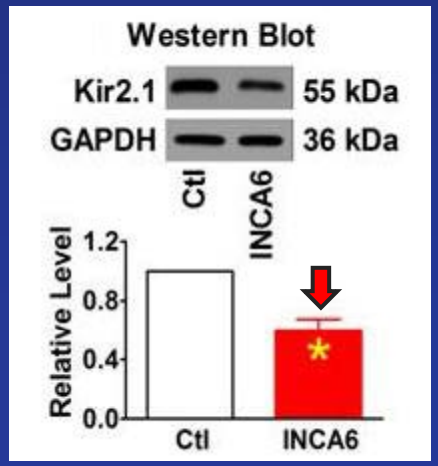
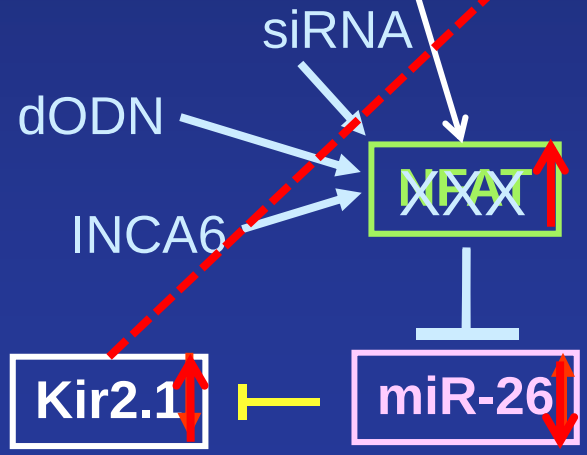




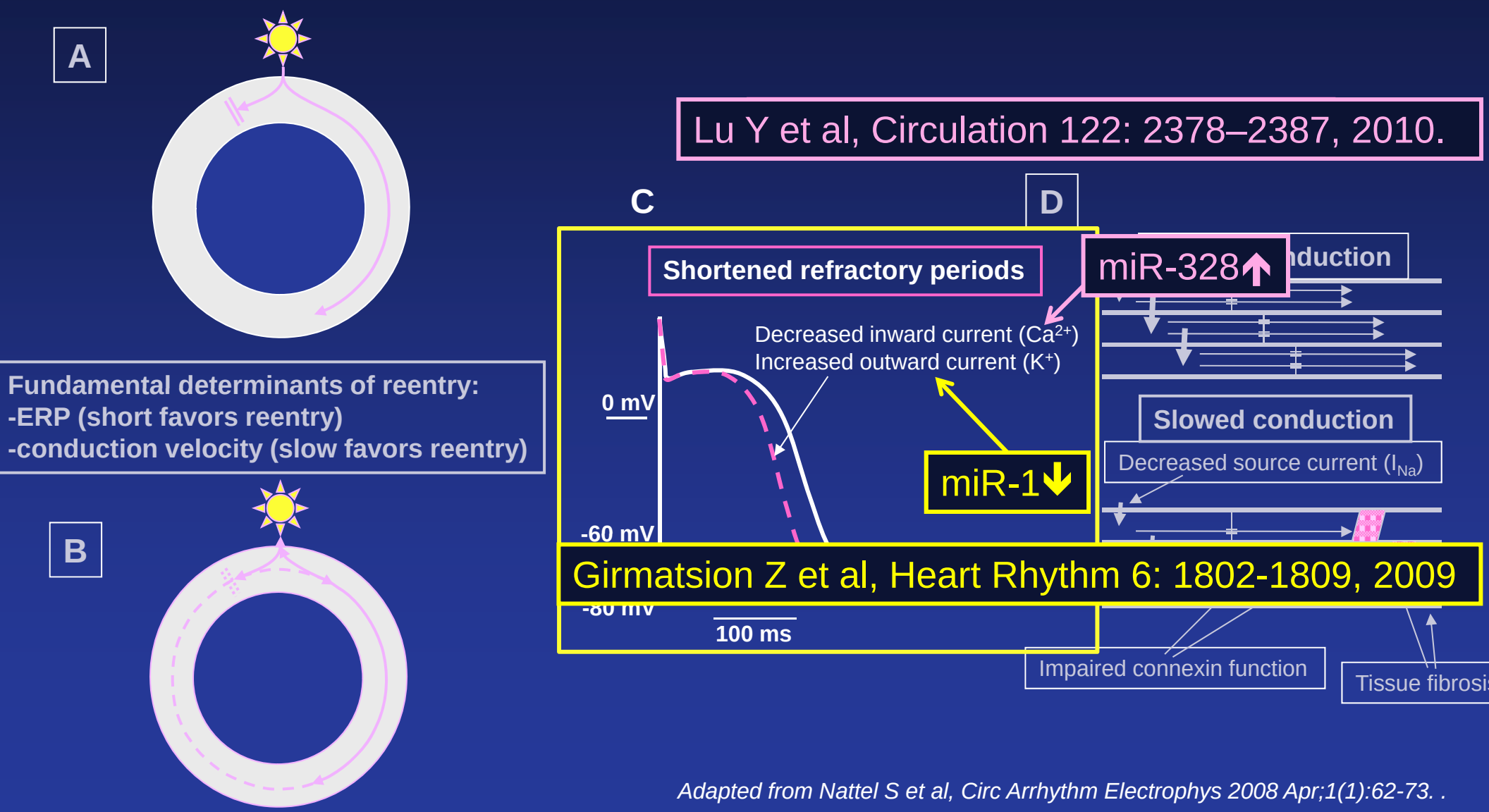






Luo X et al, J Clin Invest 123:1939-51, 2013

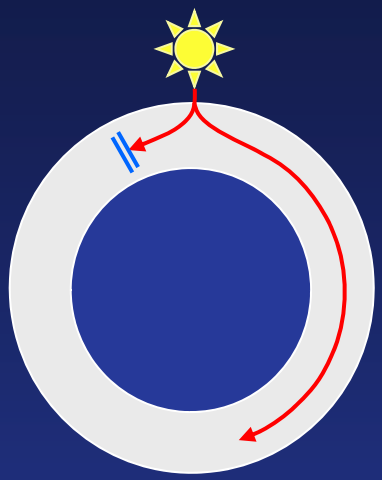
Reentry substrate in AF: Changed refractoriness: Other miRs



Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

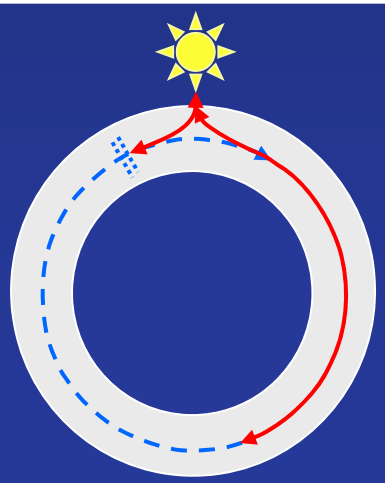
Substrate for Reentry in AF

A



Fundamental determinants of reentry:
-ERP (short favors reentry)
-conduction velocity (slow favors reentry)

B

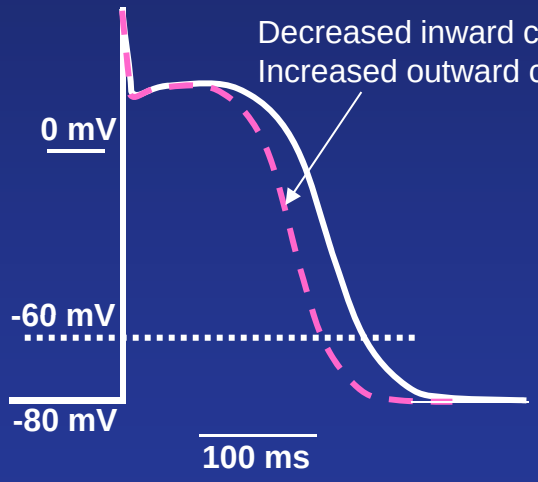


How remodeling pro

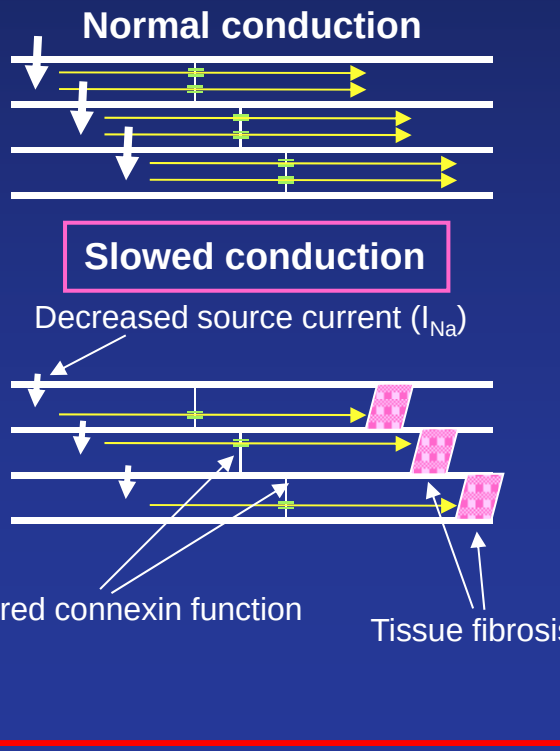
Impaired conduction and dilated atria

C

Shortened refractory periods



D



Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

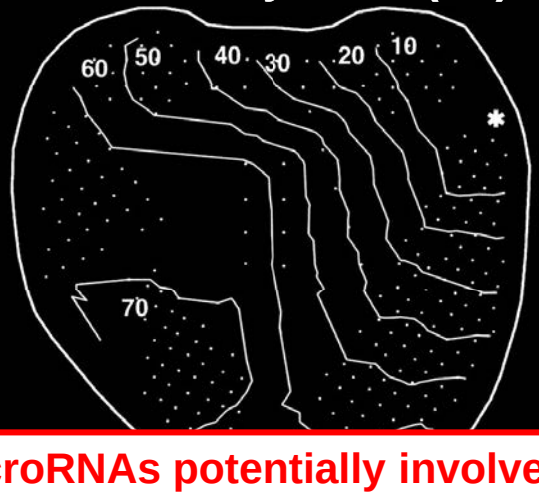
MicroRNAs implicated in AF via remodeling of atrial structure

Conduction Abnormalities and Atrial Fibrosis in CHF (Paradigm of Structural Remodeling)

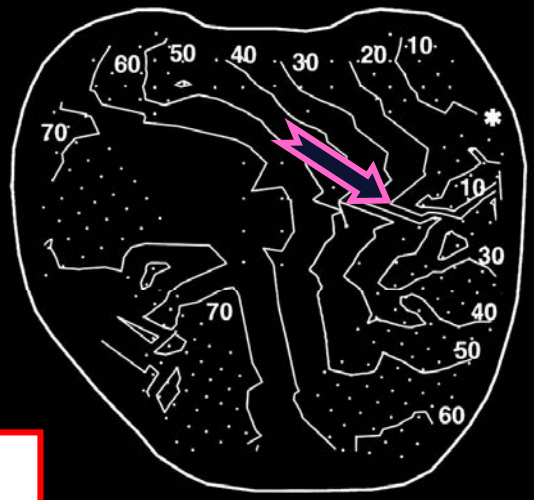
Epicardial maps

Control

Atrial tachycardia (AF)

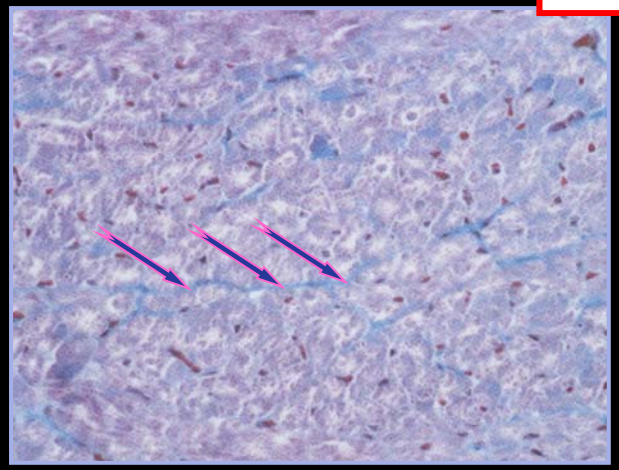


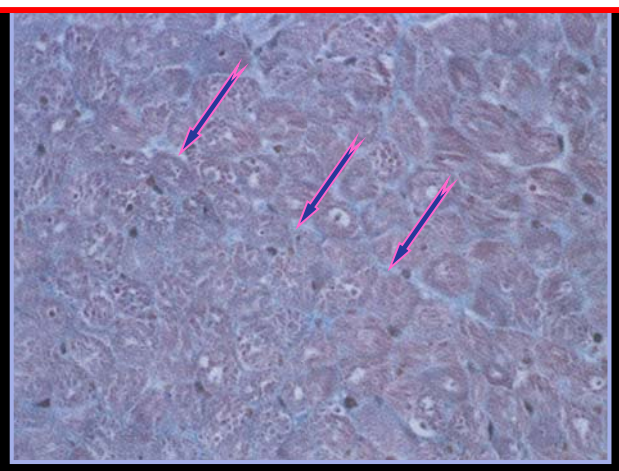
CHF

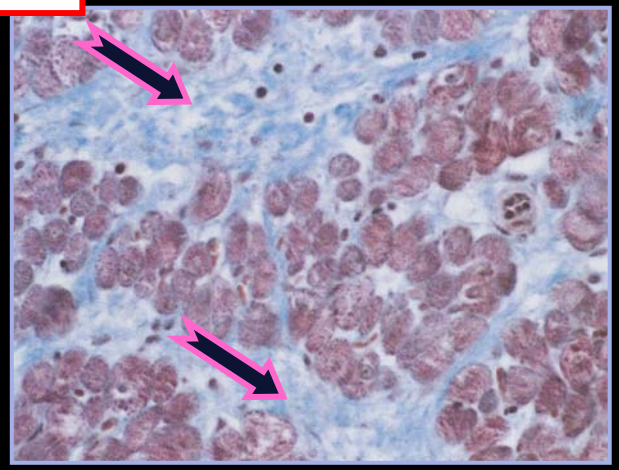


MicroRNAs potentially involved in atrial structural remodeling

Histology



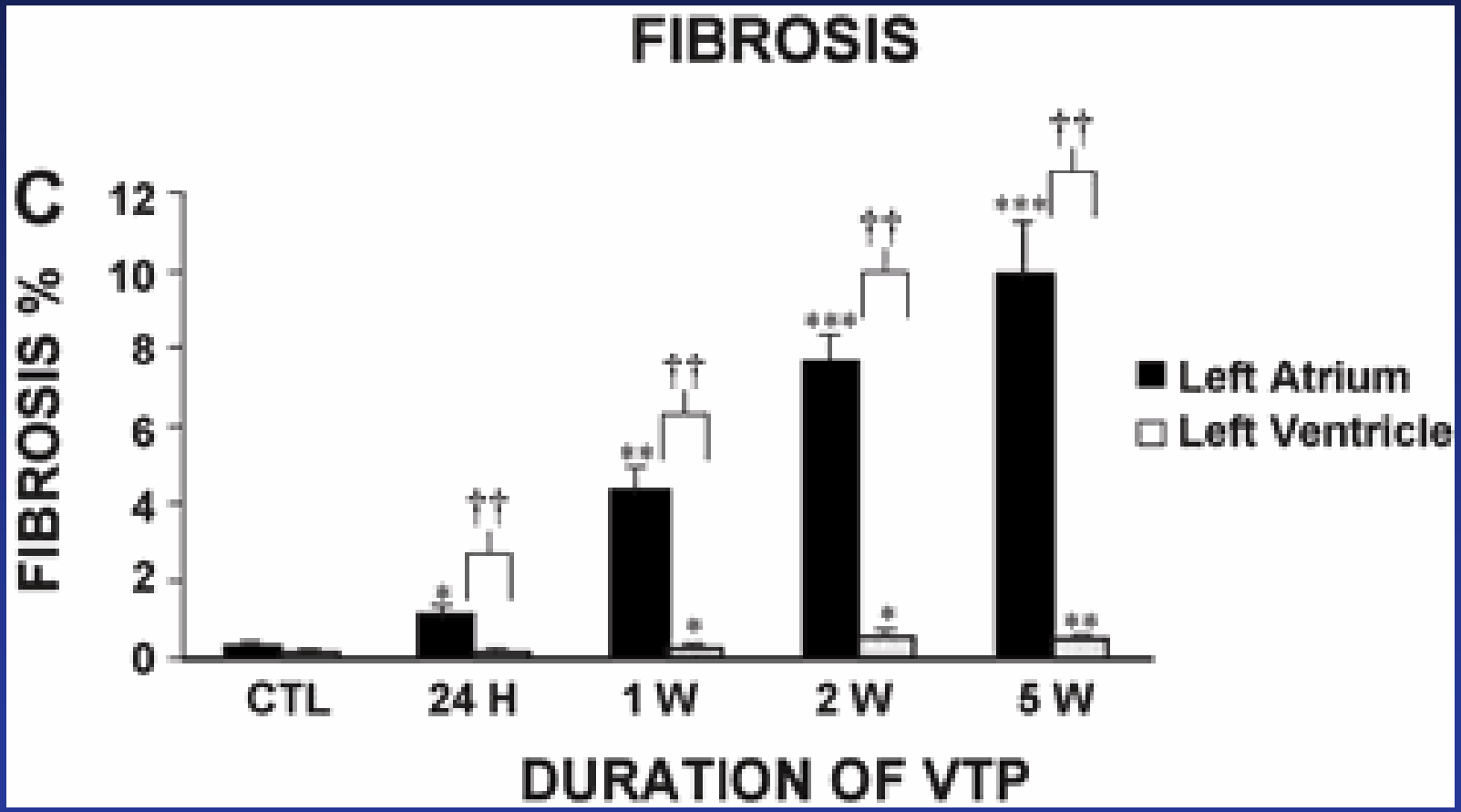




LI et al, *Circulation 1999; 100:87-95*

Differences in remodeling between left atrium and ventricle of CHF dogs

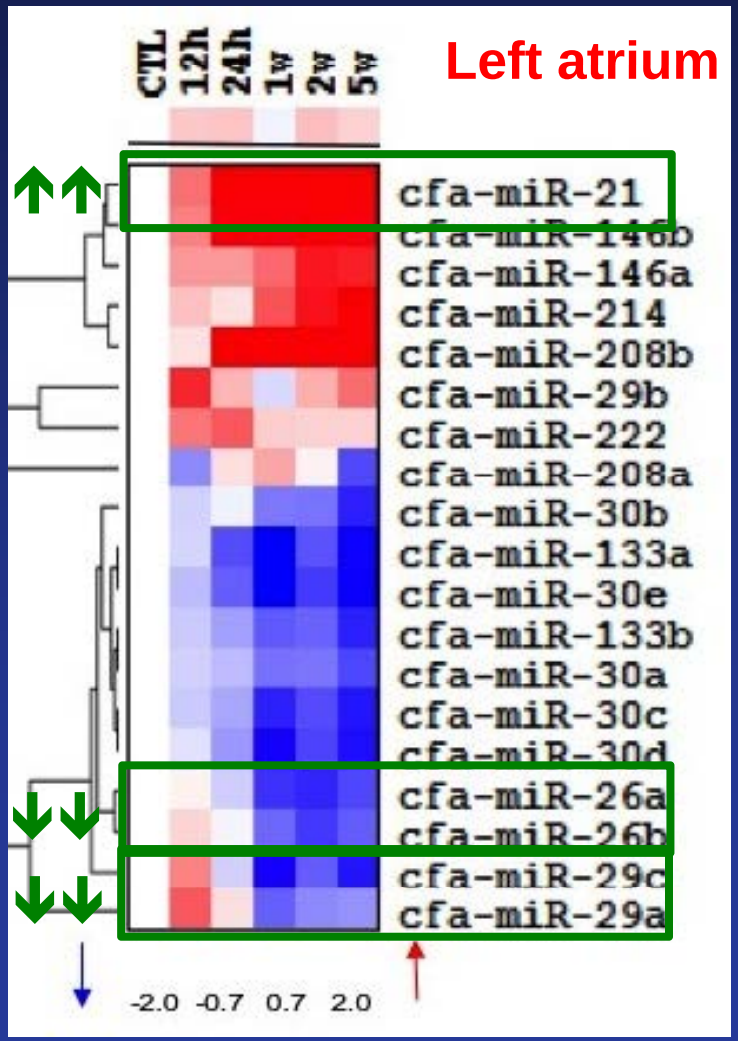
Atrium changes much greater than ventricle

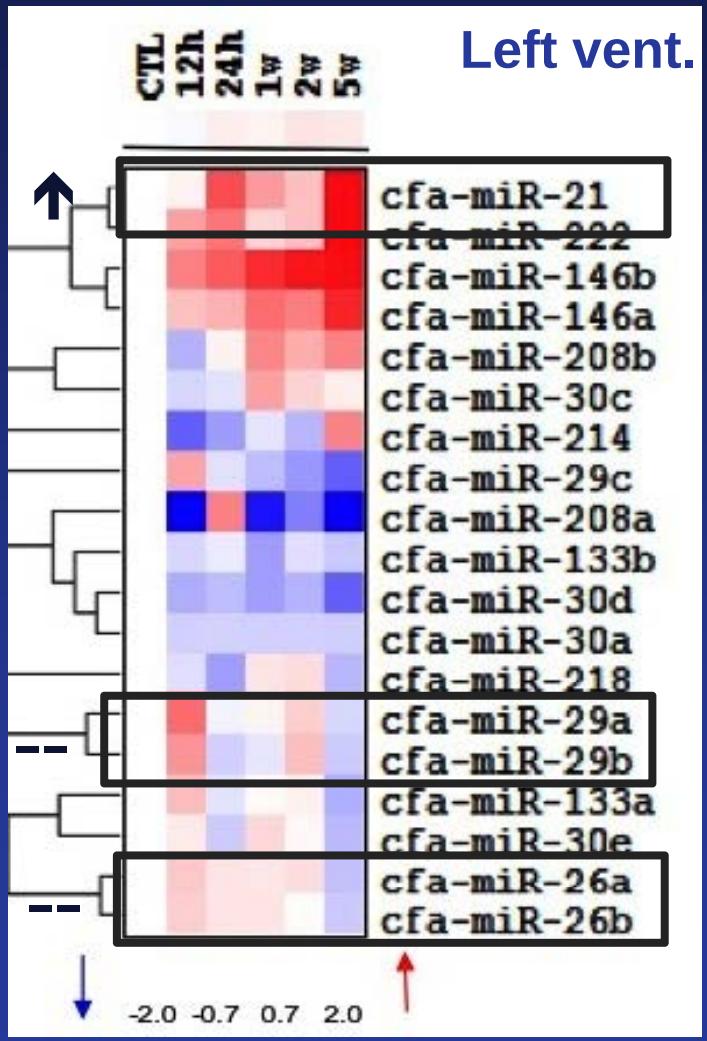


Hanna N et al, Cardiovasc Res2004;63:236-44

Gene microarray screening for miR expression changes in left atrium and ventricle of CHF dogs (VTP X 2 wks)

Atrium changes much greater than ventricle

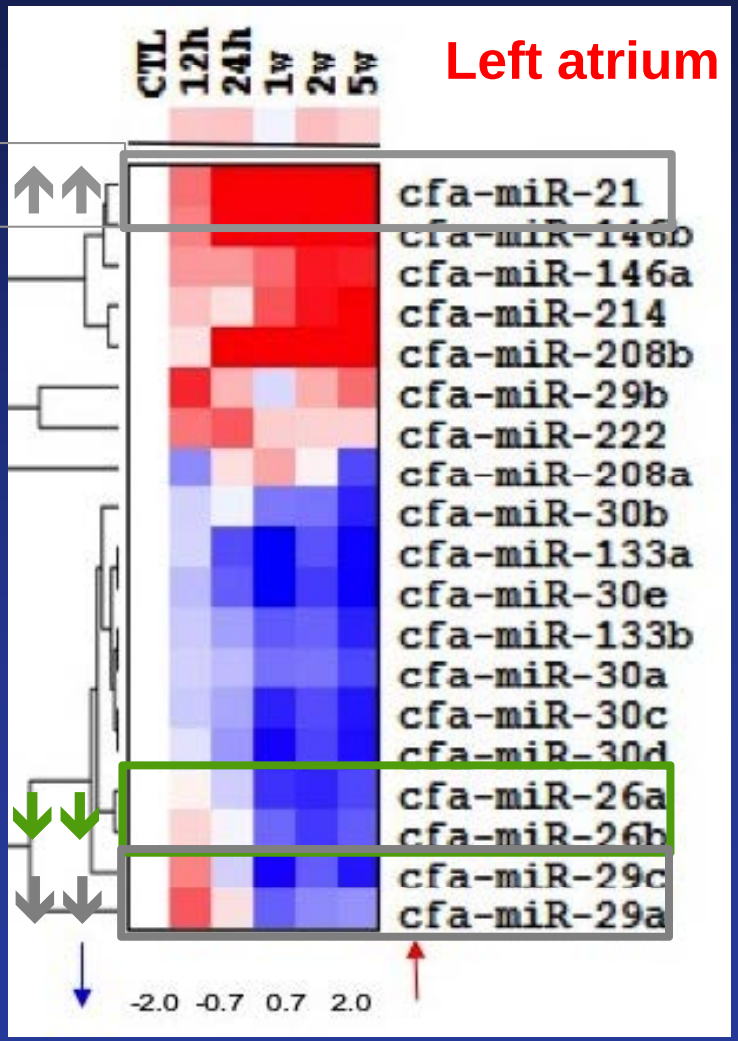


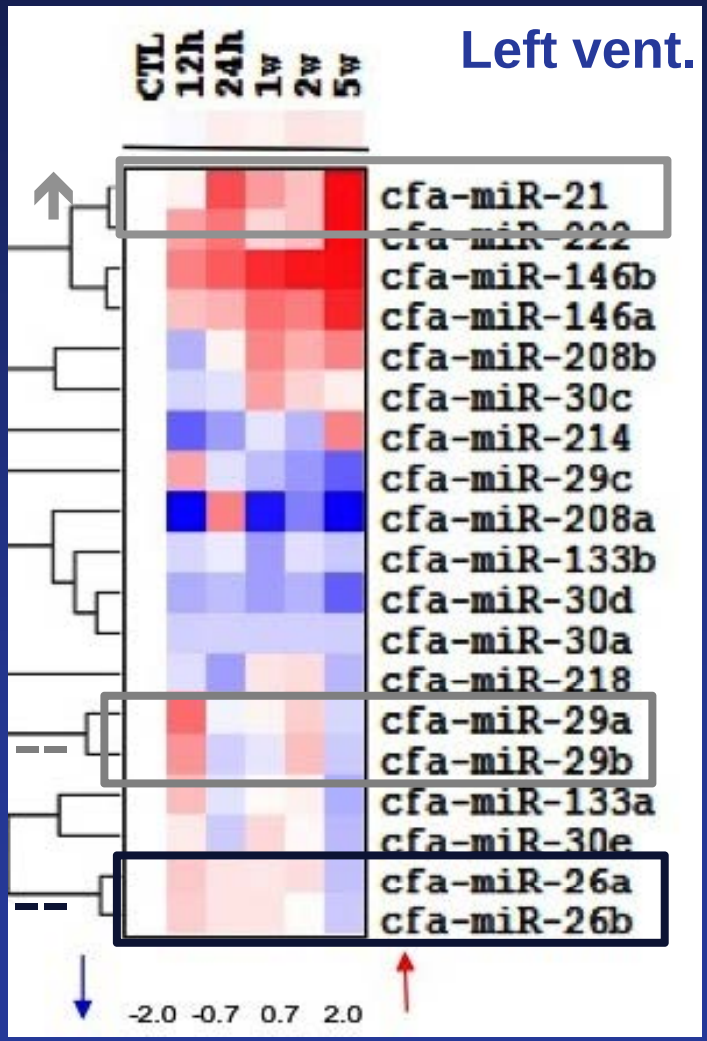


Chen Y et al, *JMCC 12: 113-124, 2014.*

Gene microarray screening for miR expression changes in left atrium and ventricle of CHF dogs (VTP X 2 wks)

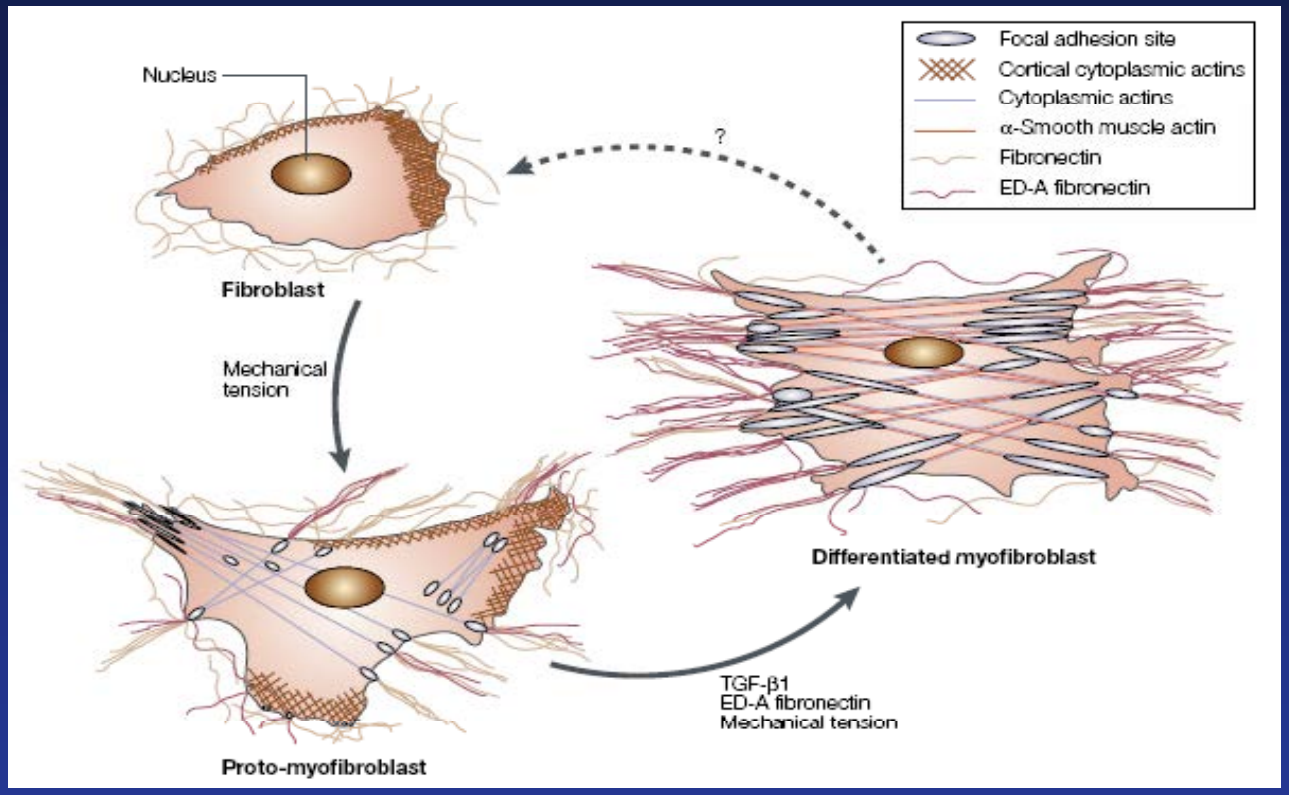
Role of miR21





Chen Y et al, *JMCC 12: 113-124, 2014.*

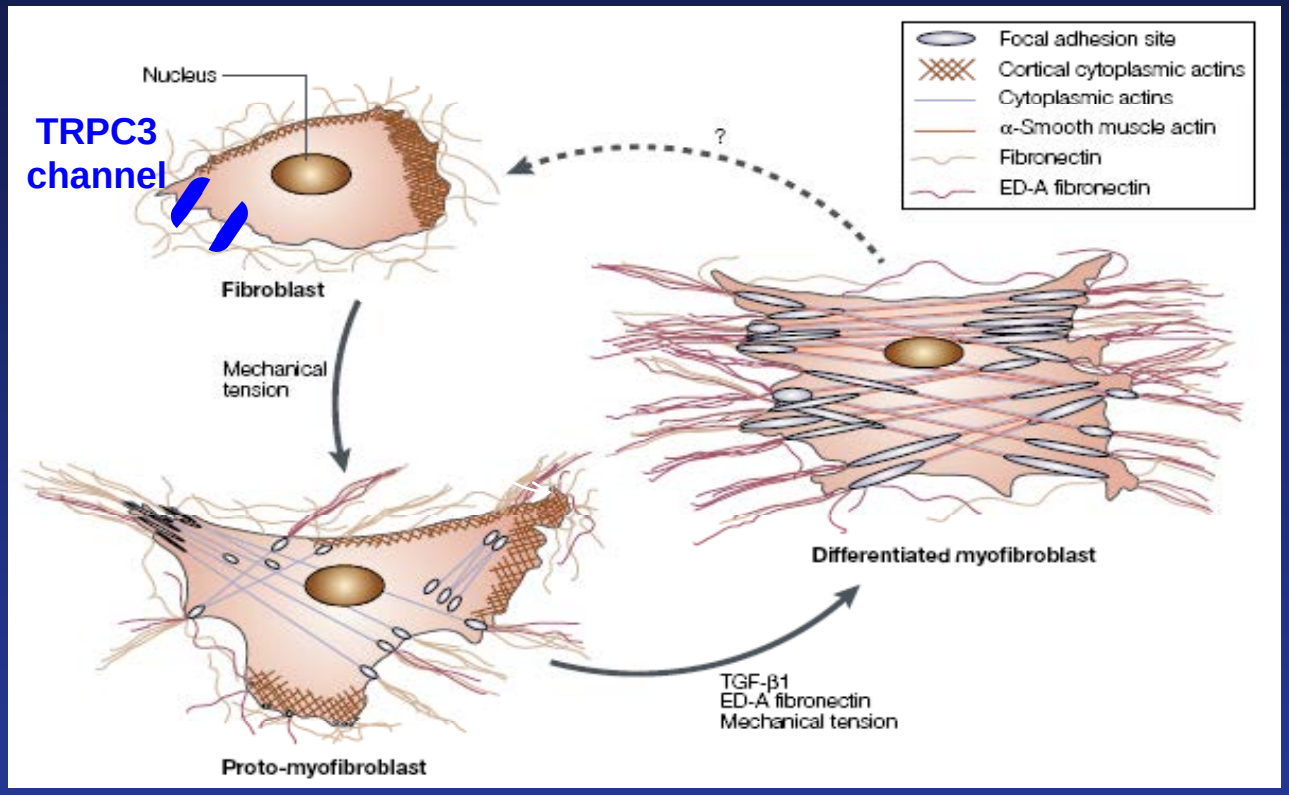
Cardiac Fibroblasts



- Represent as much as ⅔ of all cardiac cells by number, produce ECM
- Differentiate during fibrosis into a highly secretory myofibroblast phenotype (αSMA^{+})
- αSMA - contractile protein thatcorrelates with increased production of ECM proteins

Tomasek et al. (2002) *Nat Rev Mol Cell Biol*.

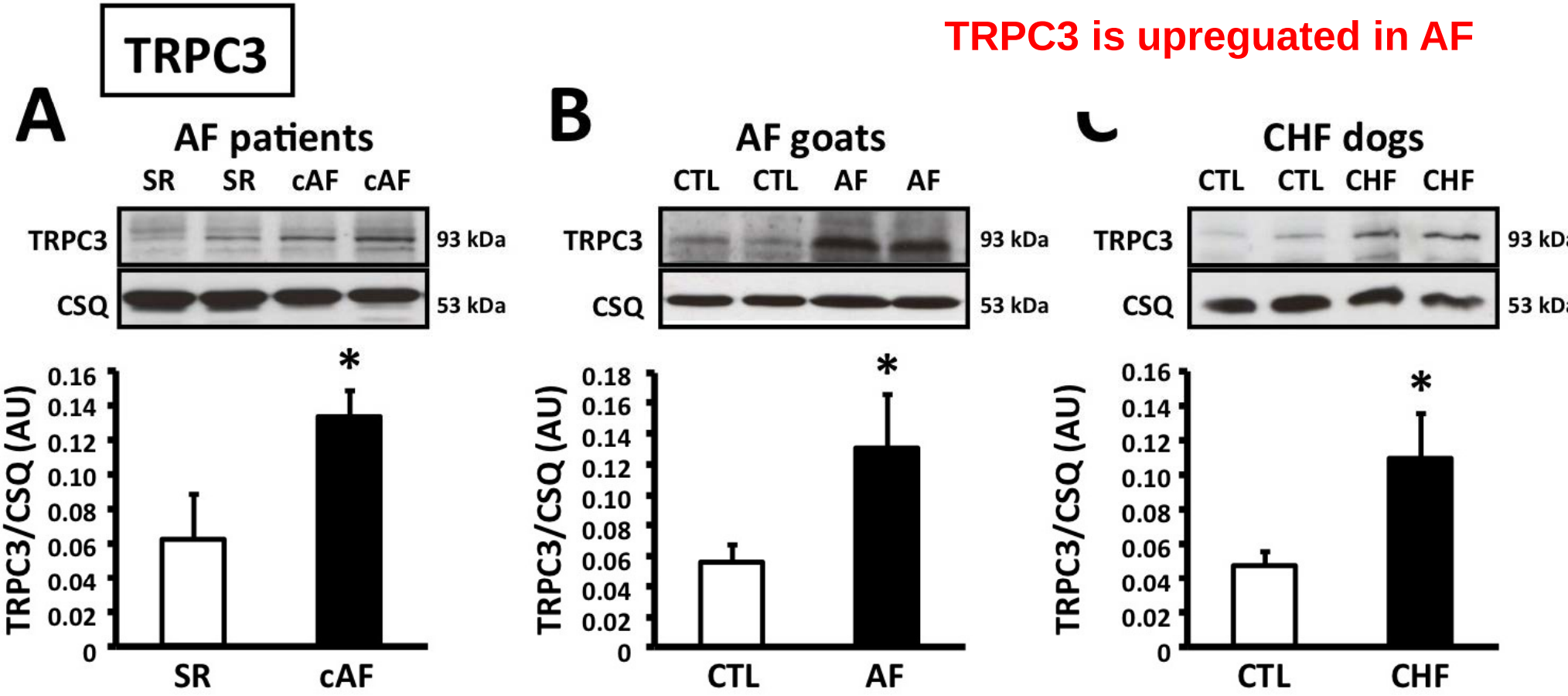
Control of Cardiac Fibroblasts by Intracellular Ca^{2+}



- Nonselective cation channels (TRPC3) allow Ca^{2+} entry into cardiac fibroblasts under mechanical and chemical stimuli

Harada M et al, *Circulation 126: 2051-2064, 2012.*

Control of Cardiac Fibroblasts by Intracellular Ca^{2+}



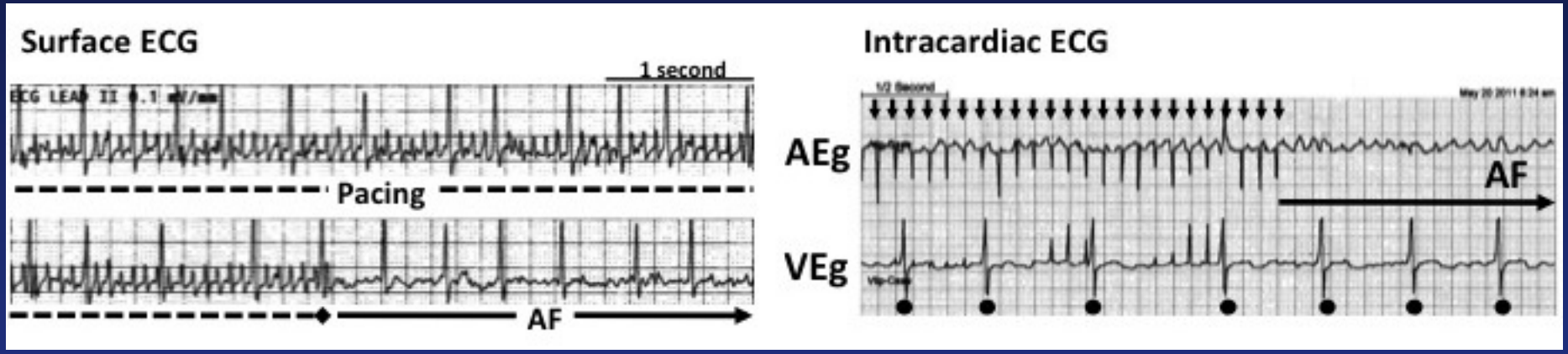
mechanical and chemical stimuli

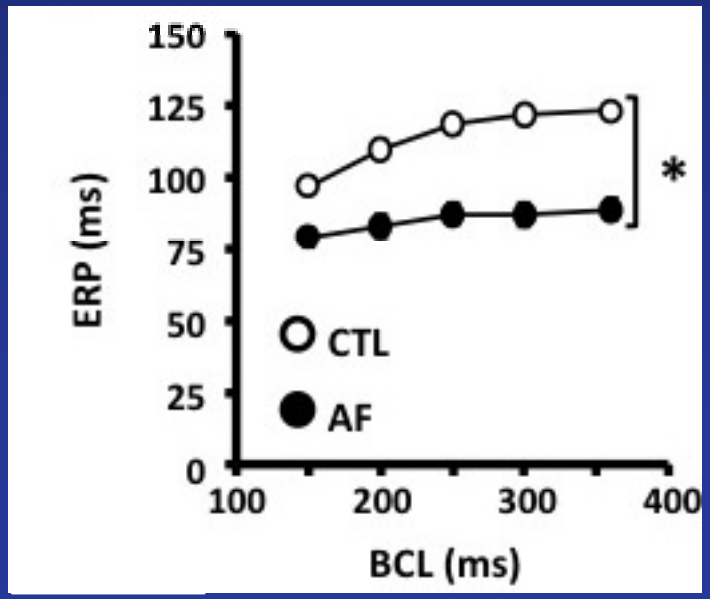
- Ca^{2+} entry causes fibroblasts to proliferate and differentiate into activated myofibroblasts

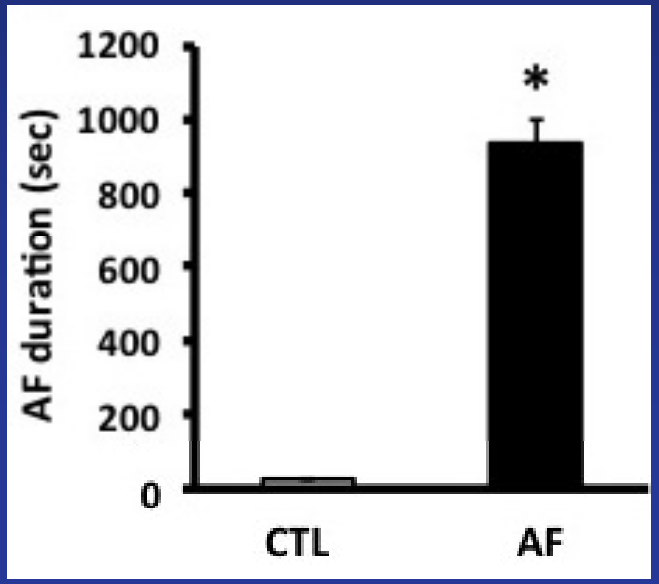
Harada M et al, *Circulation 126: 2051-2064, 2012.*

Dog model of electronically-maintained AF

AF maintained electrically for 1 week

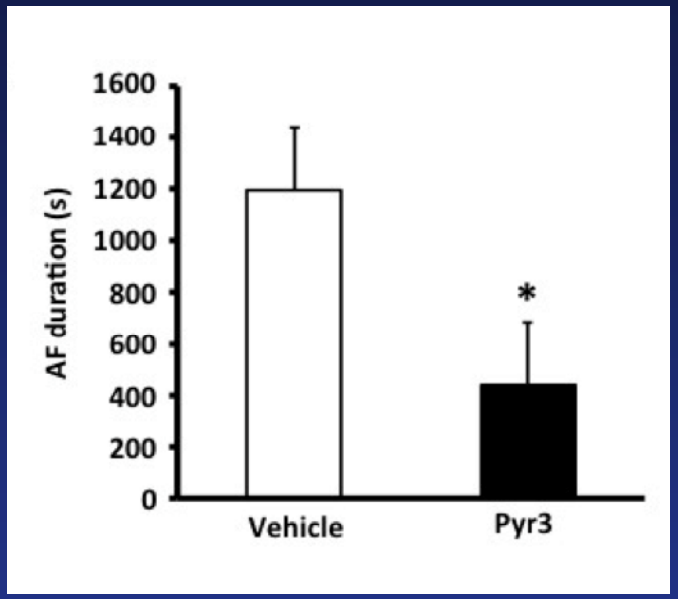


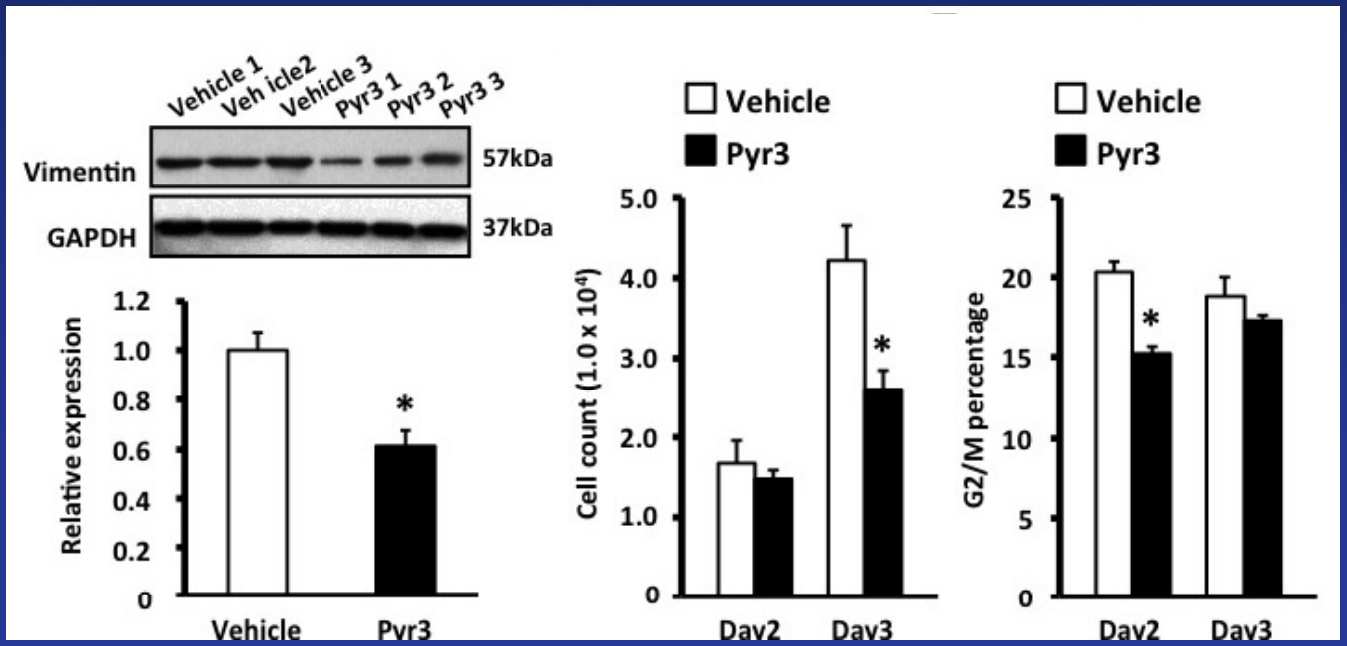




Harada M et al, *Circulation 126: 2051-2064, 2012.*

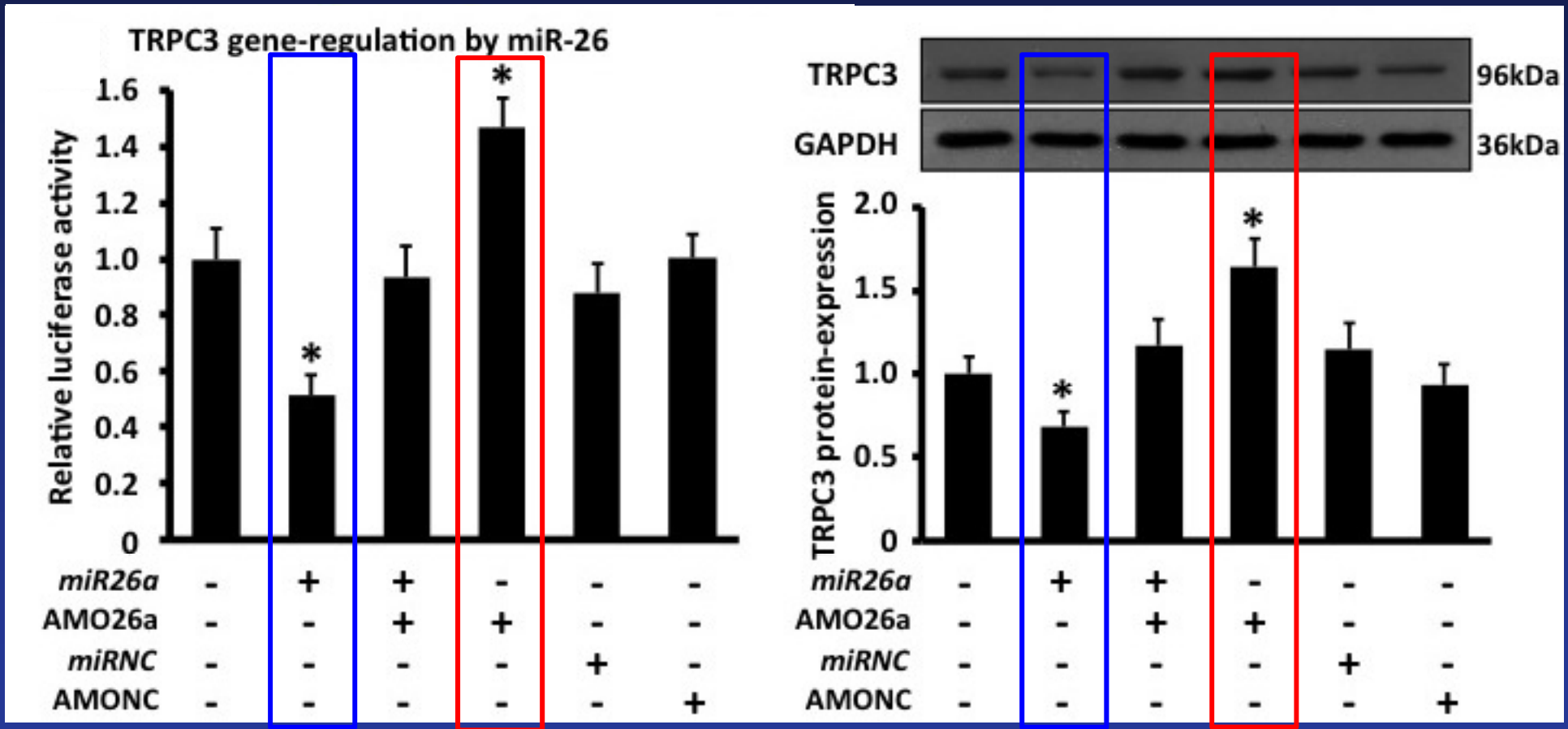
Effects of in vivo TRPC3 block on development of the AF substrate and fibroblast activation





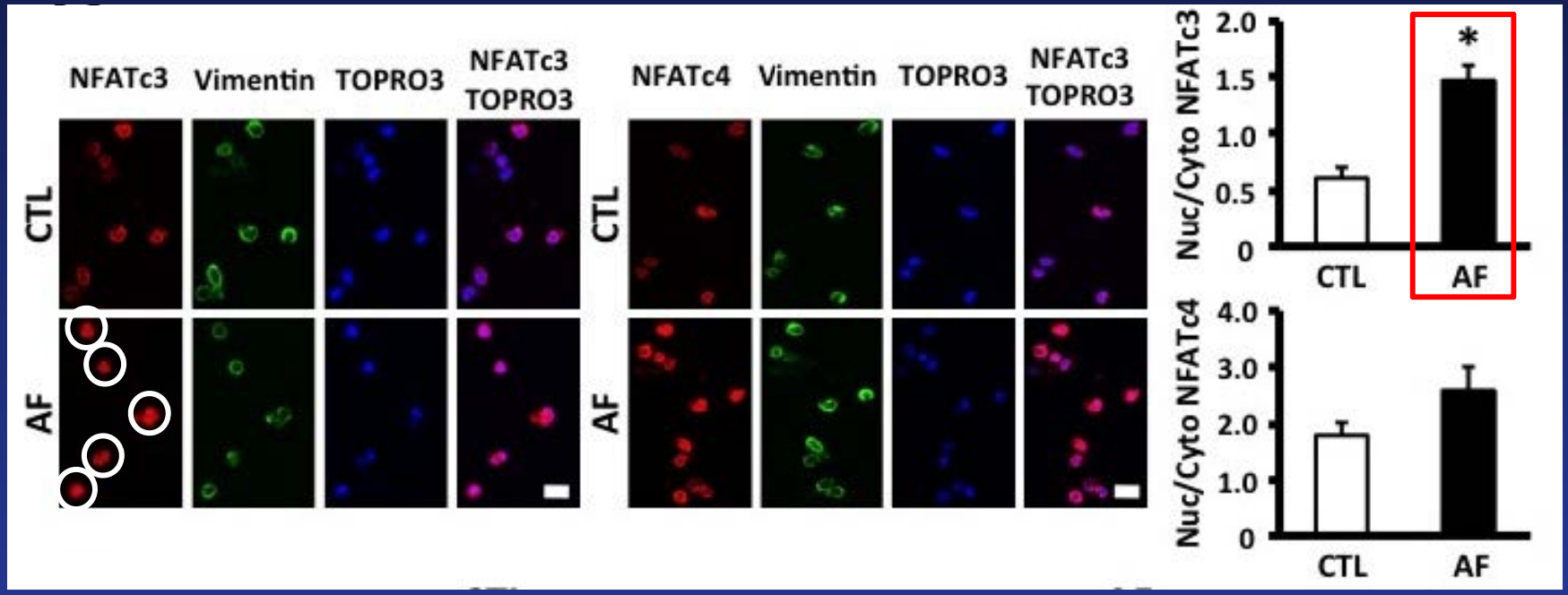
Harada M et al, *Circulation 126: 2051-2064, 2012.*

What causes TRPC3 upregulation in AF?



Harada M et al, *Circulation 126: 2051-2064, 2012.*

What causes miR-26 downregulation in fibroblasts?

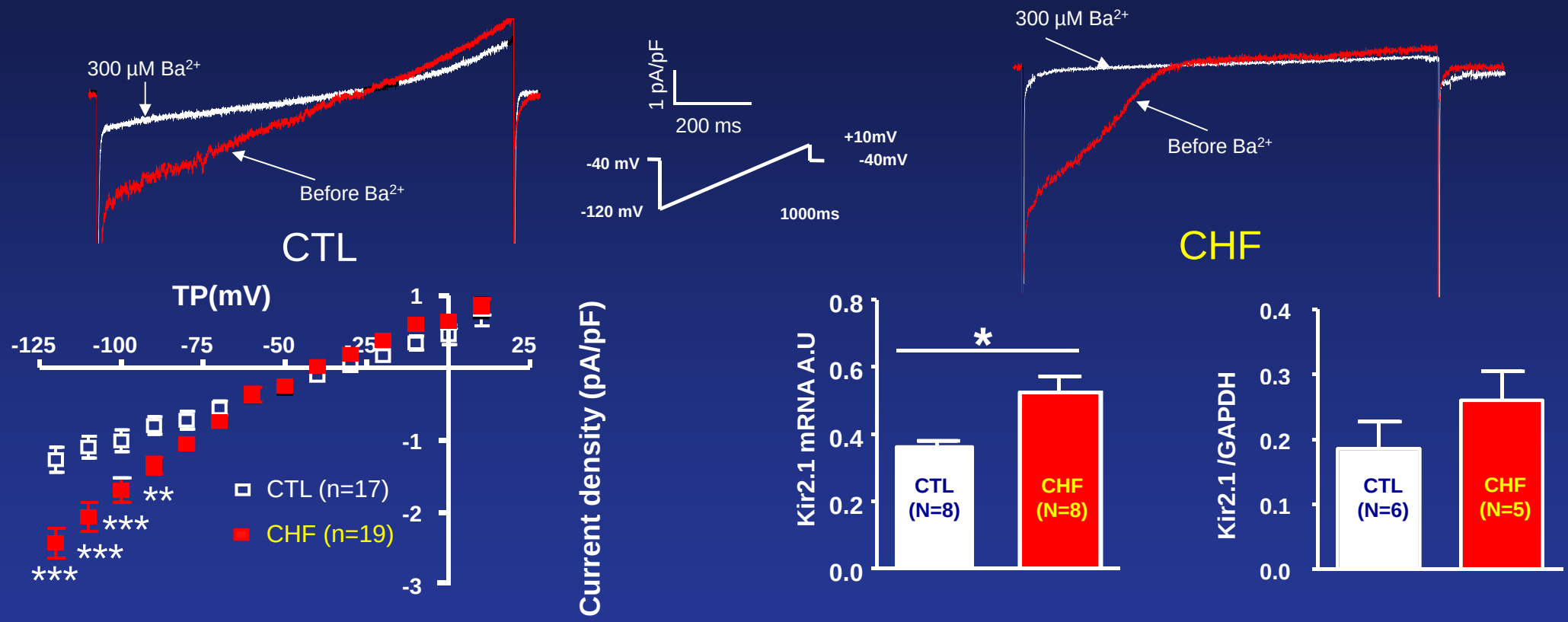


- NFATc3 nuclear translocation occurs in AF fibroblasts
- As in cardiomyocytes, NFAT suppression of fibroblast miR26 transcription downregulates miR26 in AF

Harada M et al, *Circulation 126: 2051-2064, 2012.*

Additional targeting of fibroblasts in AF: K^+ current and Ca^{2+} entry

CHF causes a fibrotic AF substrate: Ba^{2+}sensitive K^+ current (I_{K1}) in CHF fibroblasts (FBs)

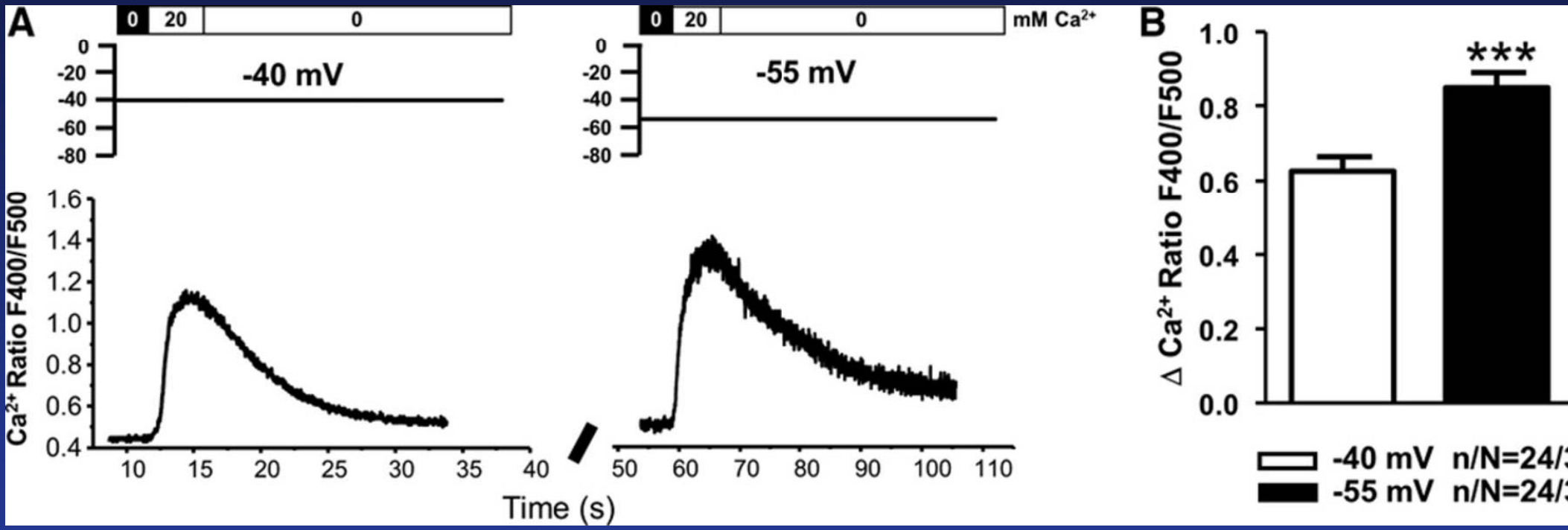


1) CHF upregulates Ba^{2+} sensitive inward rectifier current (I_{K1}) and Kir2.1 in FBs

2) CHF increases FB resting potential (from about -40 to about -55 mV)

Qi XY et al, Circ Res 2015;116:836-45.

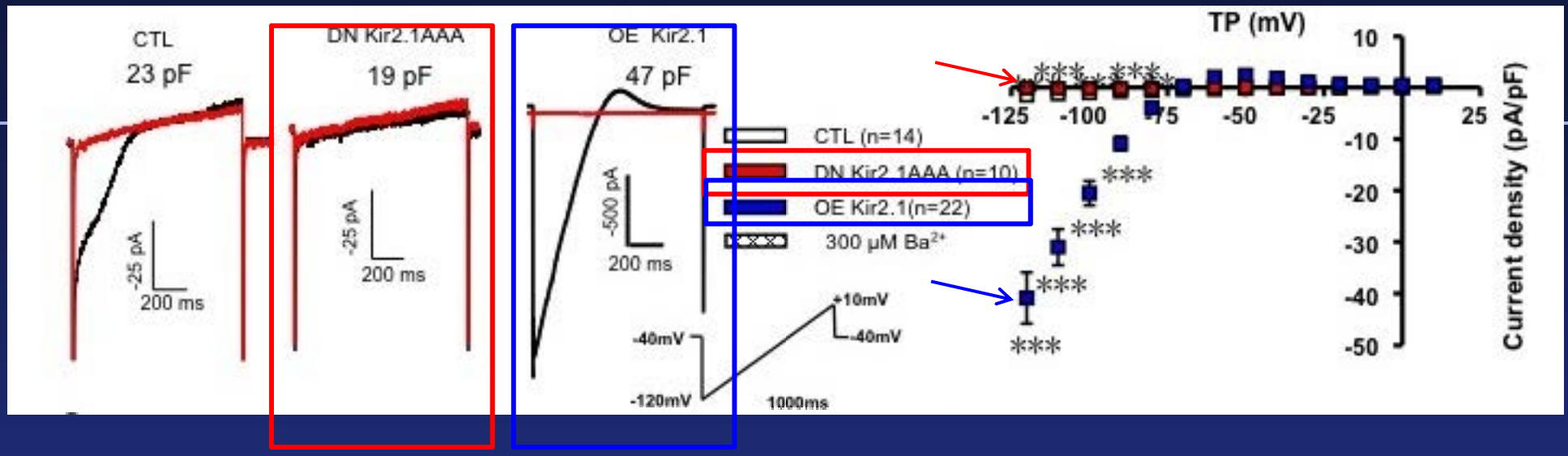
Effects on Ca^{2+} entry



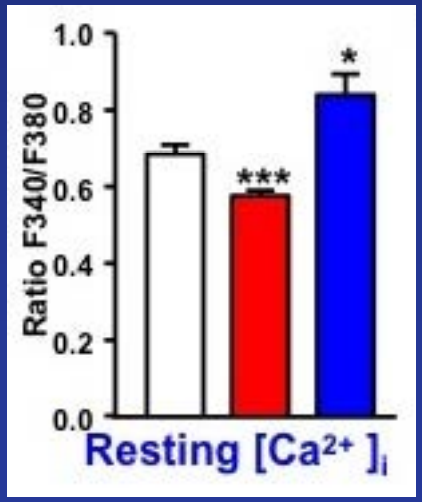
Hyperpolarization increases FB Ca^{2+} entry

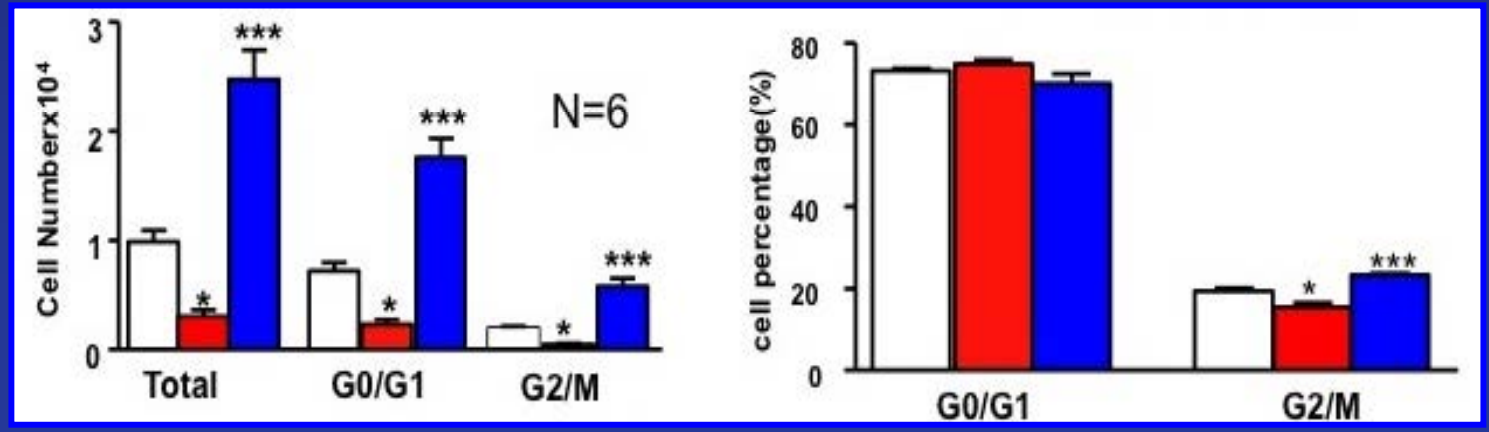
Qi XY et al, Circ Res 2015;116:836-45.

I_{K1} modulation of fibroblast Ca^{2+} and proliferation



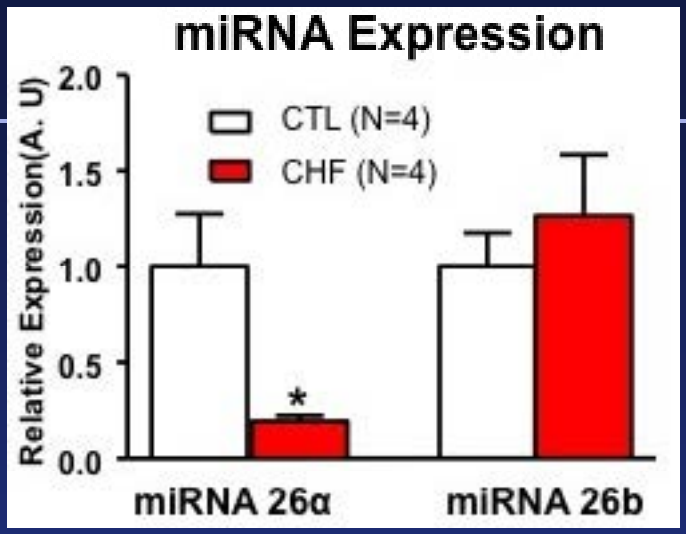
Kir2.1-induced changes in resting membrane potential alter Ca^{2+} entry and control proliferation

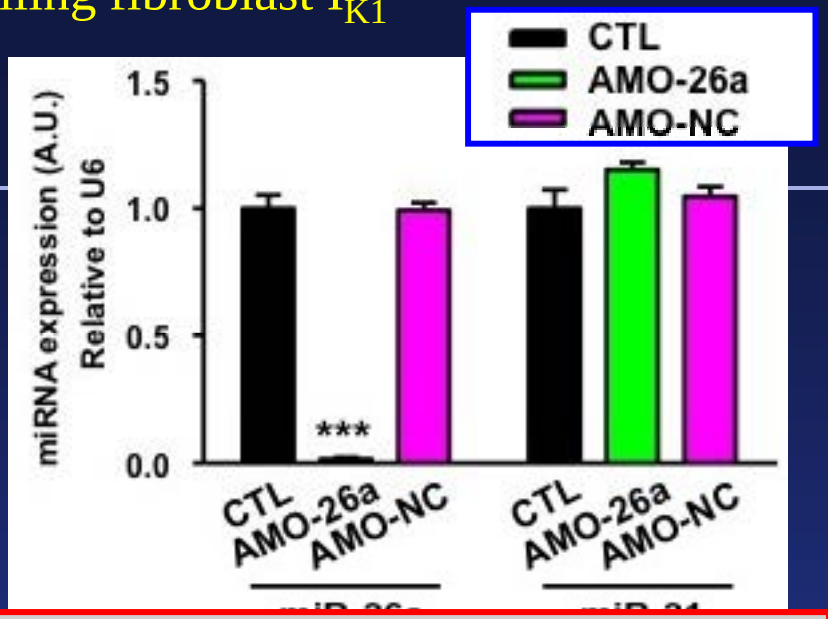




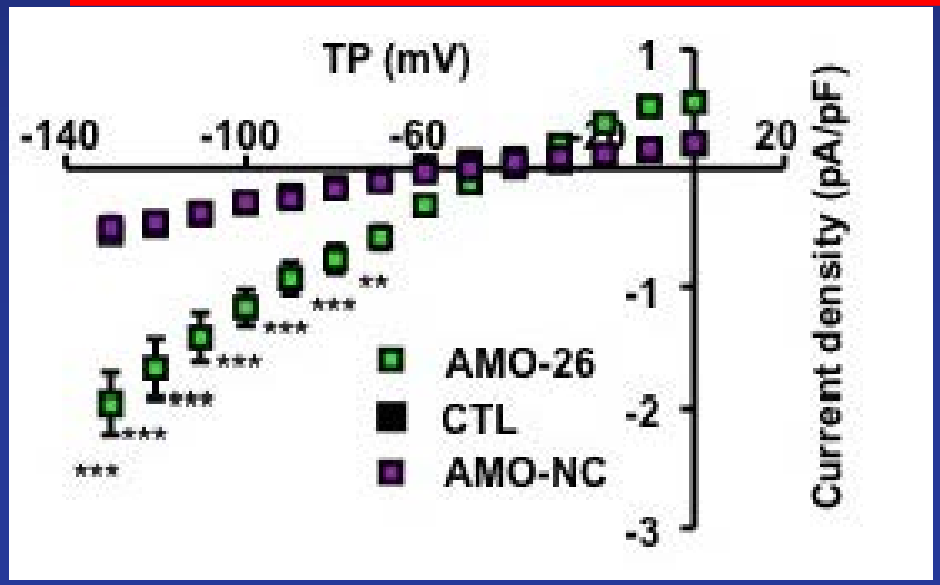
Qi XY et al, Circ Res 2015;116:836-45.

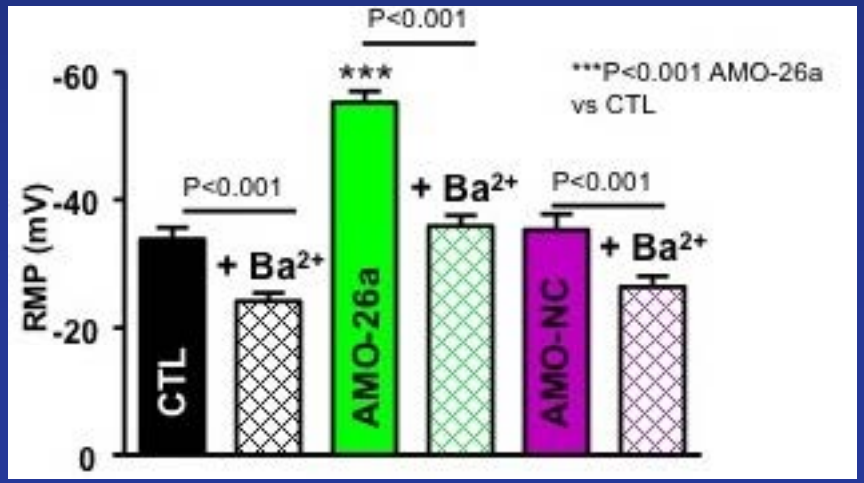
Role of miR-26 in controlling fibroblast I_{K1}





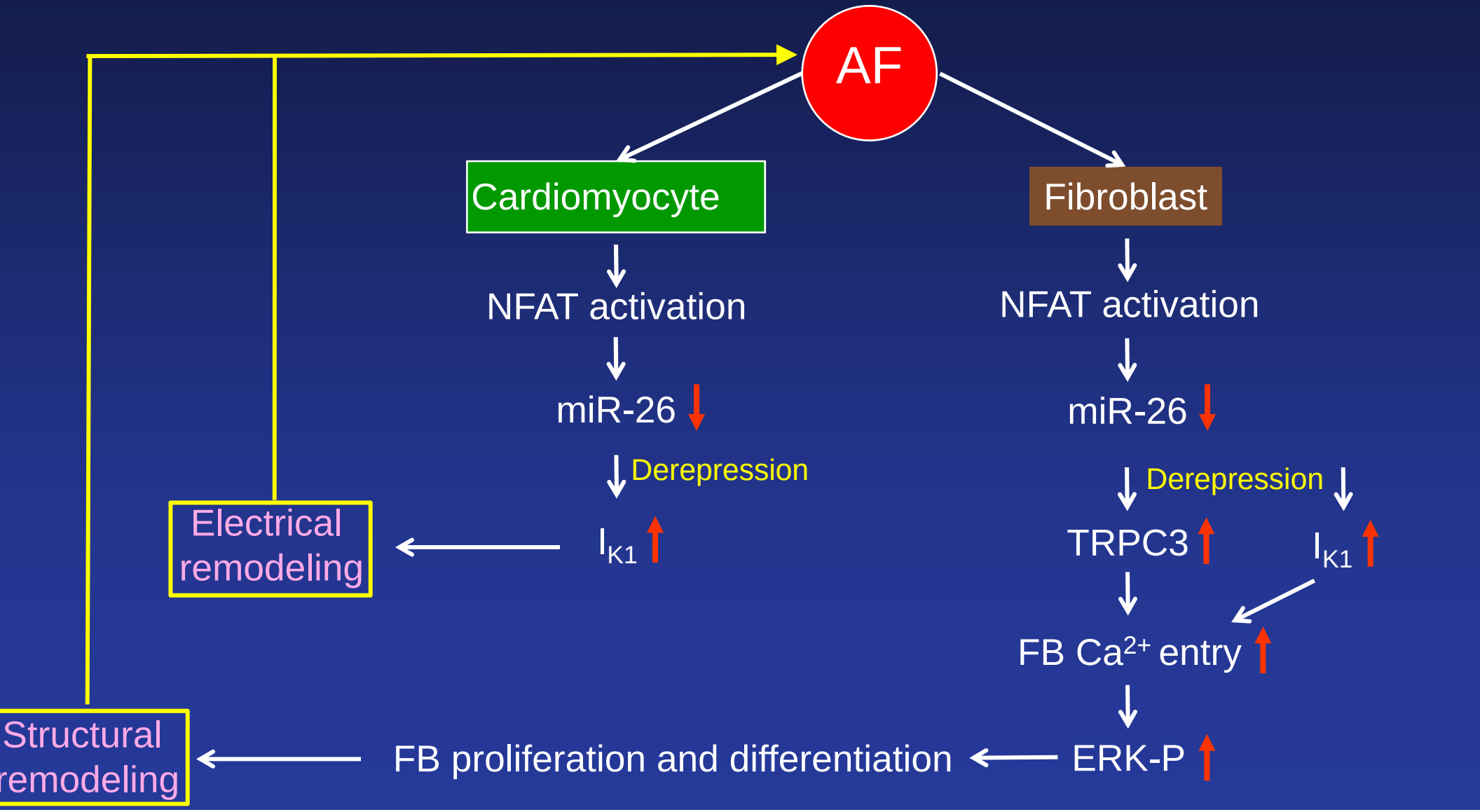
miR-26 expression is downregulated in atrial fibroblasts by CHF and causes I_{K1} enhancement/RMP hyperpolarization



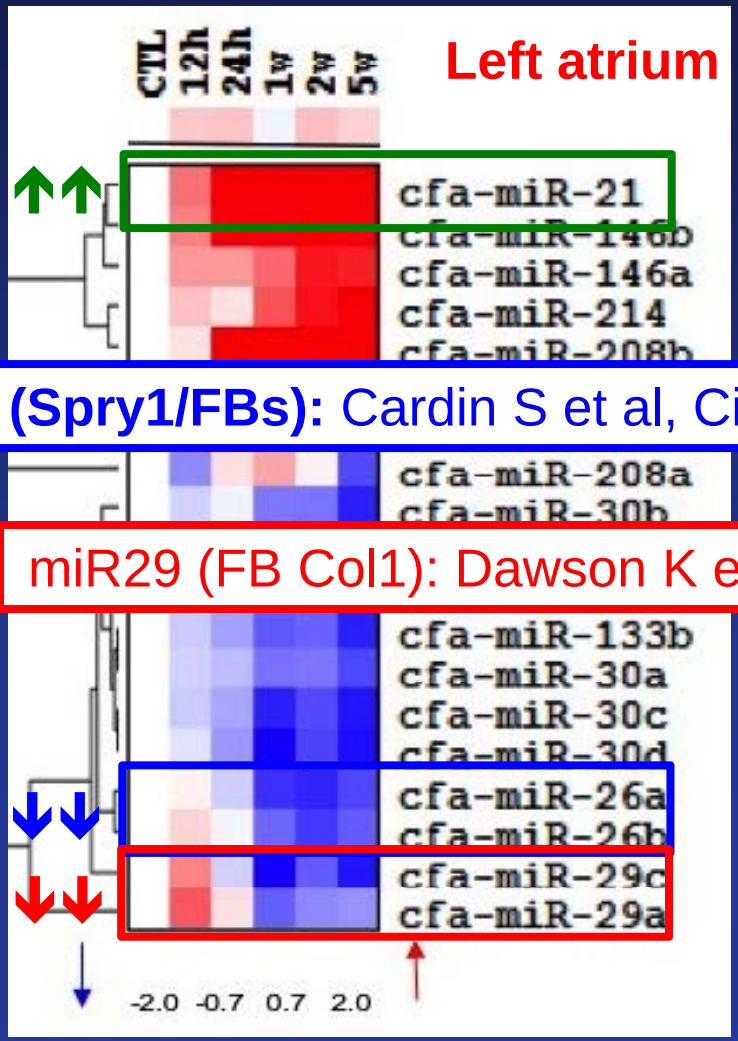


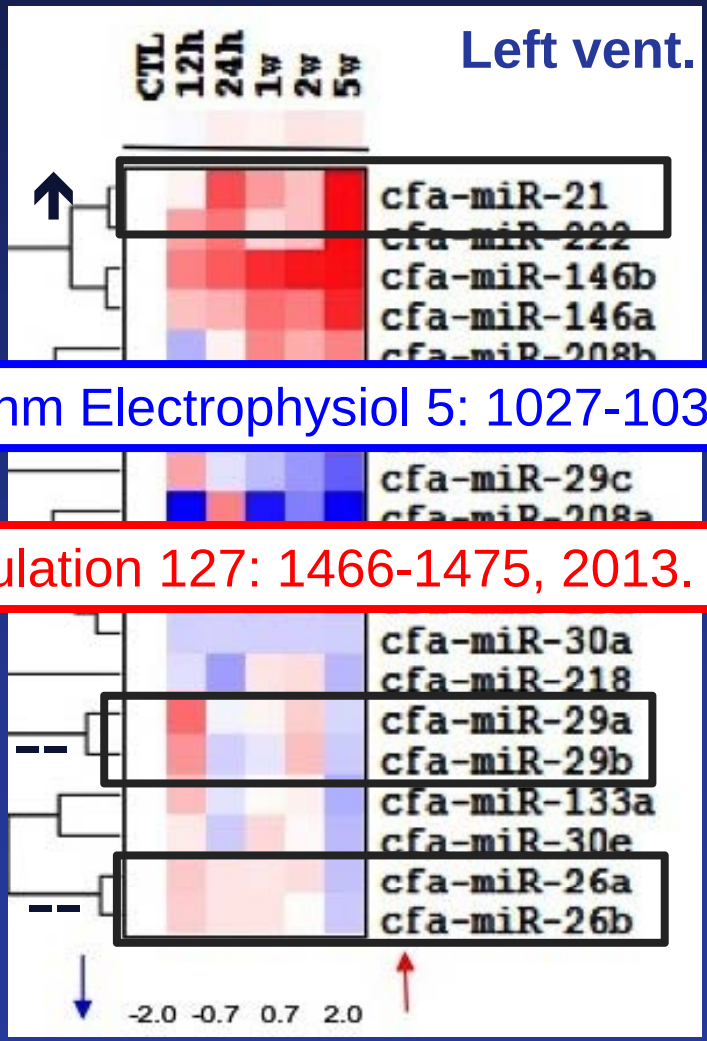
Qi XY et al, Circ Res 2015;116:836-45.

Summary of role of miR-26 in AF



Biological Evidence for Roles of miR-26 and miR-29 in AF via Profibrotic miRNA Downregulation





miR21 (Spry1/FBs): Cardin S et al, Circ Arrhythm Electrophysiol 5: 1027-1035, 2012

miR29 (FB Col1): Dawson K et al, Circulation 127: 1466-1475, 2013.

Chen Y et al, *JMCC 12: 113-124, 2014.*

Conclusions

- MicroRNAs appear to be important players in both electrical and structural atrial remodeling

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- MicroRNAs might be interesting targets for new molecularly based therapeutic approaches for AF

Conclusions

- MicroRNAs appear to be important players in both electrical and structural atrial remodeling
- MicroRNAs might be interesting targets for new molecularly based therapeutic approaches for AF
- **MicroRNAs may also be useful as novel therapeutics to prevent AF progression**

Thank you!

Merci!

Outline

- Coronary artery disease therapy and prevention
- The evolution of AF pathophysiology understanding
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MicroRNAs as AF biomarkers

MicroRNAs as AF biomarkers

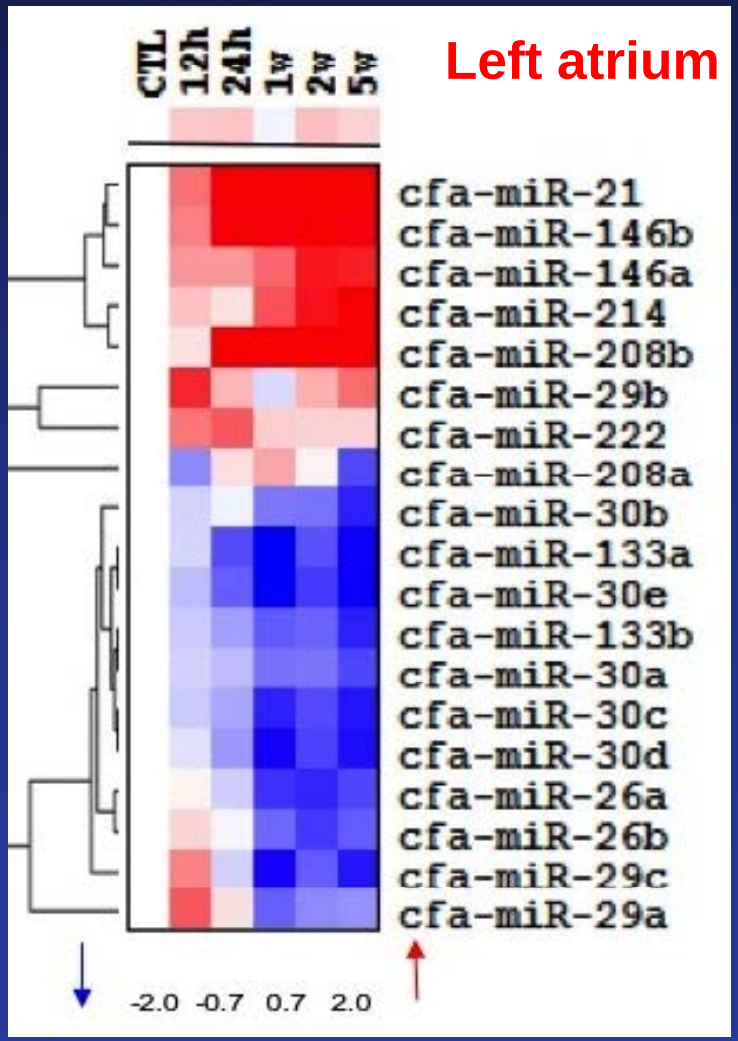
Table 2 | Studies of circulating miRNAs as potential biomarkers for AF

Patients	Methods	Findings
Plasma (initial MPSS): healthy control ($n=5$); paroxysmal AF ($n=5$); persistent AF ($n=5$) Plasma (subsequent qPCR): healthy control ($n=30$); paroxysmal AF ($n=30$); persistent AF ($n=30$)	MPSS, qPCR	Four candidates (miR-19, miR-146a, miR-150, and miR-375) passed the initial screening criteria by MPSS; confirmation of lower plasma levels of miR-150 in both paroxysmal and persistent AF by subsequent qPCR analysis in an independent cohort of 90 samples[51]
Platelet: healthy control ($n=35$); AF with congestive heart failure ($n=41$)	qPCR	Reduced miR-150 in platelets of patients with AF and congestive heart failure[52]
Plasma: control ($n=30$); AF with congestive heart failure ($n=16$); AF without congestive heart failure ($n=17$)	qPCR	Reduced plasma levels of miR-29b in patients with AF with or without congestive heart failure[53]
Plasma: control ($n=2,185$); incident AF ($n=107$); prevalent AF ($n=153$)	qPCR	miR-328 is the only circulating miRNA found to be correlated with prevalent AF (reduced levels in AF)[54]

Abbreviations: AF, atrial fibrillation; MPSS, massively pa
real-time polymerase chain reaction.

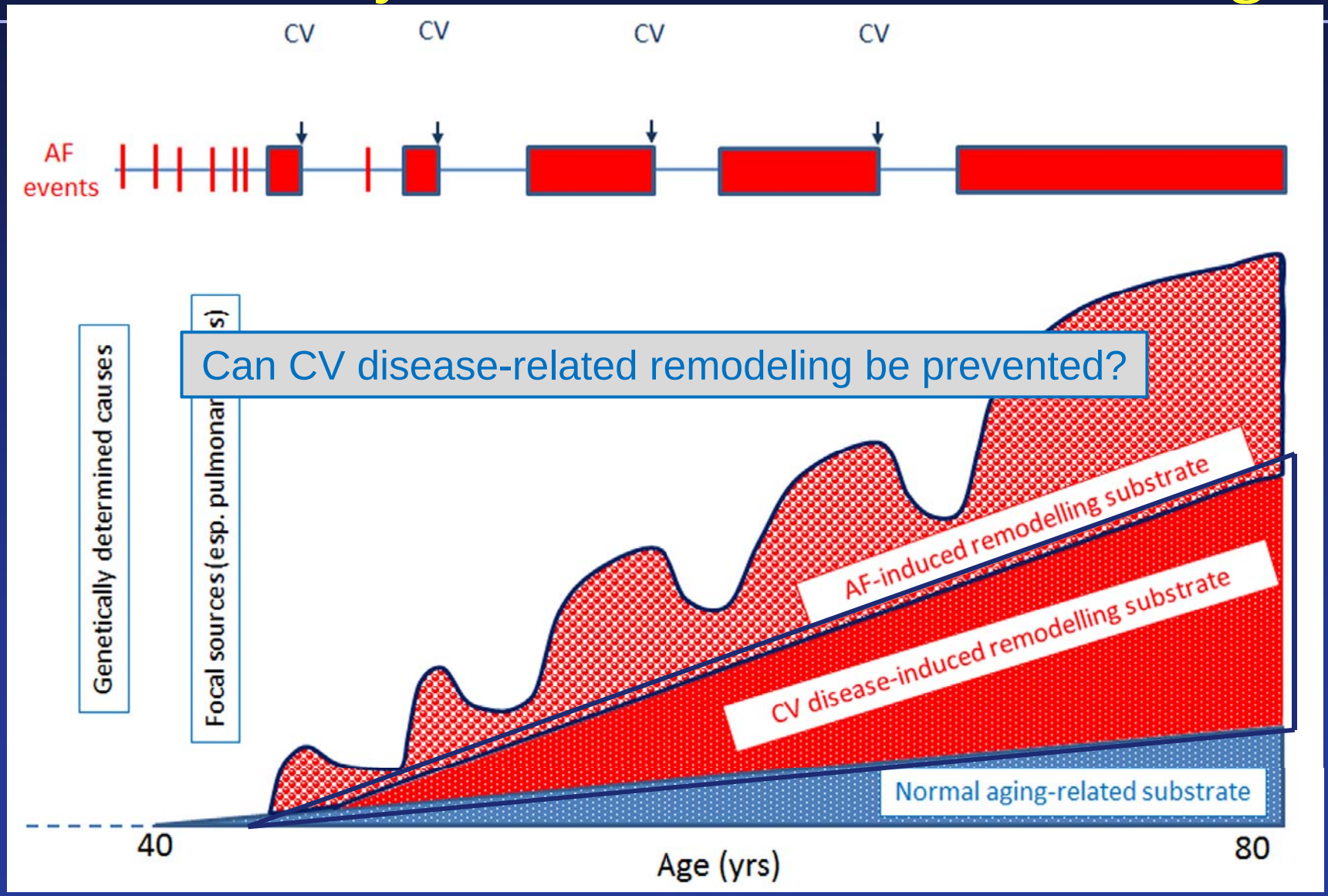
McManus DD et al, Heart Rhythm 11, 663–669 (2014).

Luo X et al, *Nat Rev Cardiol 12: 80-90, 2015.*


CTL
12h
24h
1w
2w
5w
Left atrium
cfa-miR-21
cfa-miR-146b
cfa-miR-146a
cfa-miR-214
cfa-miR-208b
cfa-miR-29b
cfa-miR-222
cfa-miR-208a
cfa-miR-30b
cfa-miR-133a
cfa-miR-30e
cfa-miR-133b
cfa-miR-30a
cfa-miR-30c
cfa-miR-30d
cfa-miR-26a
cfa-miR-26b
cfa-miR-29c
cfa-miR-29a
-2.0 -0.7 0.7 2.0

Nattel S *et al. EHJ 2014 Jun 7;35(22):1448-56.*

To understand and prevent AF-associated remodelling: It's not only about AF-induced remodeling



Population attributable AF risk due to various risk factors (ARIC study)

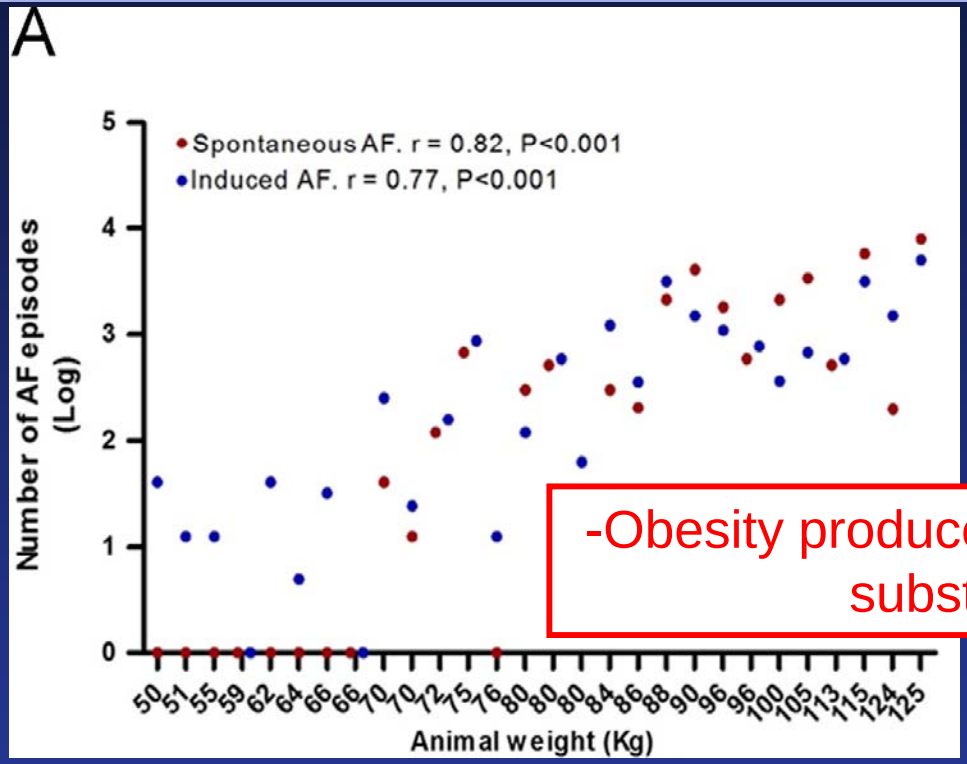
Table 4. Incidence Rate, Relative Hazard (95% Confidence Intervals), and Population-Attributable Fractions for Atrial Fibrillation for Risk Factors in the Atherosclerosis Risk in Communities Study, 1987 to 2007

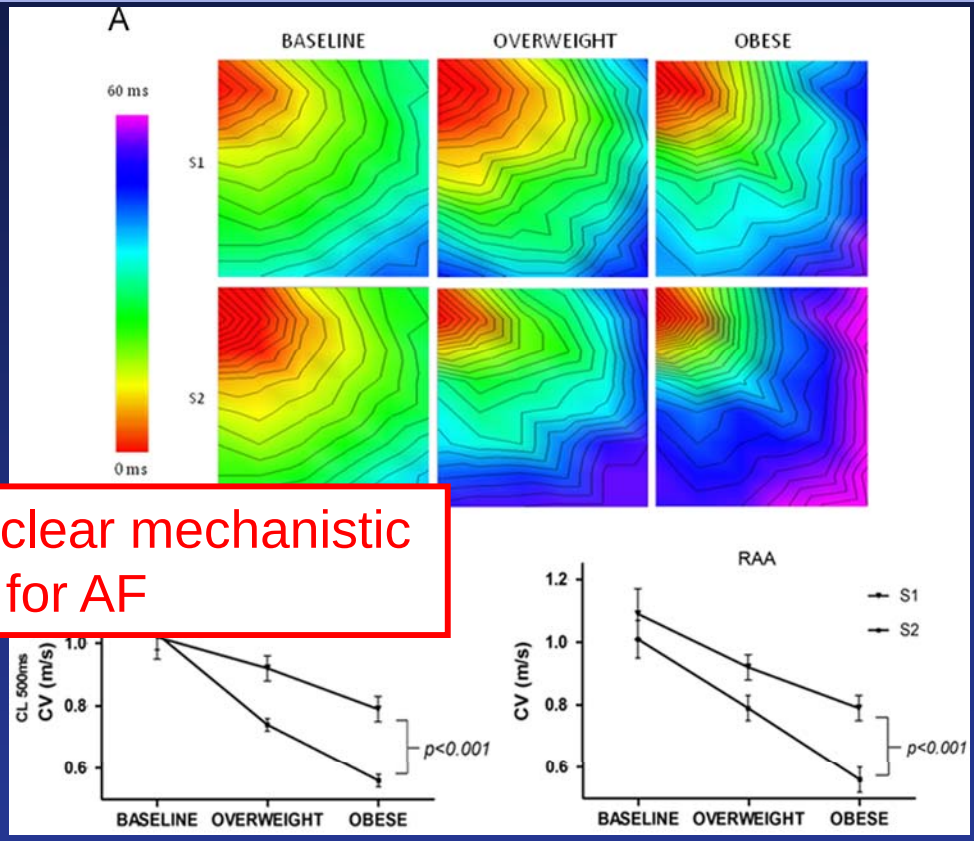
	At Risk, n	Incident AF, n	IR	RH (95% CI)*	PAF, %	95% CI
History of cardiac disease, %						
Optimal	13 398	1259	5.00	0.54 (0.46–0.62)	0.00	…
Elevated	1200	261	12.17	1 (Reference)	5.35	3.32–7.45
Blood pressure, %						
Optimal	5626	381	3.93	0.55 (0.48–0.63)	0.00	…
Borderline	3317	304	4.72	0.65 (0.56–0.74)	2.89	−0.11–5.64
Elevated	5655	835	7.65	1 (Reference)	21.6	16.8–26.7
BMI, %						
Optimal	4889	389	4.27	0.65 (0.56–0.74)	0.00	…
Borderline	5767	591	5.28	0.70 (0.62–0.79)	5.16	0.93–9.26
Elevated	3942	531	7.36	1 (Reference)	12.7	9.30–16.3
Diabetes mellitus, %						
Optimal	7558	645	4.68	0.67 (0.58–0.78)	0.00	…
Borderline	5491	617	5.83	0.71 (0.61–0.82)	0.78	−3.52–4.84
Elevated	1533	253	8.77	1 (Reference)	3.08	0.91–5.30
Smoking, %						
Optimal	6077	510	4.23	0.55 (0.48–0.62)	0.00	…
Borderline	4769	550	5.76	0.60 (0.52–0.68)	2.06	−2.05–6.05
Elevated	3752	460	7.45	1 (Reference)	9.78	6.74–12.9

Huxley RR et al, Circulation. 2011;123:1501-1508.)

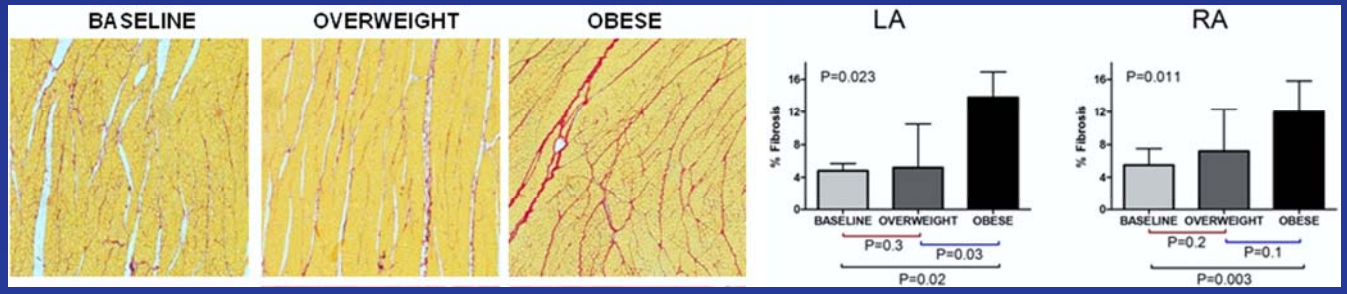
Abed HS *et al. Heart Rhythm Journal 2013;10:90-100*

Obesity produces an AF substrate in overfed sheep





-Obesity produces a clear mechanistic substrate for AF



Abed HS et al. *JAMA* 2013;310:250-260.

Effects of weight loss on AF substrate in man

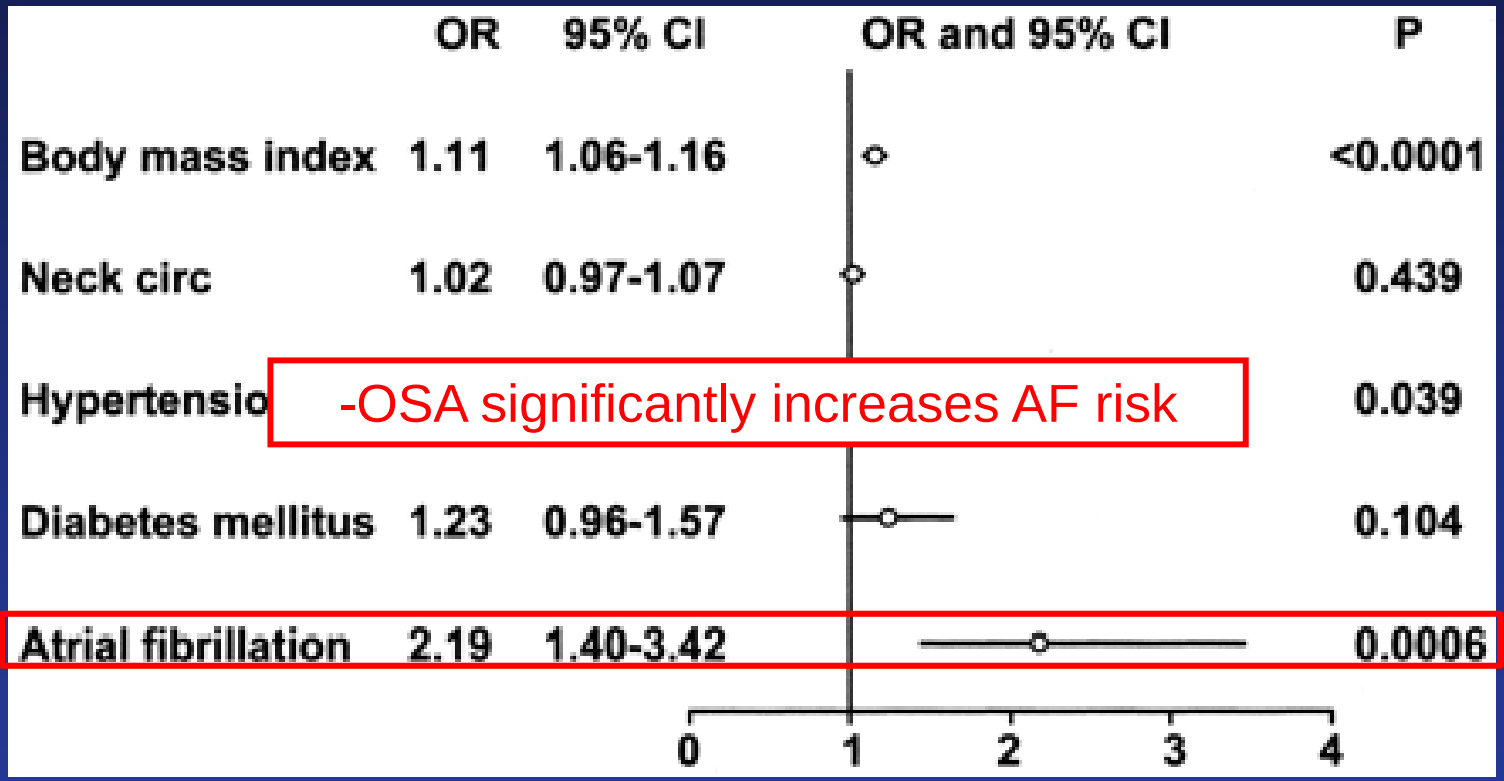
Table 2. Anthropometric Measures, Serum Biochemistry Values, Blood Pressure, and Atrial Fibrillation Frequency and Duration at Baseline and Follow-up

	Mean (95% CI)				
	Intervention		Control		
Variable	Baseline (n = 75)	Follow-up[a] (n = 42)	Baseline (n = 75)	Follow-up[a] (n = 39)	*P* Value[b]
Anthropometric measures					
Waist circumference, cm	110 (108 to 112)	92.8 (89.5 to 96.1)	112 (110 to 114)	107 (103 to 111)	<.001
Weight, kg	99 (96 to 102)	80 (76 to 84)	101 (97 to 105)	96 (90 to 102)	<.001
BMI[c]				to 33.9)	<.001
AFSS score, change from b					
Symptom burden	11.8 (10.0 to 13.6)		2.6 (0.8 to 4.3)		<.001
Symptom severity score	8.4 (5.9 to 10.9)		1.7 (−0.5 to 3.9)		<.001
Atrial fibrillation detected by 7-d continuous ambulatory rhythm recording					
	n = 75	n = 57	n = 75	n = 52	
≥1 episode, No. (%)	49 (65)	9 (21)	43 (57)	22 (56)	<.001
No. of episodes	3.3 (1.6 to 4.9)	0.62 (0.19 to 1.0)	2.8 (1.7 to 4.0)	2.0 (1.1 to 3.0)	<.001
Total duration, min	1176 (720 to 1632)	491 (159 to 822))	1394 (795 to 1994)	1546 (782 to 2308)	<.001

Reversing obesity reverses AF substrate

There is therefore a rationale for identifying and aggresively managing CV risk factors to prevent substrate progression

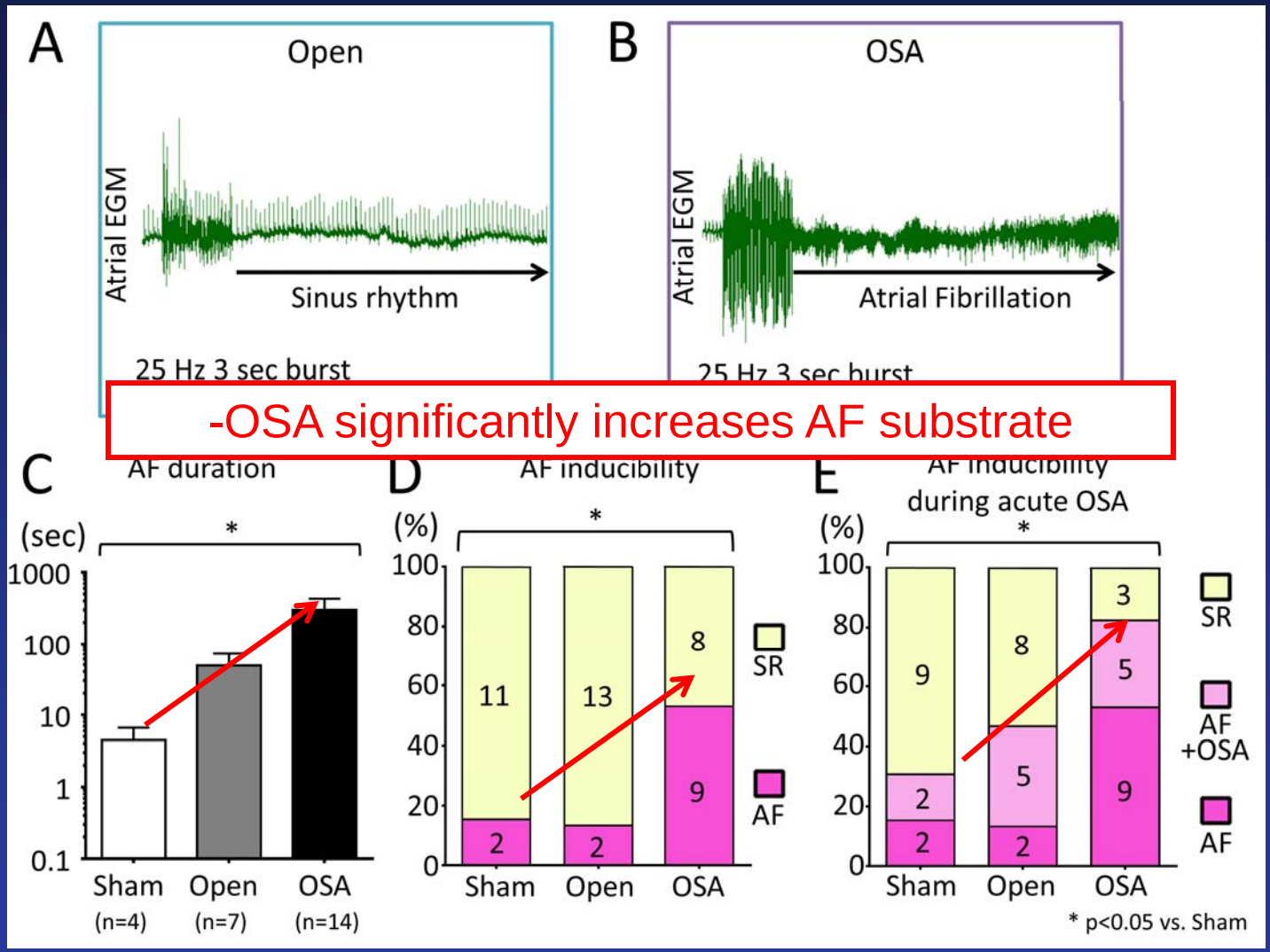
Obstructive sleep apnea and AF



-OSA significantly increases AF risk

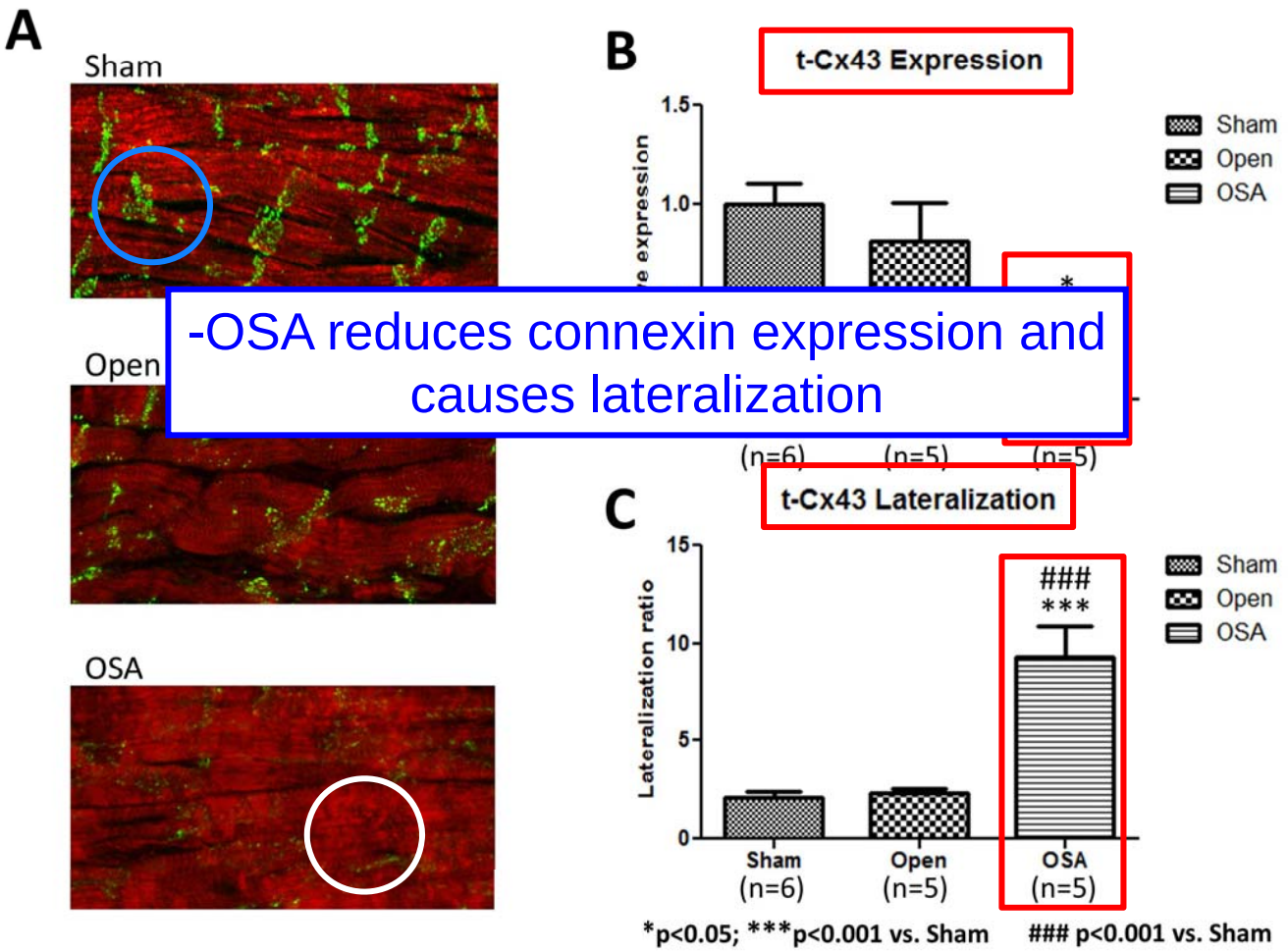
***Gami AS et al**, Circulation. 2004;110:364–367.*

Obstructive sleep apnea and AF



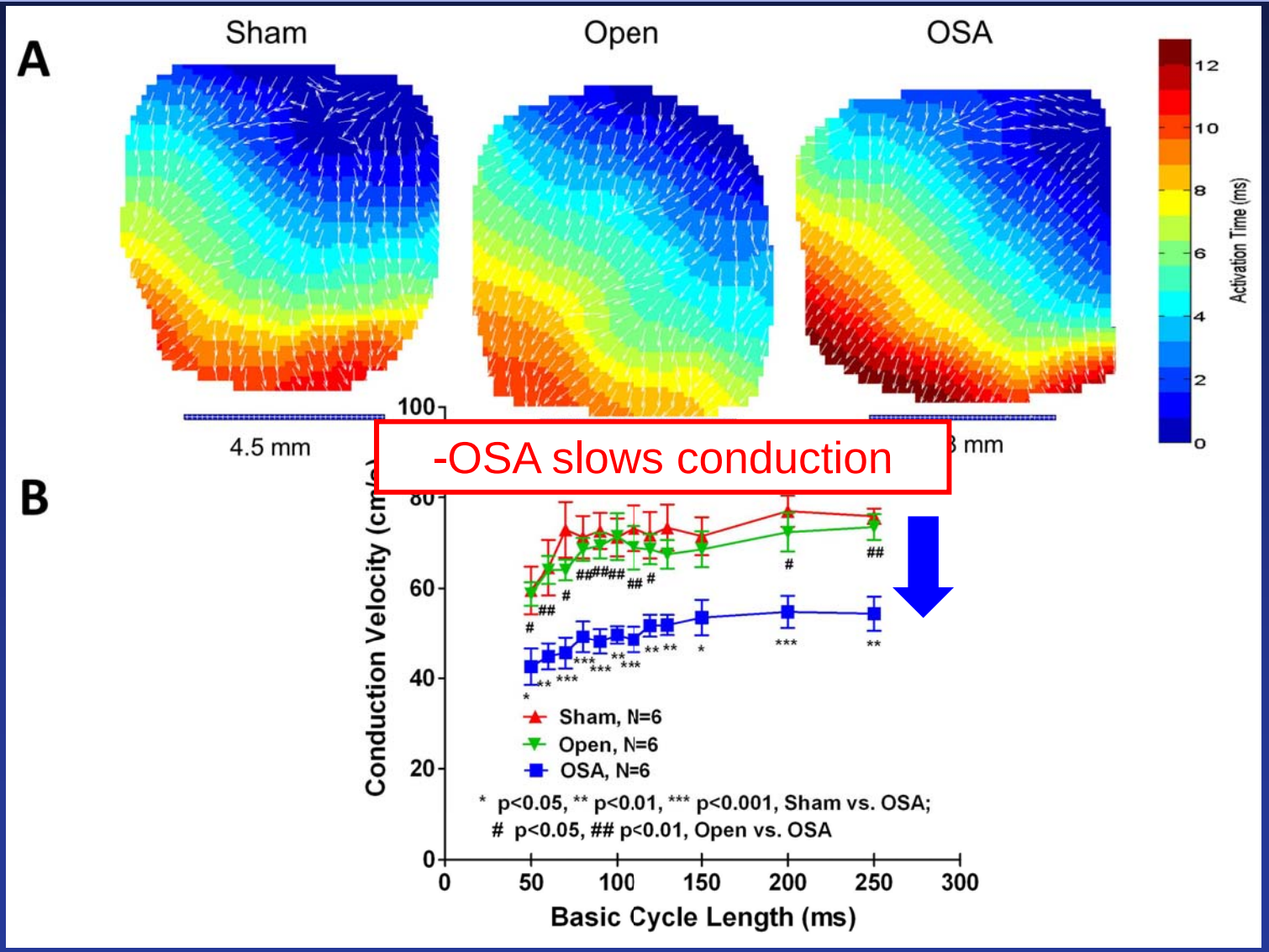
***Iwasaki Y et al**, J Am Coll Cardiol, 64:2013-2023, 2014.*

Obstructive sleep apnea and AF: effects on connexins



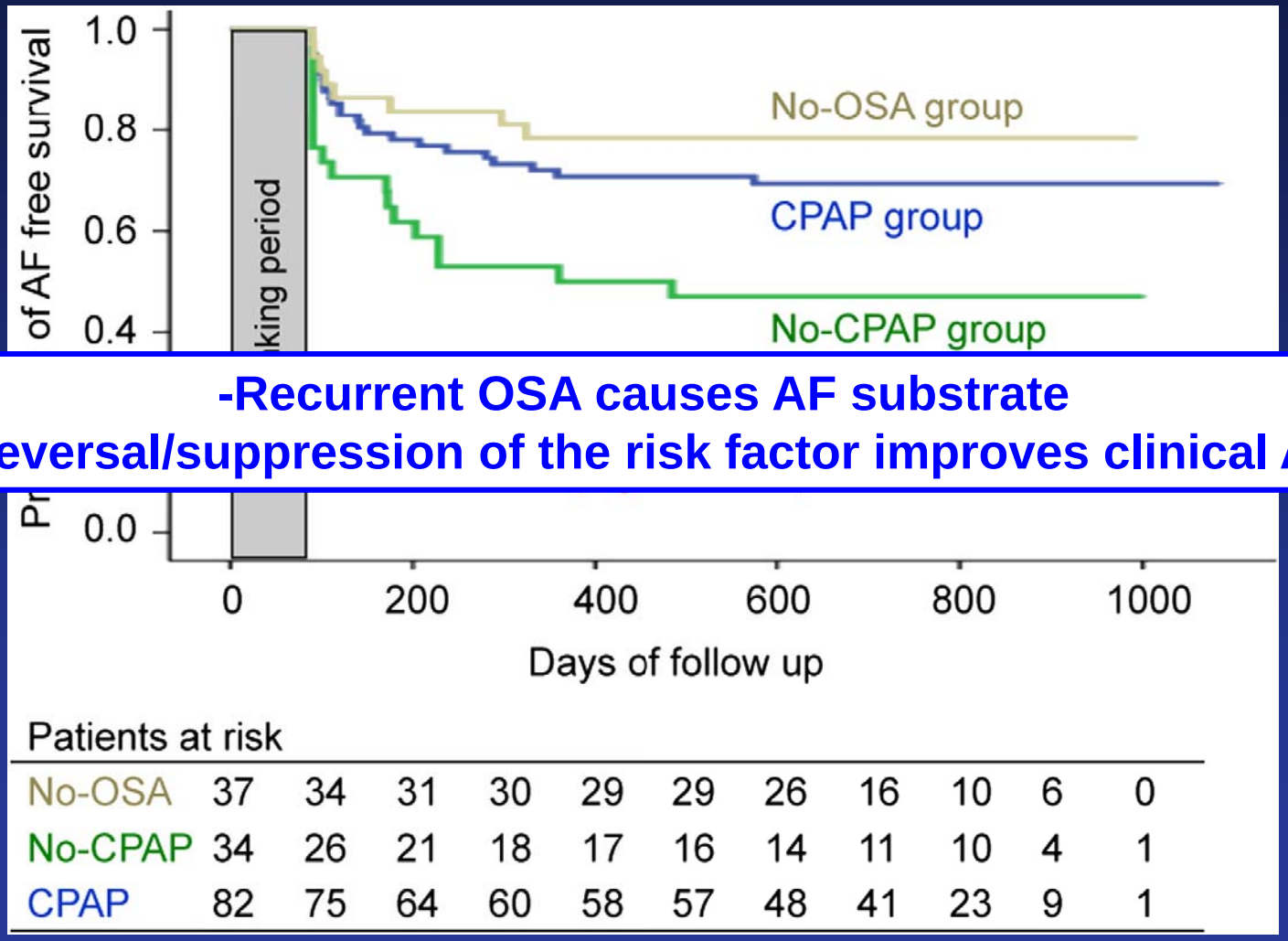
Iwasaki Y et al, *J Am Coll Cardiol*, 64:2013-2023, 2014.

Obstructive sleep apnea and AF: effects on conduction



Iwasaki Y et al, J Am Coll Cardiol, 64:2013-2023, 2014.

Obstructive sleep apnea, CPAP and AF



-Recurrent OSA causes AF substrate
-Reversal/suppression of the risk factor improves clinical AF

Naruse Y et al, *Heart Rhythm 2013;10:331–337.*

Outline

- Coronary artery disease therapy and prevention
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Atrial remodeling

Outline

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Challenge of AF Progression

Clinical Outcome at 12 Months in 90 (87%) Patients of the Study Population

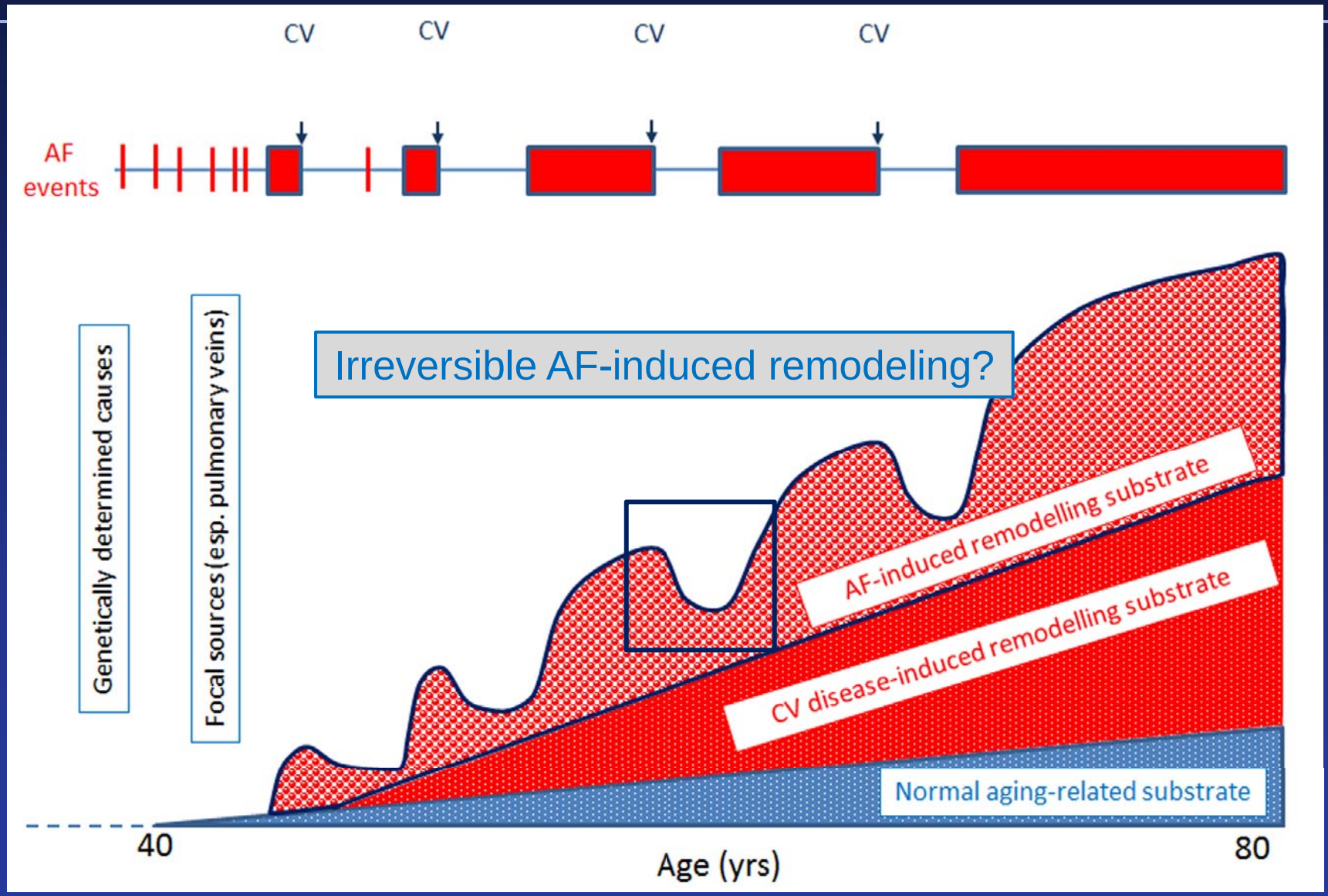
		Atrial Tachycardia		Atrial Fibrillation		AF-Free,*
	Sinus Rhythm, n (%)	Paroxysmal	Persistent	Paroxysmal	Persistent	%
Based on continuous AF duration						
Presenting in sinus rhythm (n=23)	17 (74)	1	1	4	0	83†
AF ≤6 mo (n=25)	17 (68)	1	3	3	1	84†
AF 7–12 mo (n=22)	14 (64)	3	2	1	2	86†
AF >12 mo (n=20)	10 (50)	0	3	1	6	65†
Total	58	14		18		

- **It has been known since the1920s that the longer AF lasts, the more resistant it becomes to therapy**

HAISSAGUERRE ET AL. *Circulation 2014; 130:530-538*

Nattel S *et al. EHJ 2014 Jun 7;35(22):1448-56.*

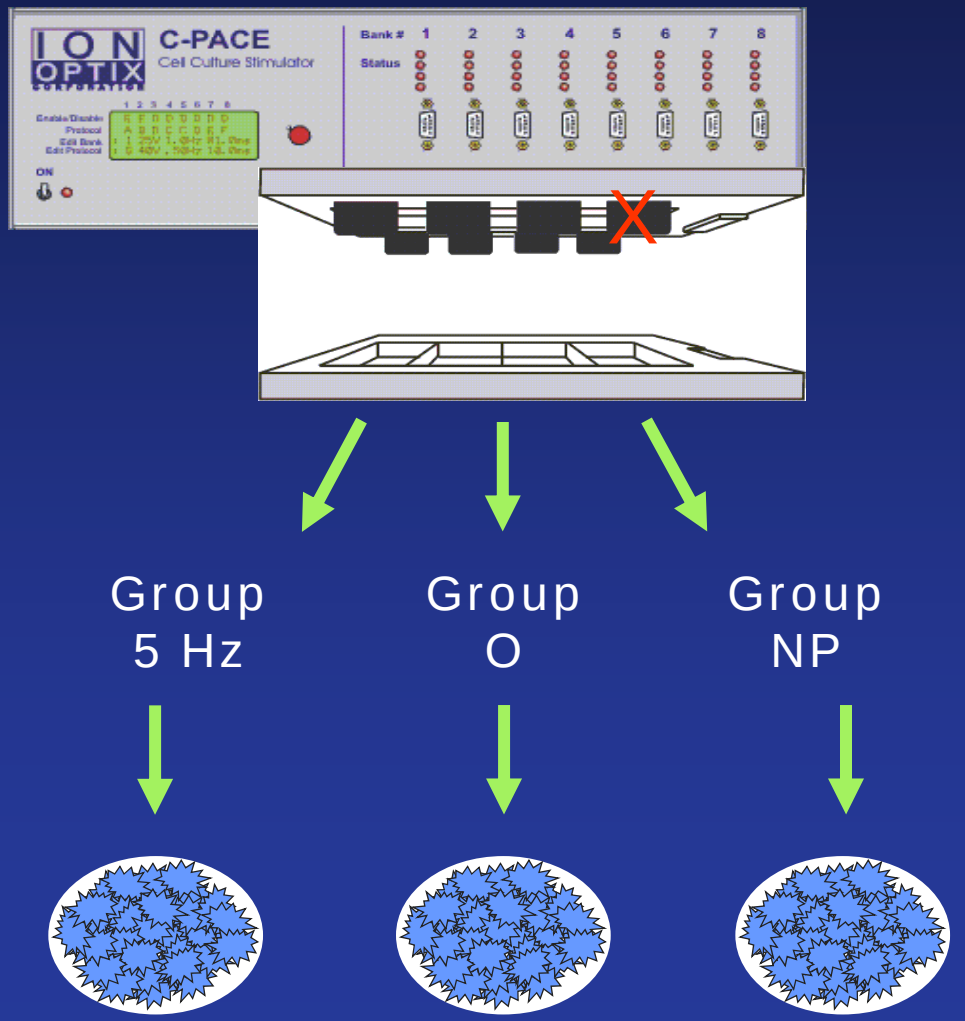
Understand and Preventing AF-induced remodelling



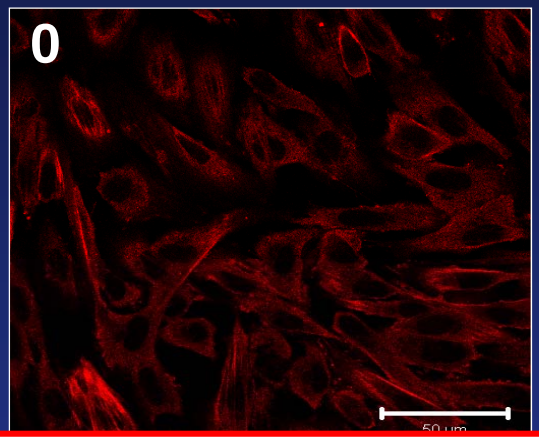
Does AF itself produce the fibrosis causing peristence?

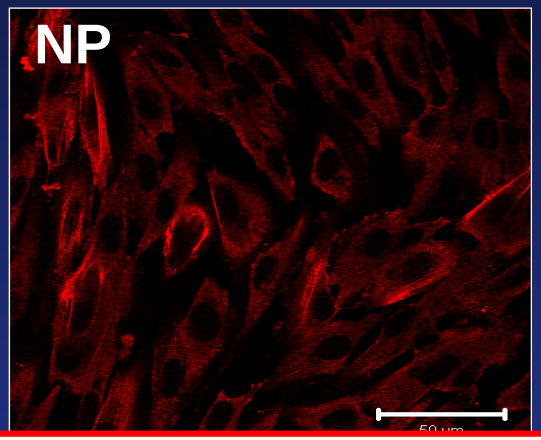
Experimental Design

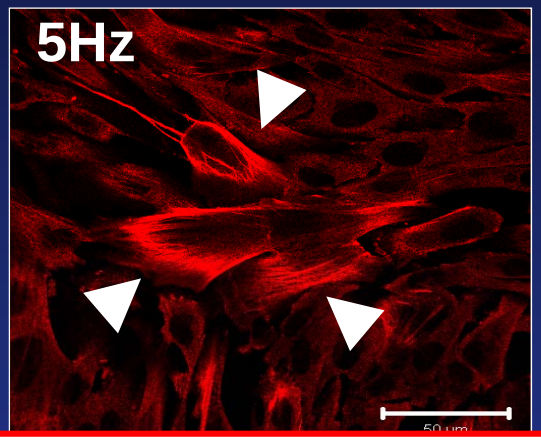
- Rapidly-paced atrial-derived cardiomyocytes 24 hrs in culture
  - Groups:
    - Rapidly-paced (5 Hz)
    - Non-paced (NP)
    - Medium alone (0)
- Collect conditioned media
- Stimulate cultured atrial fibroblasts
- Analyze fibroblast responses



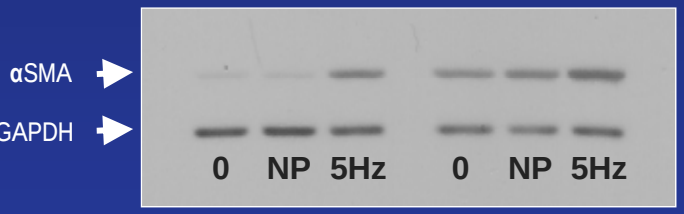
Fibroblast Responses

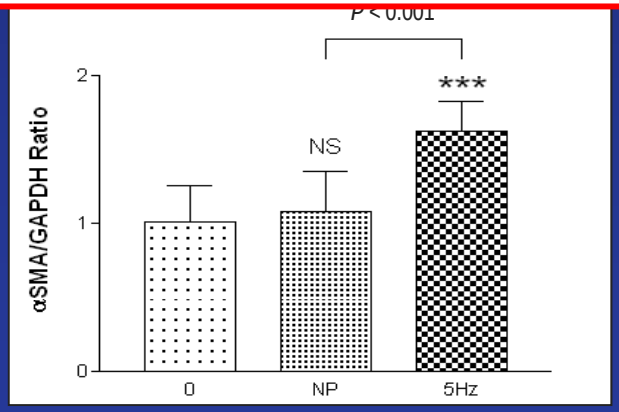


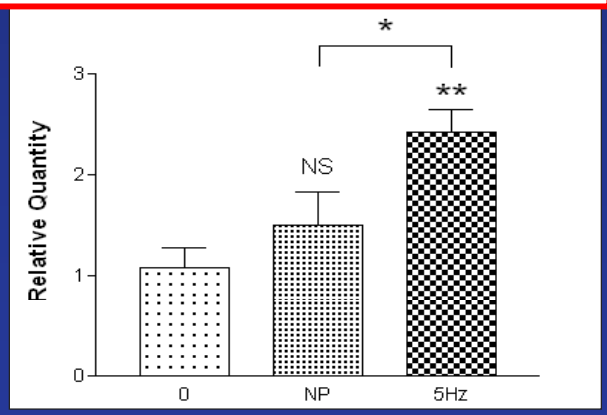




Rapidly firing atrial cardiomyocytes release substances that activate fibroblasts and cause them to produce more collagen

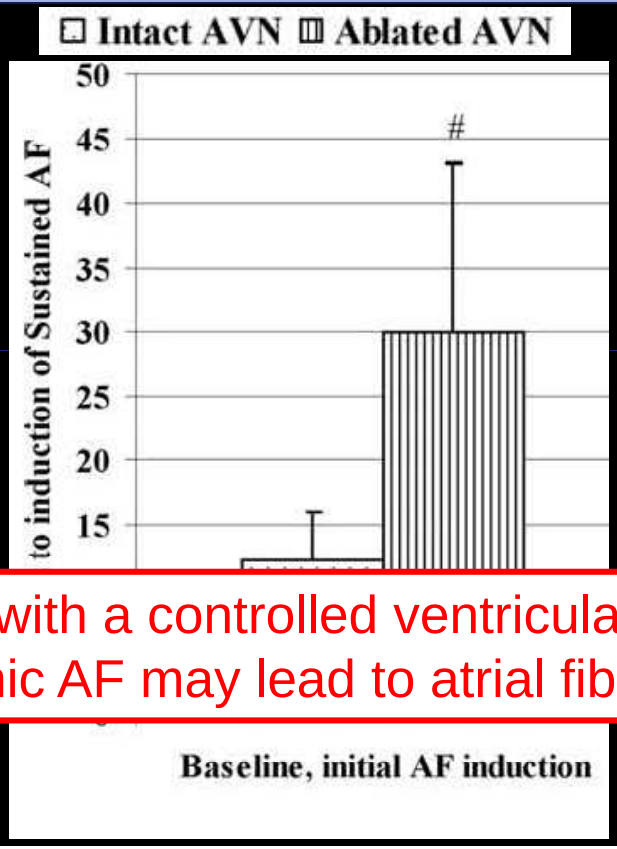






Burstein et al. (2007) *Cardiovasc Res*.

Intact AV node function and fibrosis in AF



Avitall B, et al. Heart Rhythm 2008;5:839-45.

Thus, even with a controlled ventricular response, chronic AF may lead to atrial fibrosis

Table 2 Percent concentration of fibrosis

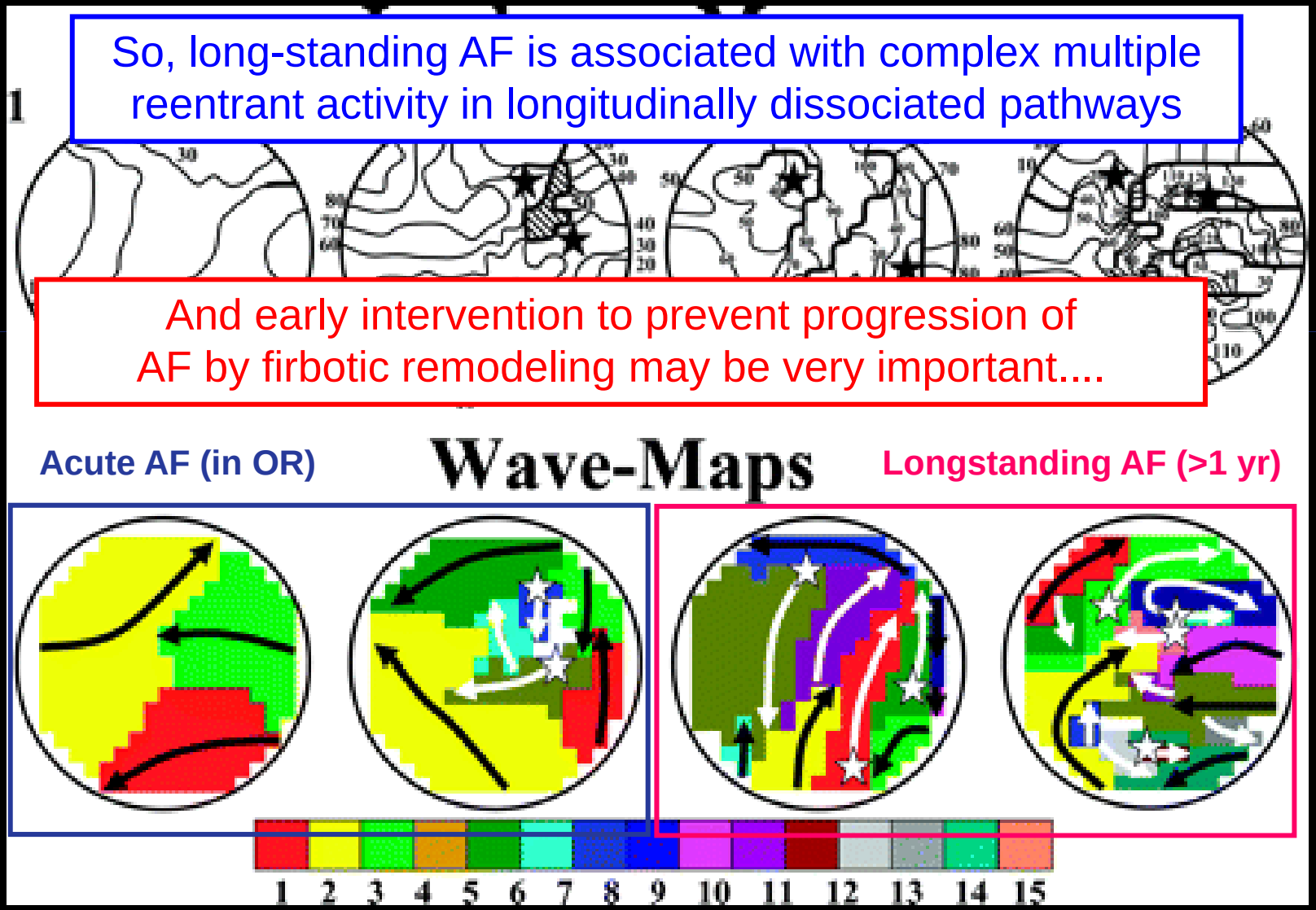
	LA	RA	LV
Intact AVN and AF	14.2% ± 5.3%*	15.8% ± 6%*	10.7% ± 4.9%*
Ablated AVN and AF	10.7% ± 5.8%†	10.7% ± 6.2%†	3.7% ± 2.2%
Sham, NL tissues	4.1% ± 2.3%	3.8% ± 1.9%	3.6% ± 1.7%

AVN = atrioventricular node; LA = left atrial; LV = left ventricular; NL = normal; RA = righ atrial.
*P <.005 ablated AVN vs intact AVN and NL tissues.
†P <.02 ablated AVN vs NL tissues.

Possible consequences of AF-induced fibrosis: Increasing complexity of long-standing AF

So, long-standing AF is associated with complex multiple reentrant activity in longitudinally dissociated pathways

And early intervention to prevent progression of AF by firbotic remodeling may be very important....



ALLESSIE MA et al, *Circ Arrhythm Electrophysiol. 2010 Dec 1;3(6):606-15.*

Outline

- Coronary artery disease therapy and prevention
- The evolution of AF pathophysiology understanding
- Mechanisms of AF progression
- Risk factors and the AF substrate
- Therapeutic implications

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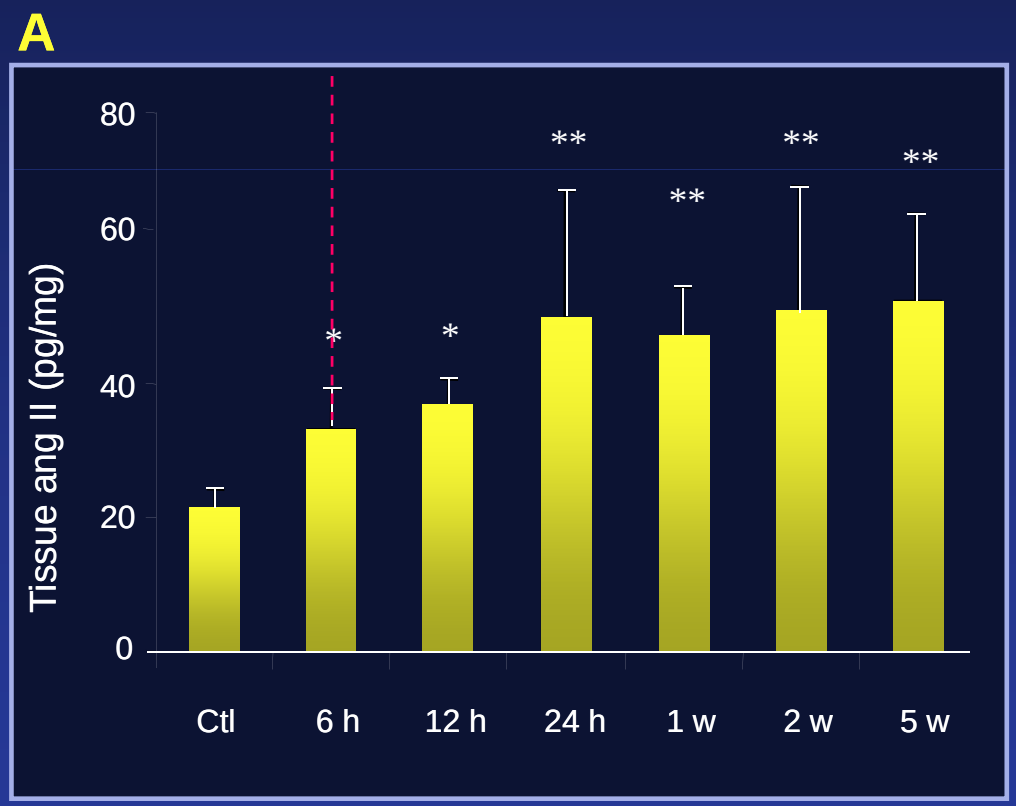
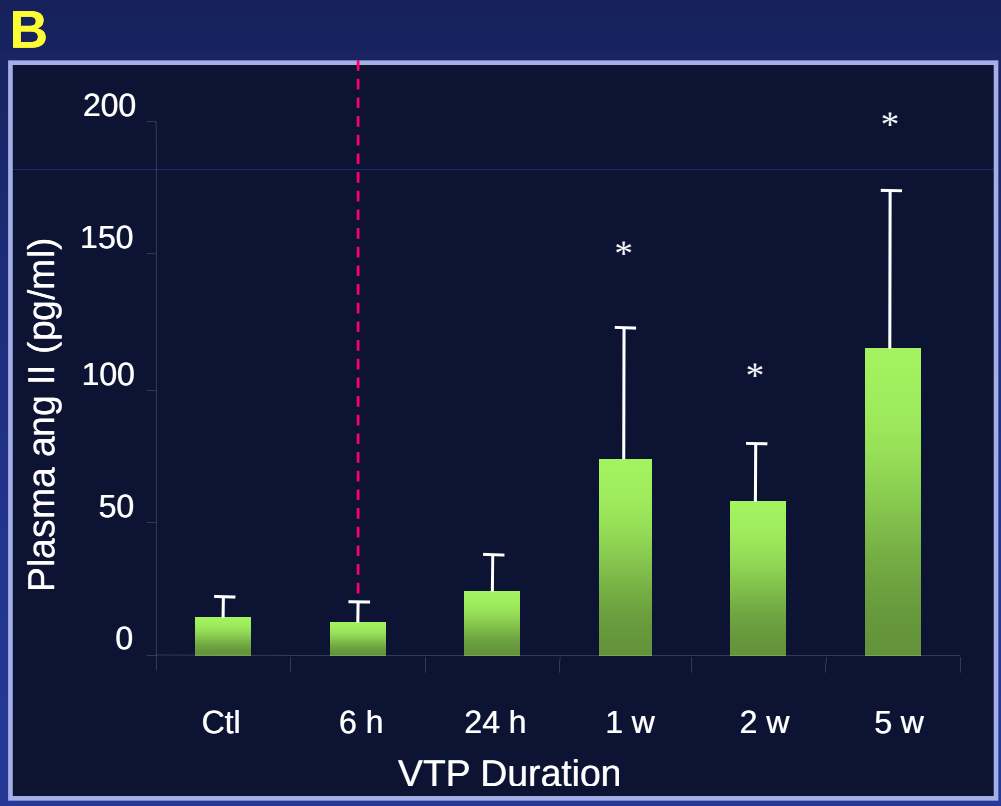
Drugs to prevent remodeling

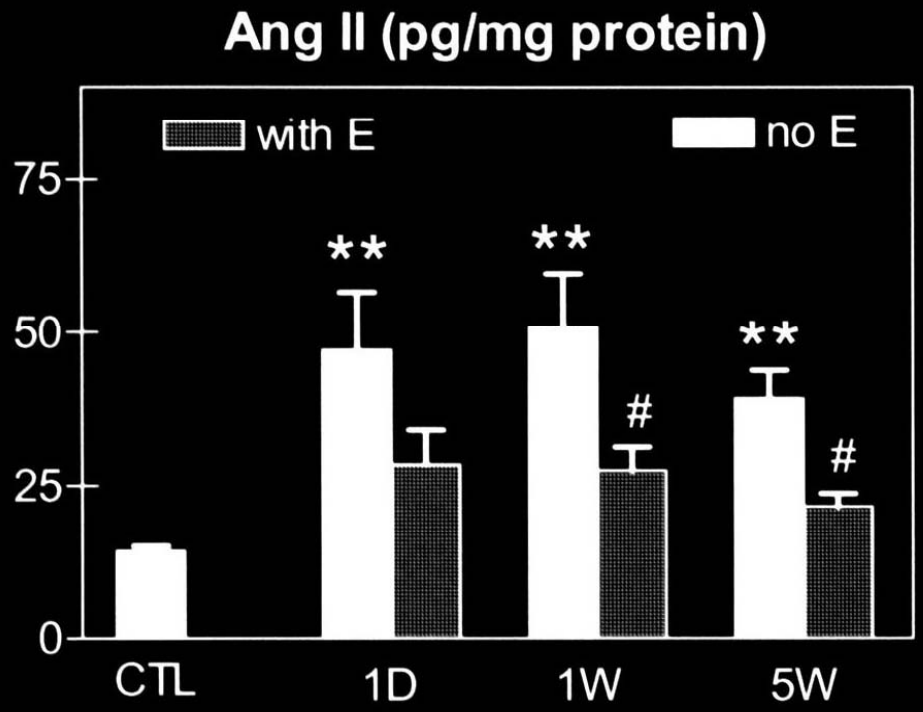
Angiotensin II changes over the course of tachycardiomyopathy-induced atrial remodeling

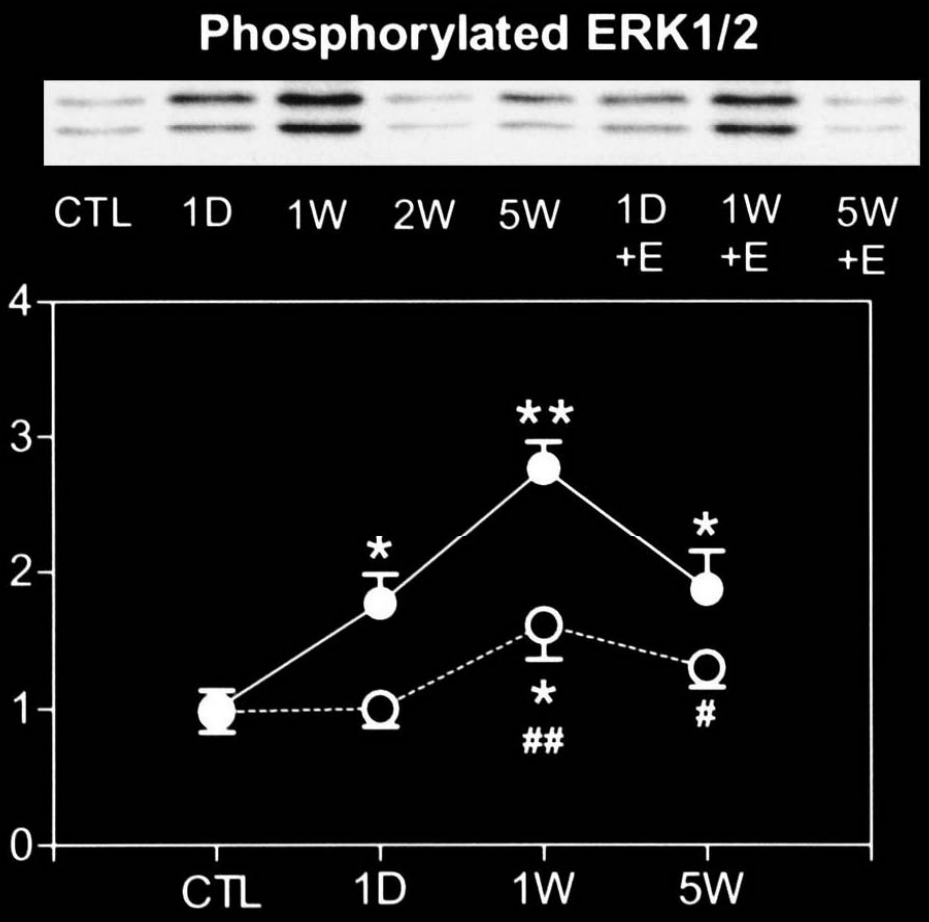




CARDIN S et al, *Cardiovasc Res 60: 315-325, 2003*

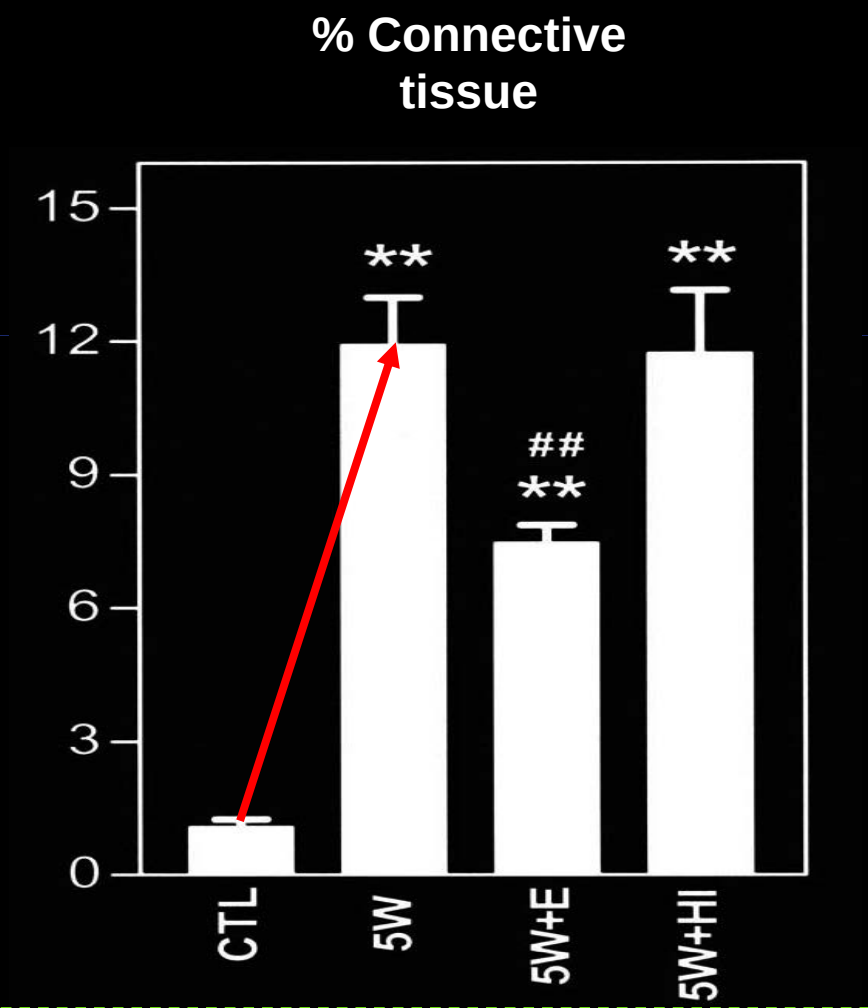
Enalapril Attenuates Angiotensin and MAPK Changes

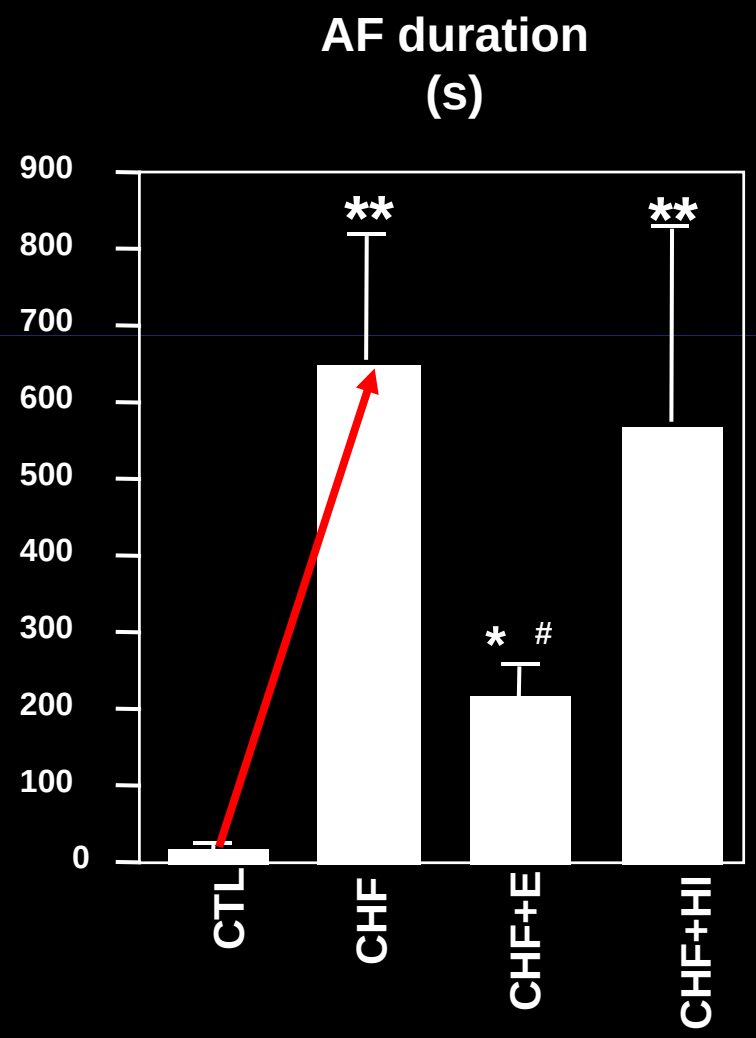




LI D et al, *Circulation 104: 2608-2614, 2001*

Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?



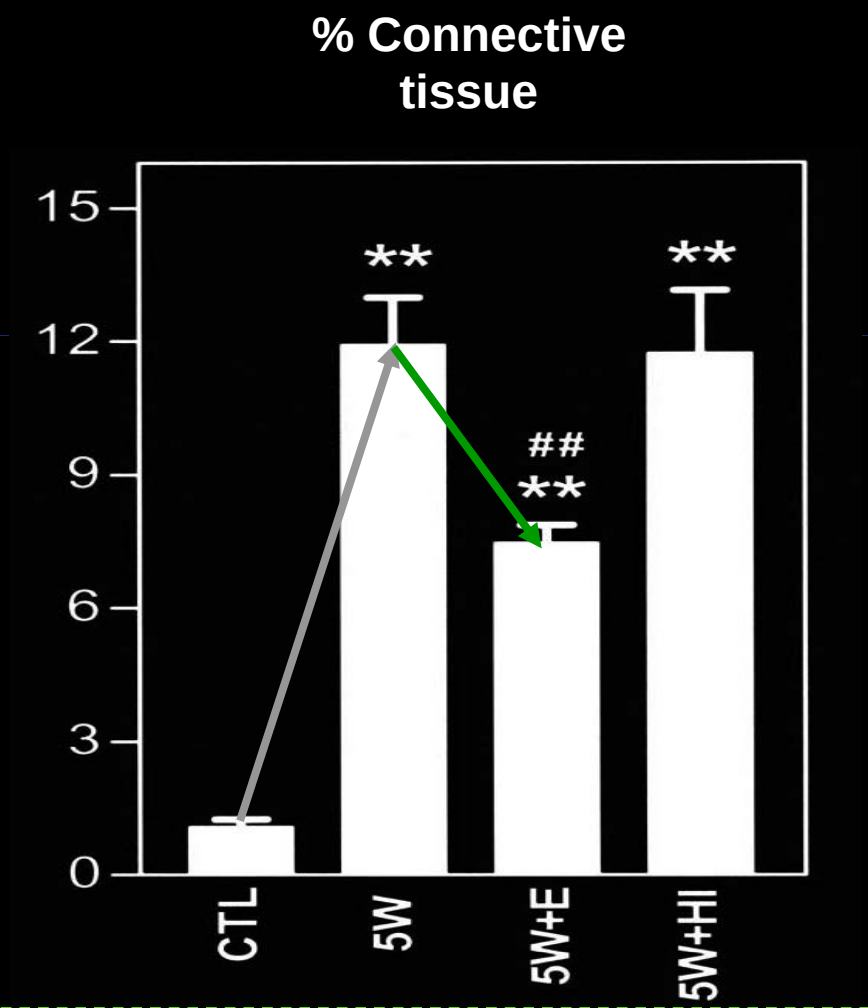


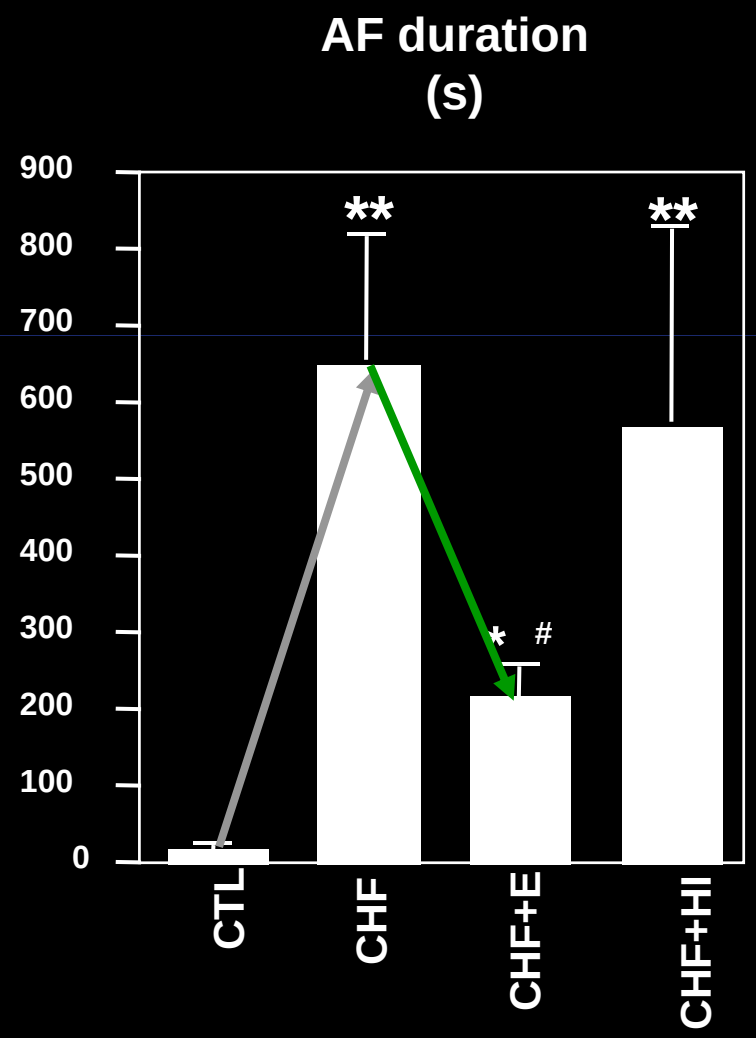
E = enalapril; HI=hydralazine/isosorbide

CHF induces fibrosis and increases AF duration

LI D et al, *Circulation 104: 2608-2614, 2001*

Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?



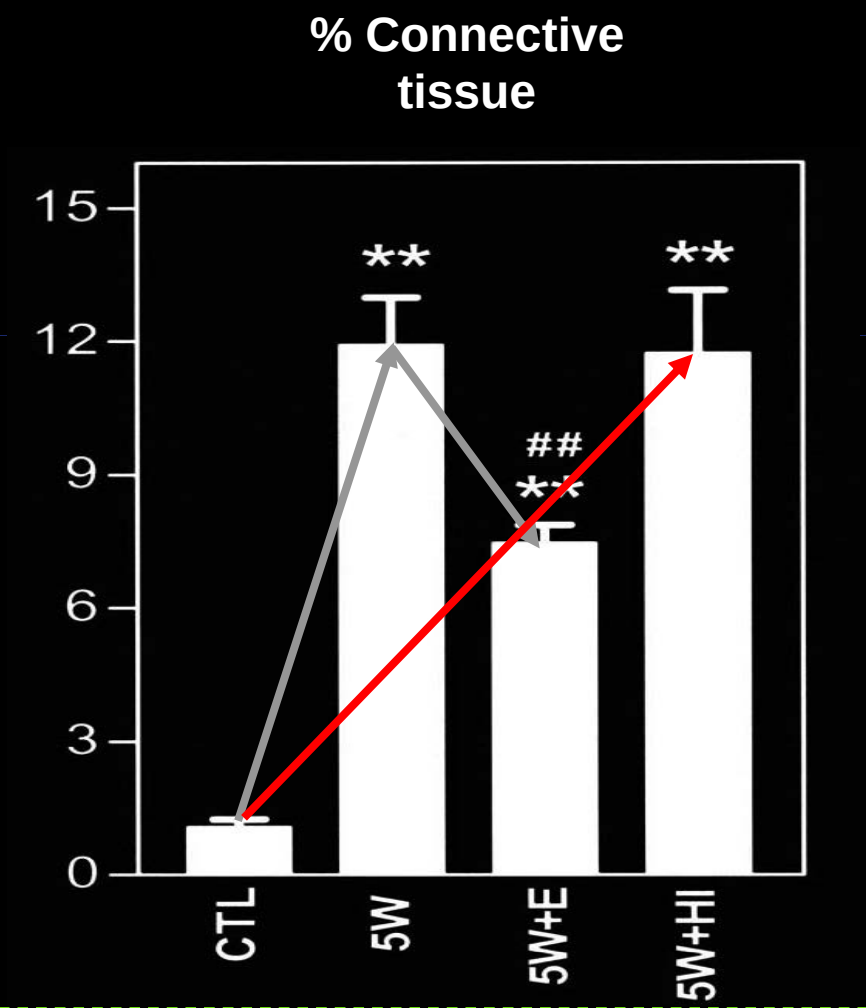


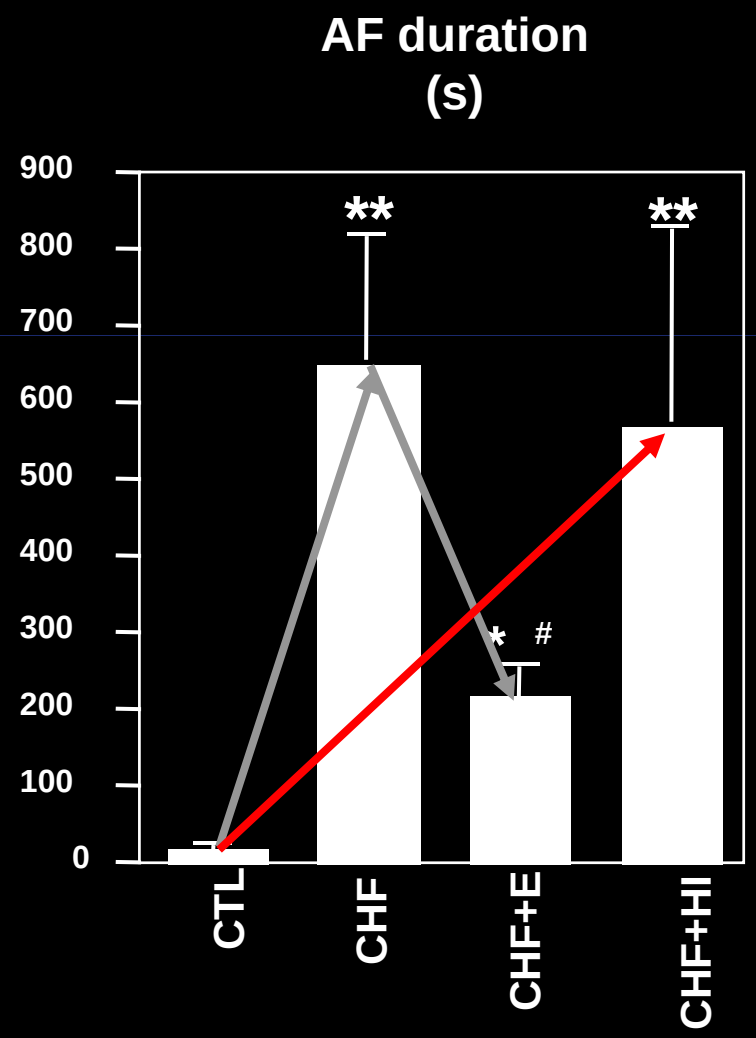
E = enalapril; HI=hydralazine/isosorbide

LI D et al, *Circulation 104: 2608-2614, 2001*

Enalapril attenuates fibrosis and AF duration increases

Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?



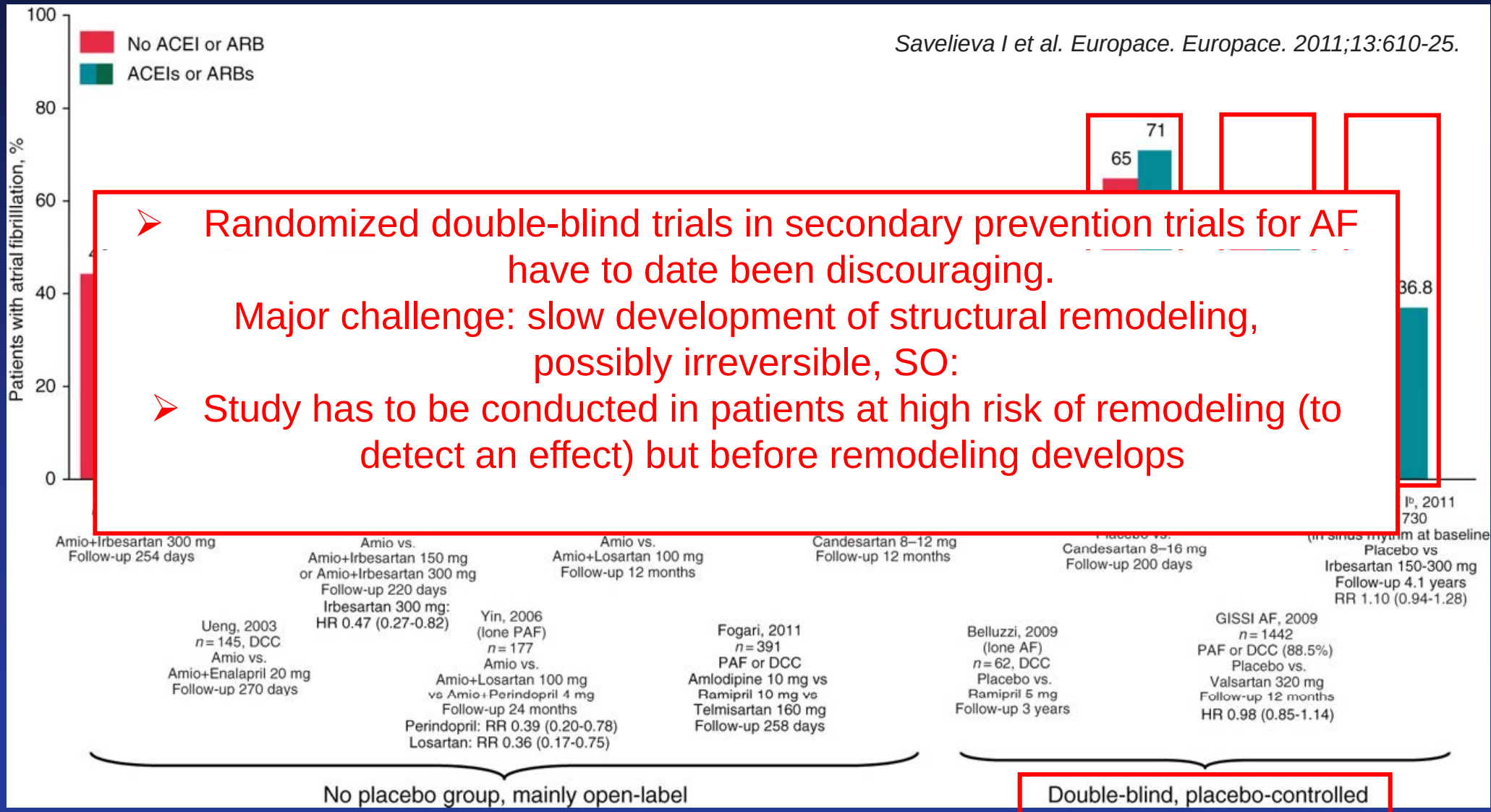


E = enalapril; HI=hydralazine/isosorbide

Vasodilator therapy does not mimic enalapril effects

LI D et al, *Circulation 104: 2608-2614, 2001*

Renin-angiotensin inhibitors in secondary prevention



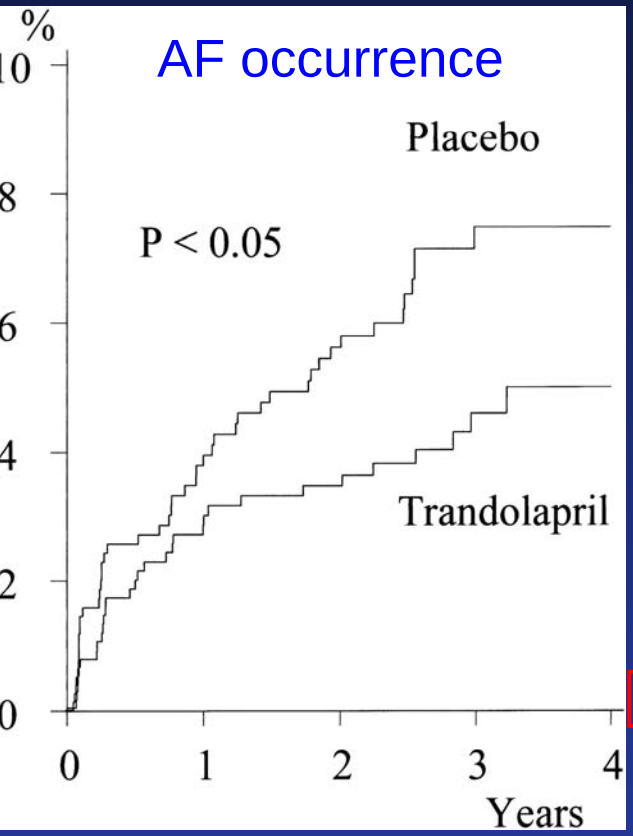
Savelieva I et al. Europace. Europace. 2011;13:610-25.

- Randomized double-blind trials in secondary prevention trials for AF have to date been discouraging.

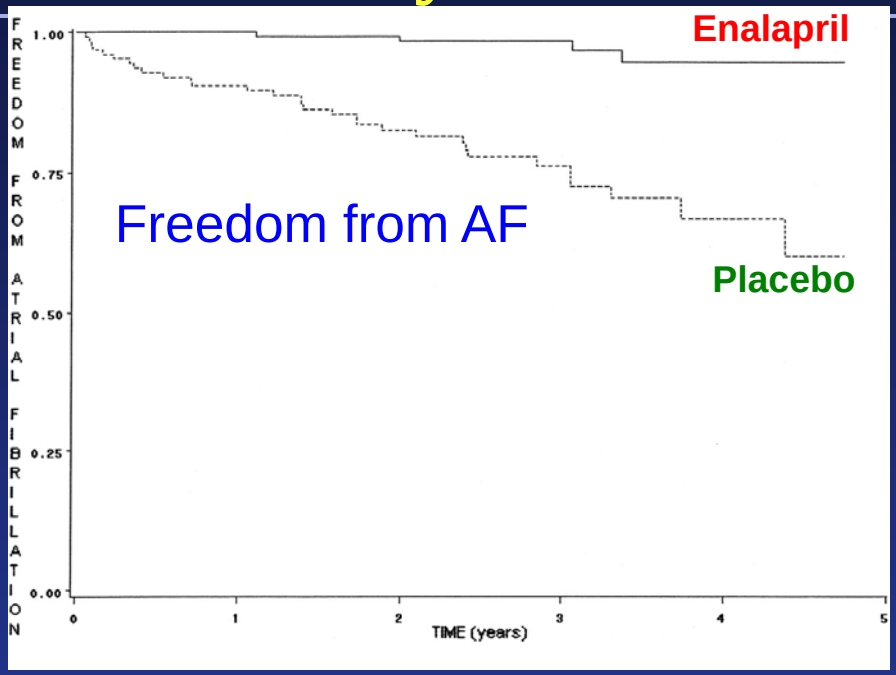
Major challenge: slow development of structural remodeling, possibly irreversible, SO:

- Study has to be conducted in patients at high risk of remodeling (to detect an effect) but before remodeling develops

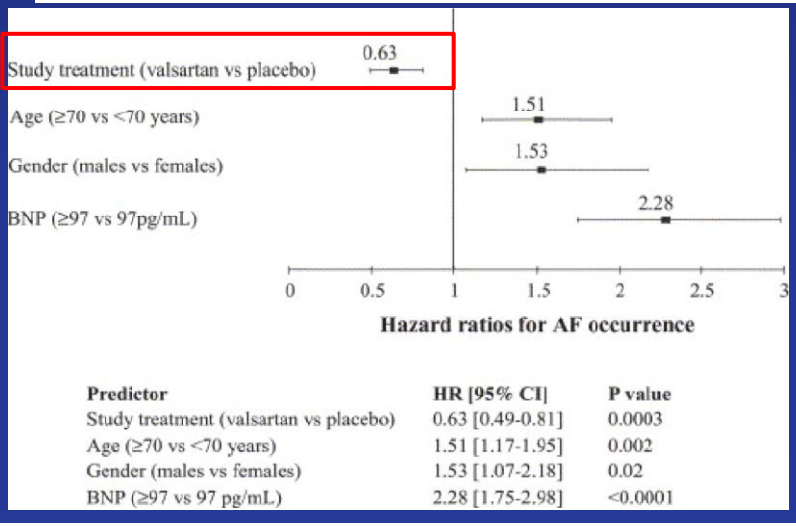
AF occurrence in prospective randomized trials of ACE inibitors/ARBs for LV dysfunction/heart failure



Pederson OD et al, Circulation, 1999



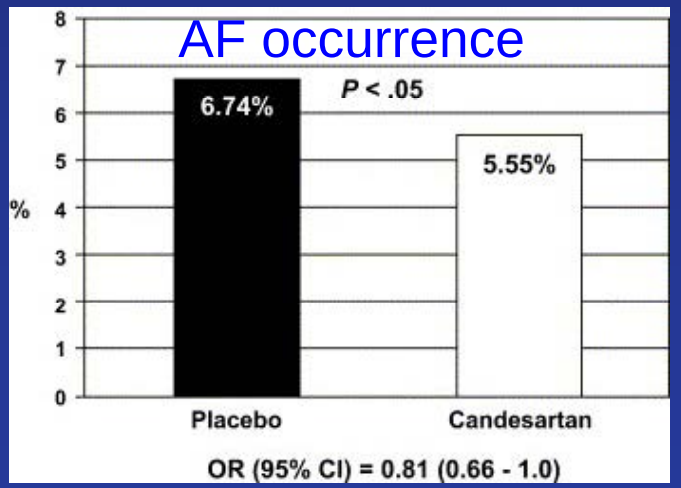
Vermes E et al, Circulation 2003.



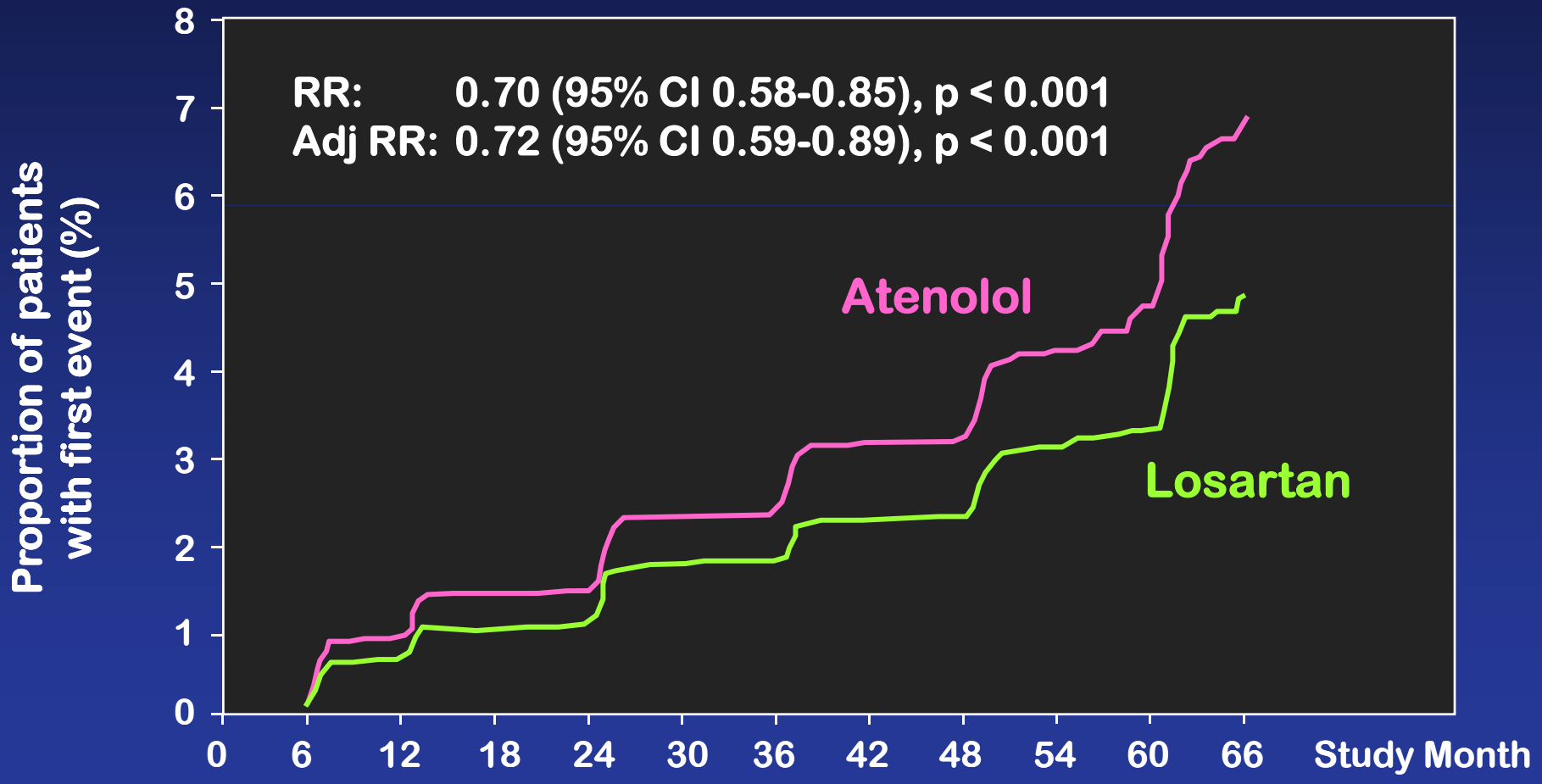
Predictor	HR [95% CI]	P value
Study treatment (valsartan vs placebo)	0.63 [0.49-0.81]	0.0003
Age (≥70 vs <70 years)	1.51 [1.17-1.95]	0.002
Gender (males vs females)	1.53 [1.07-2.18]	0.02
BNP (≥97 vs 97 pg/mL)	2.28 [1.75-2.98]	<0.0001

Maggioni AP et al, AHJ, 2005

Ducharme A et al, AHJ, 2006

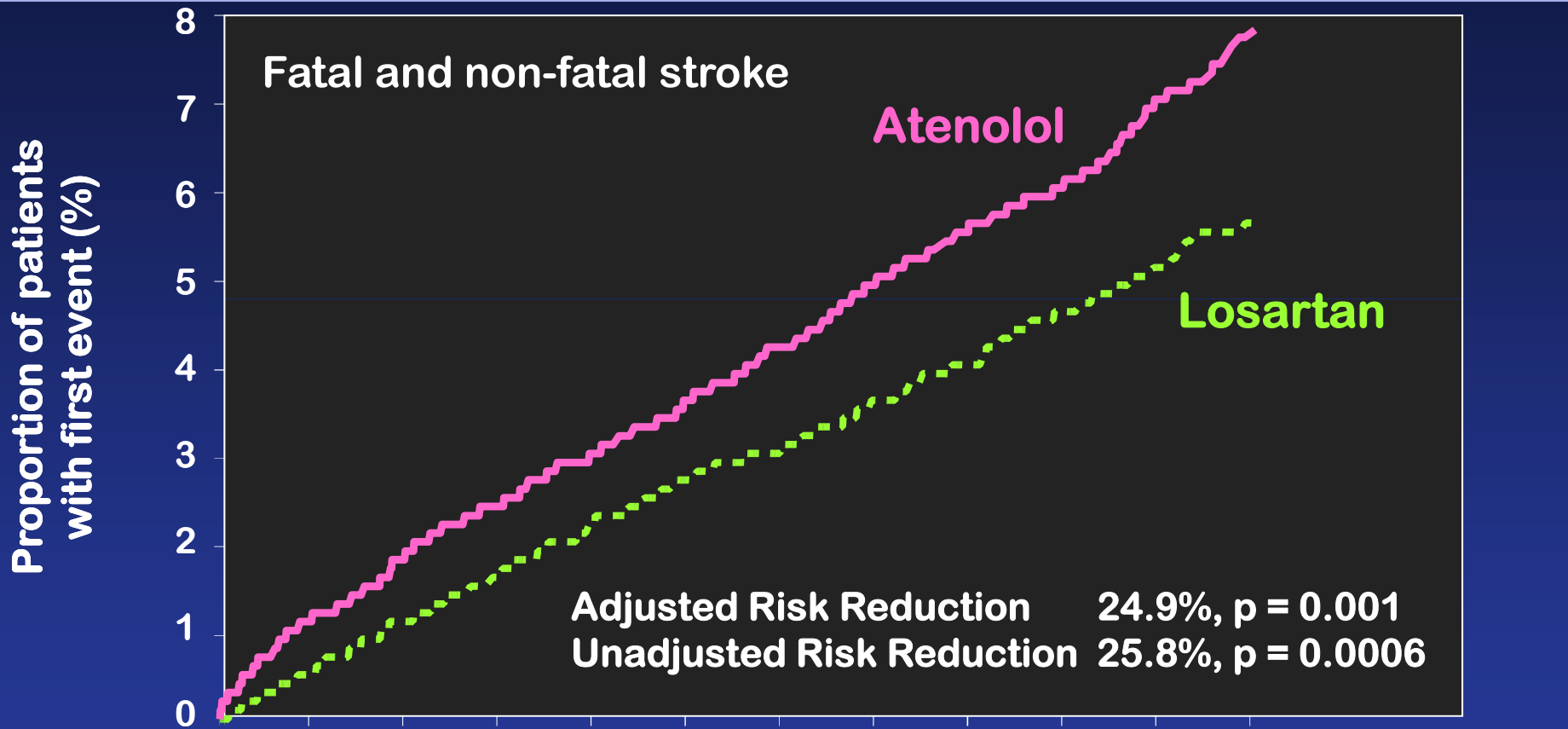


New-onset atrial fibrillation by treatment group in LIFE Trial (Losartan in Hypertension/LVH)



European Heart Journal Vol 24, Abstr. Suppl. August/September 2003, page 504 (poster presented at ESC 2003, Vienna)

Reduction in the Risk of Stroke



Number at risk

Losartan	4605	4528	4469	4408	4332	4273	4224	4166	4117	3974	1928	925
Atenolol	4588	4490	4424	4372	4317	4245	4180	4119	4055	3894	1901	897

Risk reduction = relative risk vs. atenolol.

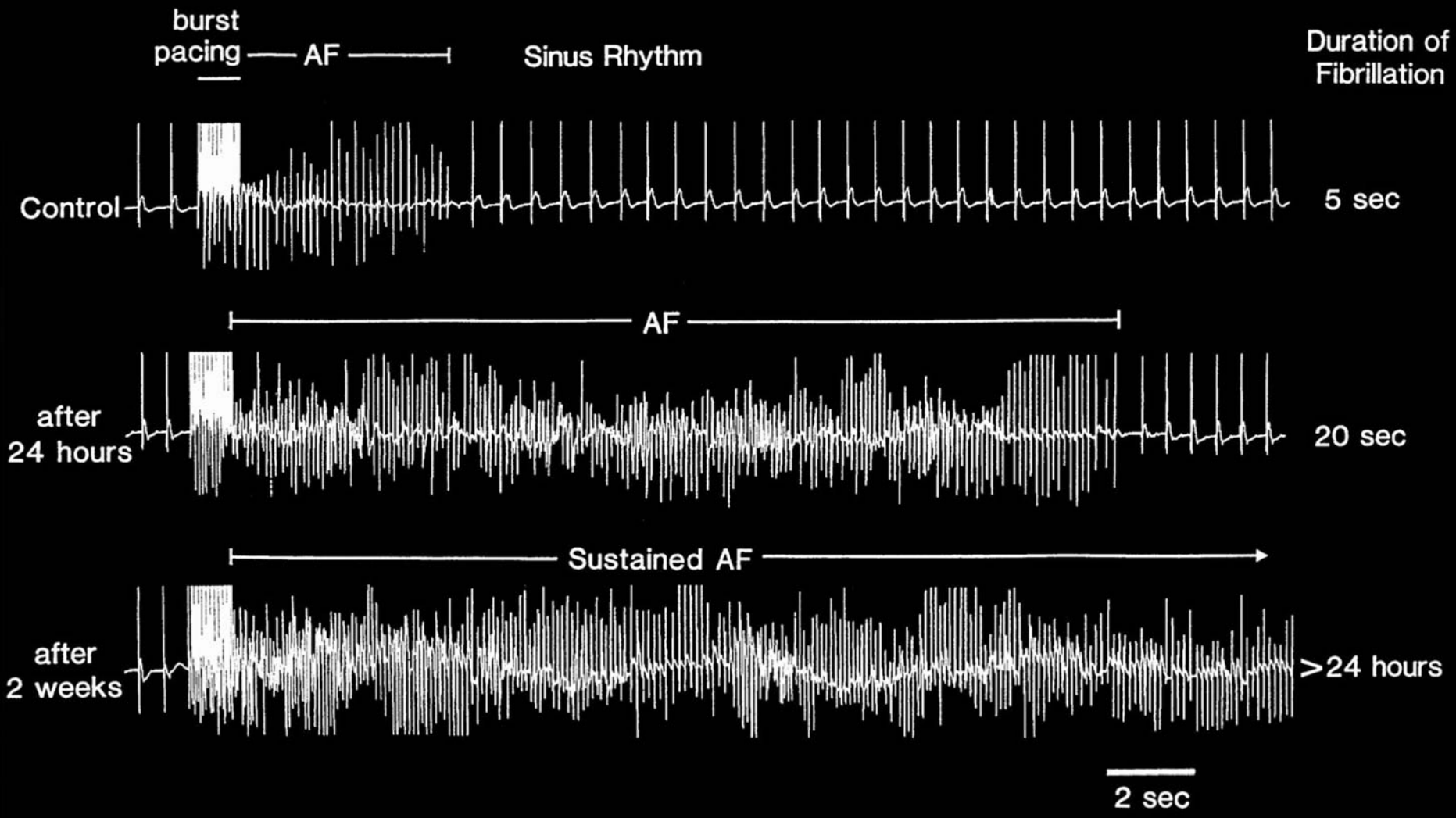
Dahlöf B et al. Lancet 2002; 359:995-1003

Risk factor intervention

Conclusions

- The CAD model includes an improved understanding of pathophysiology, with management of complications but also prevention
- Much has been learned about AF mechanisms in the past 20 years, which can (and has) been translated into better treatment and prevention
- Risk factor intervention is effective but impact likely slow
- Drug therapy to prevent progression is still in its infancy but looks promising

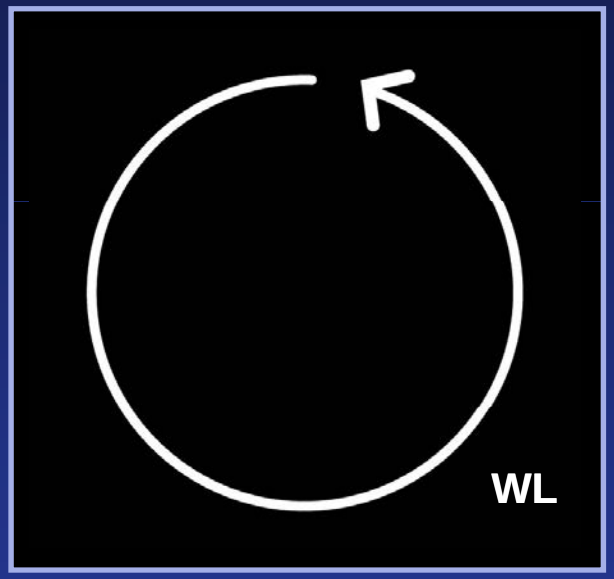
Atrial tachycardia remodeling: AF Begets AF



Wijffels MCEF, Kirchhof CJHJ, Dorland R, et al. Circulation 1995; 92:1954-1968

Reentry: Role of Refractory Period, Conduction and Wavelength Changes

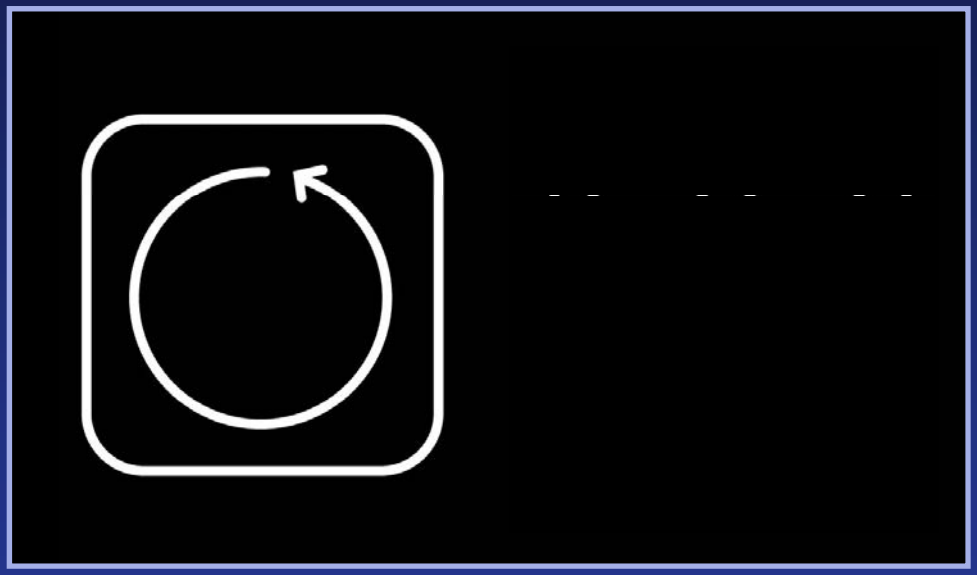
A



Wavelength (WL) =
refractory period x conduction velocity

- minimal path length for reentry
- size of functional reentry circuits

B

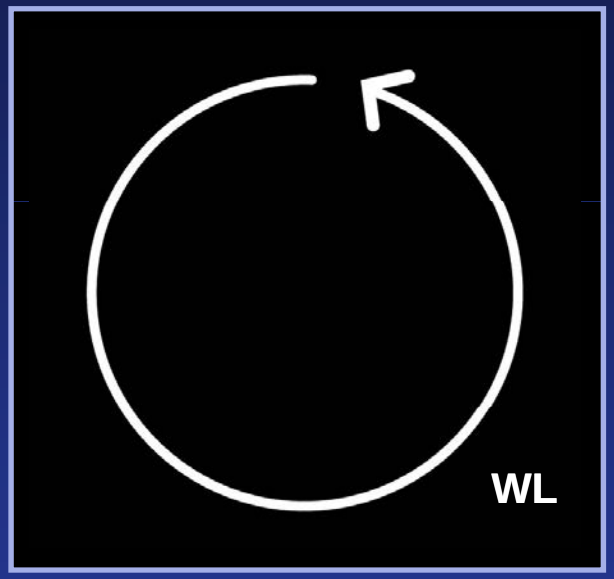


Normal atrial size
Normal WL

- reentry unstable
- AF not sustained

Reentry: Role of Refractory Period, Conduction and Wavelength Changes

A



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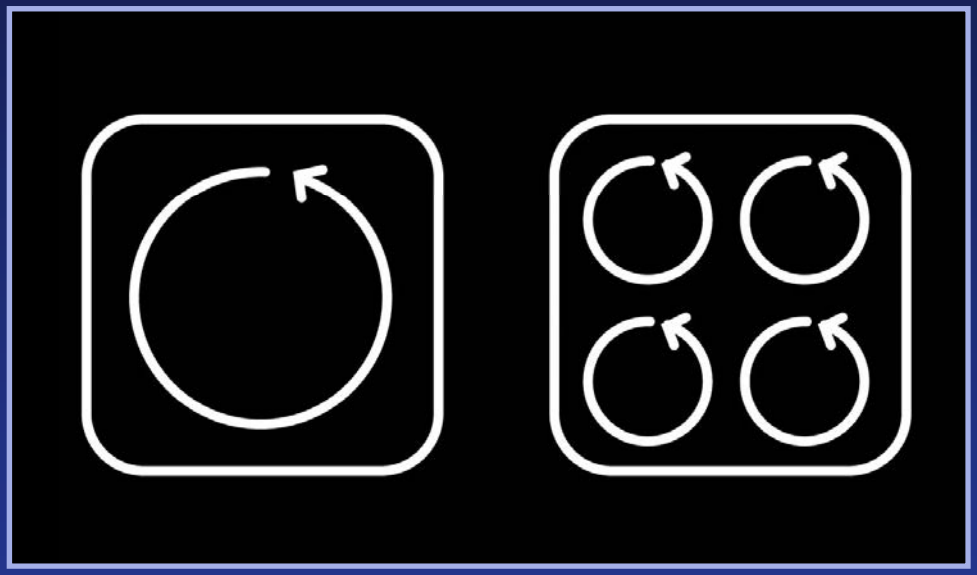


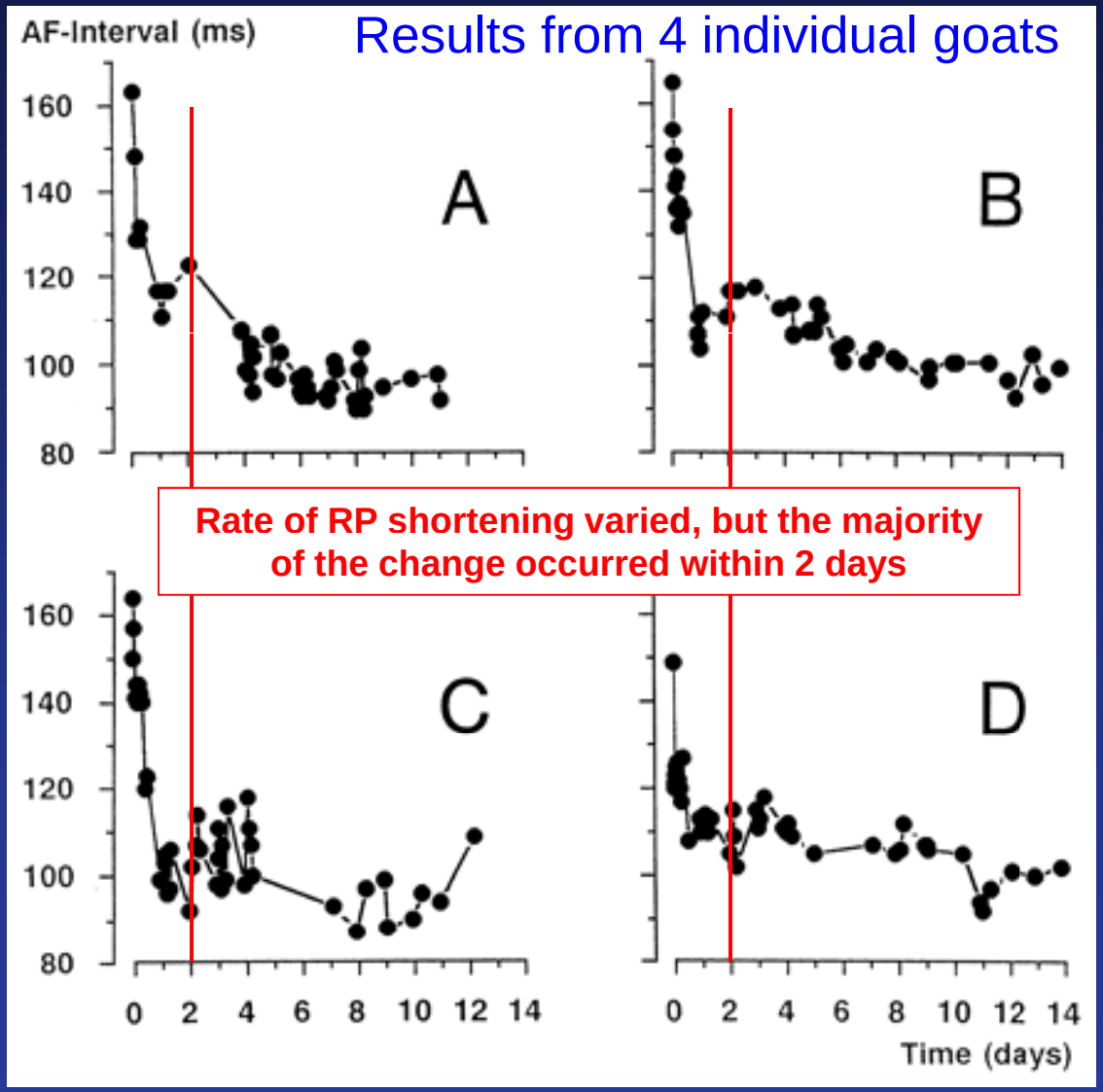
Normal atrial size
Normal WL

- reentry unstable
- AF not sustained

Normal atrial size
Short WL
(↓RP, ↓CV)

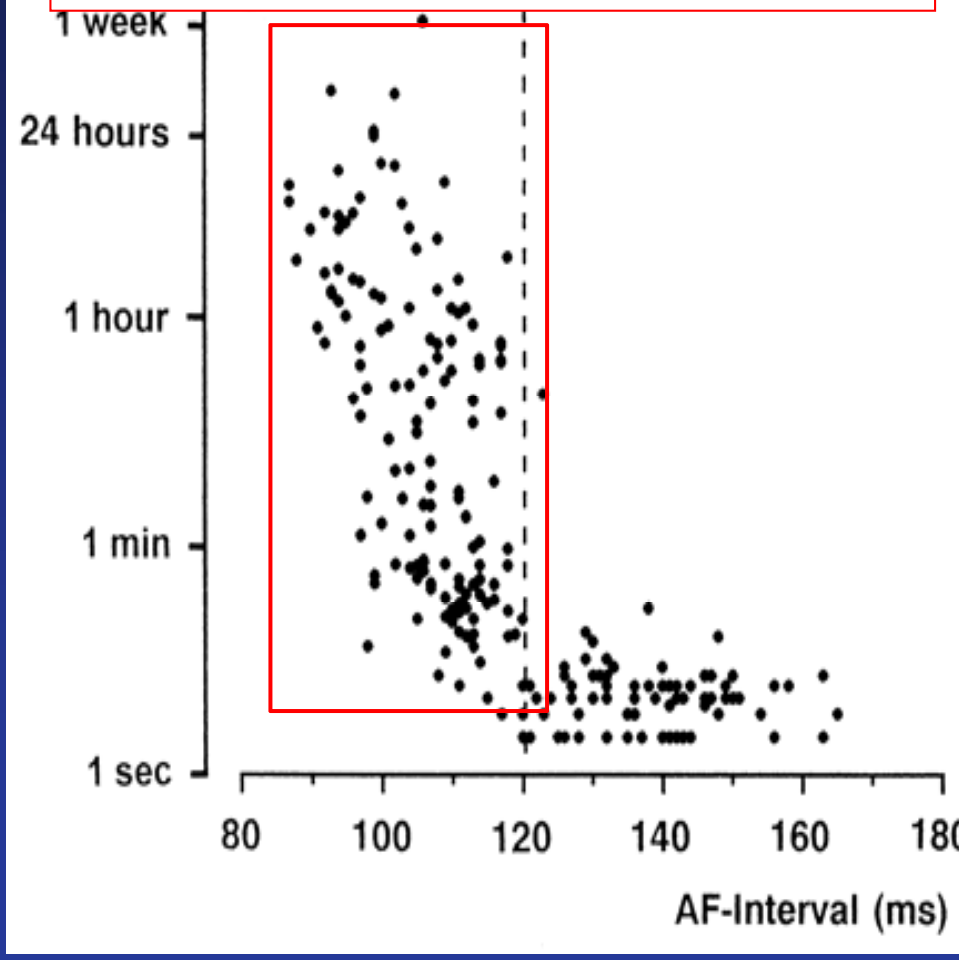
- AF sustained

Changes in atrial refractory period with AF

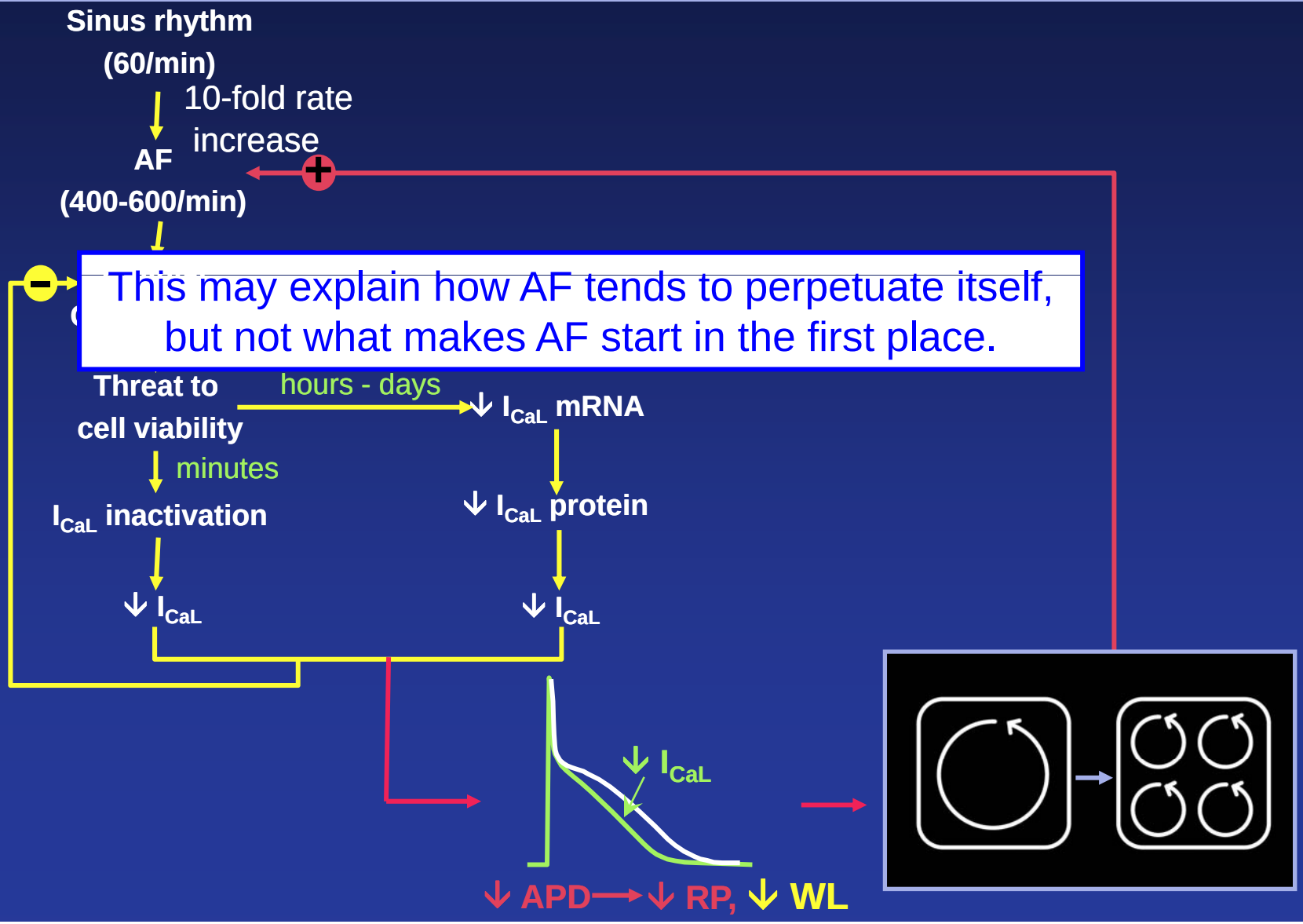


Rate of RP shortening varied, but the majority of the change occurred within 2 days

Substantial RP shortening coincided with AF prolongation, but RP differences were certainly not the only determinant of AF duration

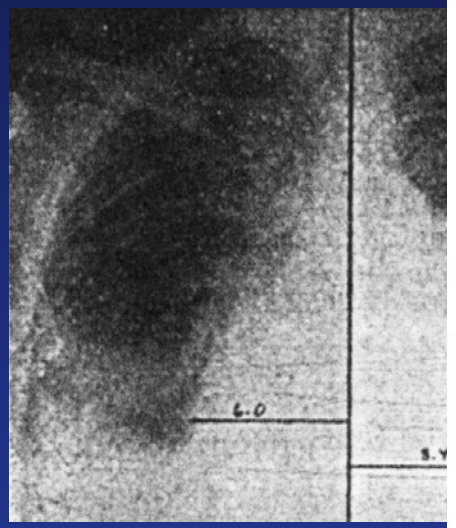


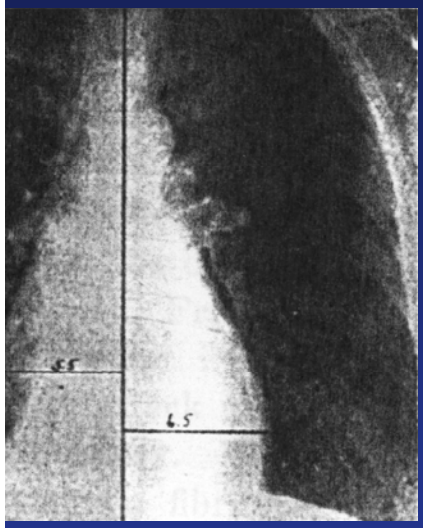
Mechanism of RP abbreviation with atrial-tachycardia remodeling ("AF begets AF")



To examine what creates the initial substrate of AF, we considered a very commo Failure

A very old m ma, dyspnea



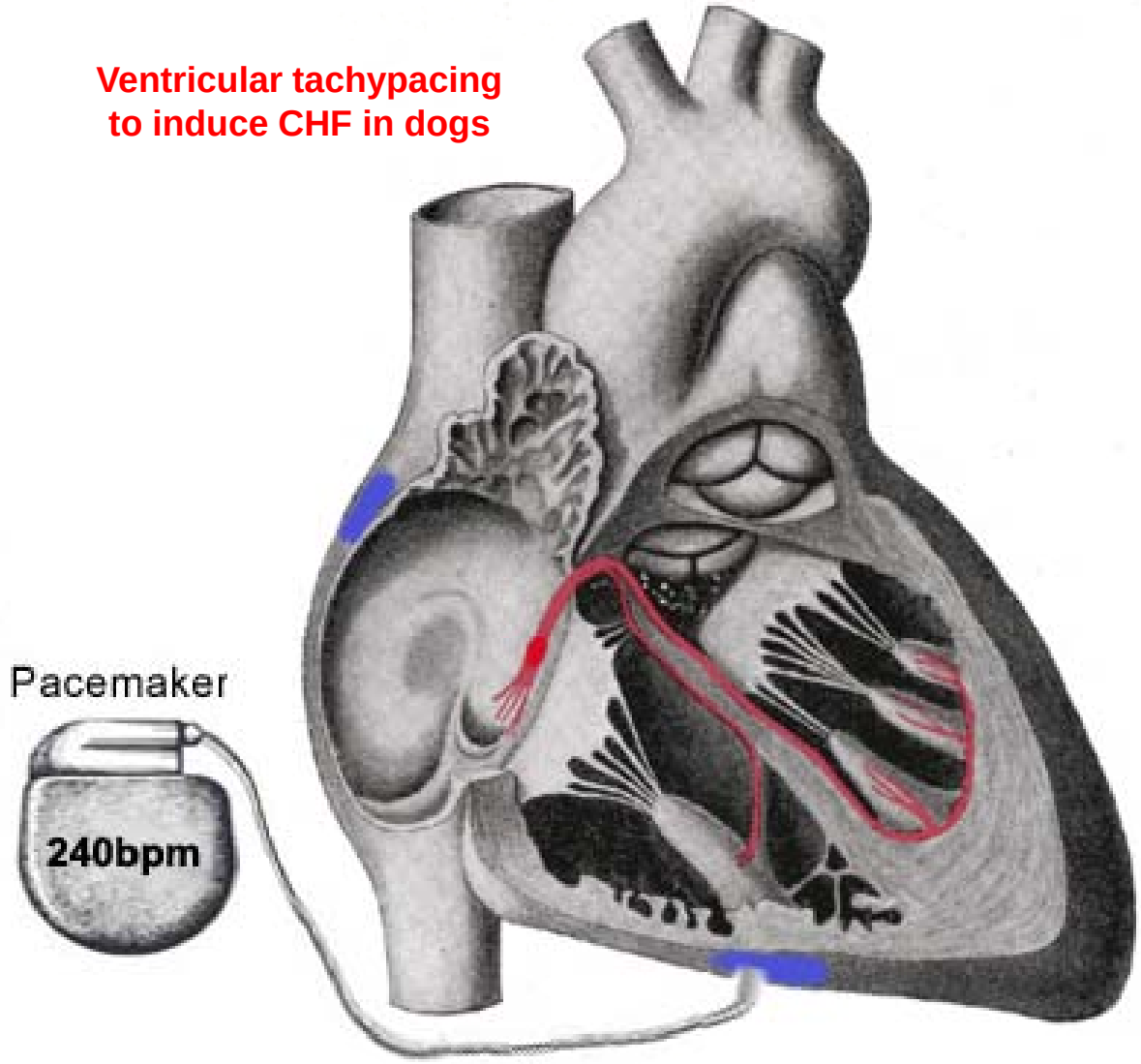


June 8, 1935 AF

Pulmonary edema, ca
pleural effusi

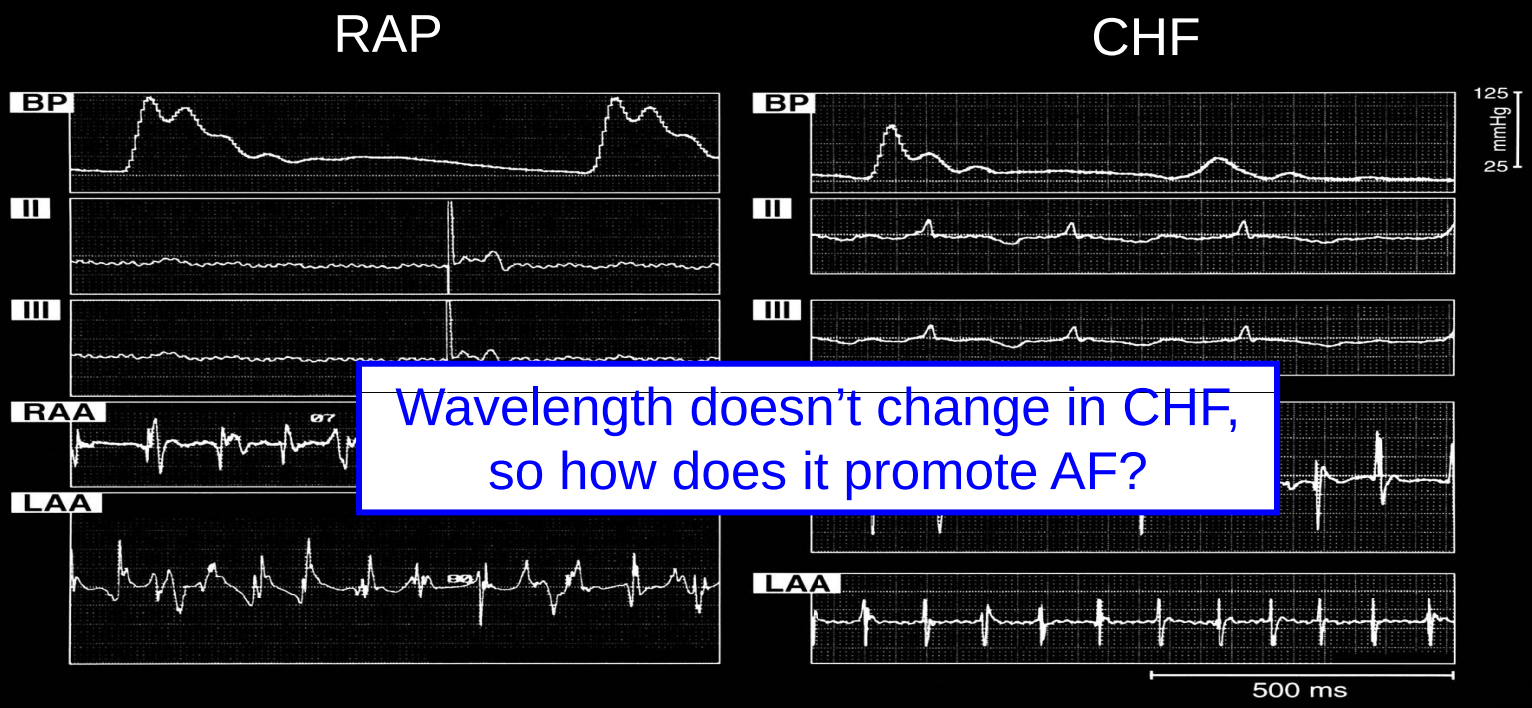
4, 1936 Quinidine
1935, 60mg Digitalis AF,
110/min
CXR normal
d edema and heart size

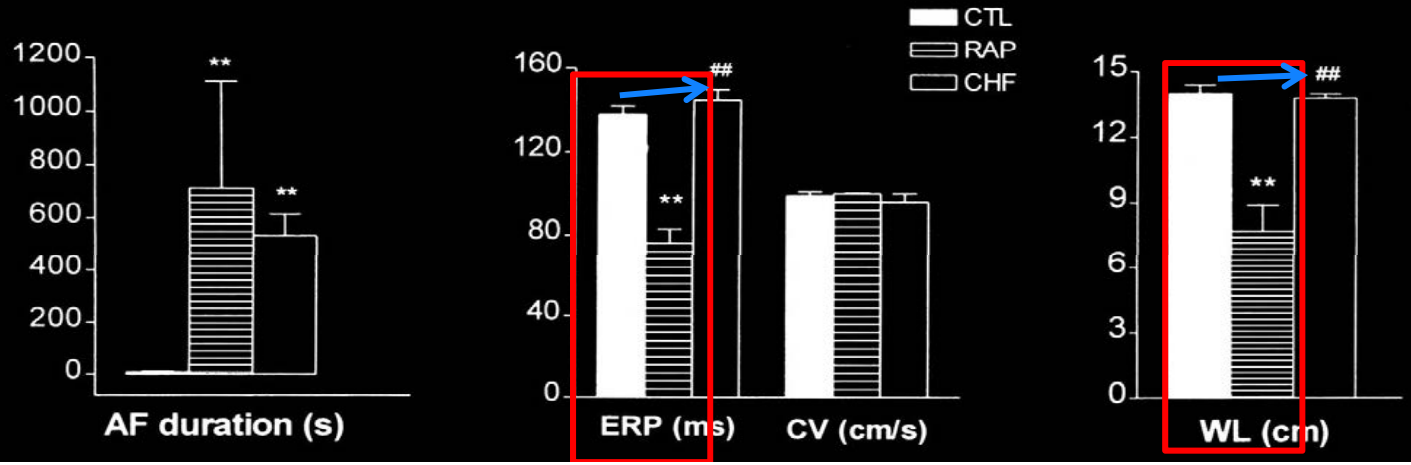
Ventricular tachypacing to induce CHF in dogs



Brill IC, Am Heart J 1937; 13:175-182

Electrophysiology of Sustained AF Substrate in Rapid Atrial Paced (RAP) vs CHF Dogs

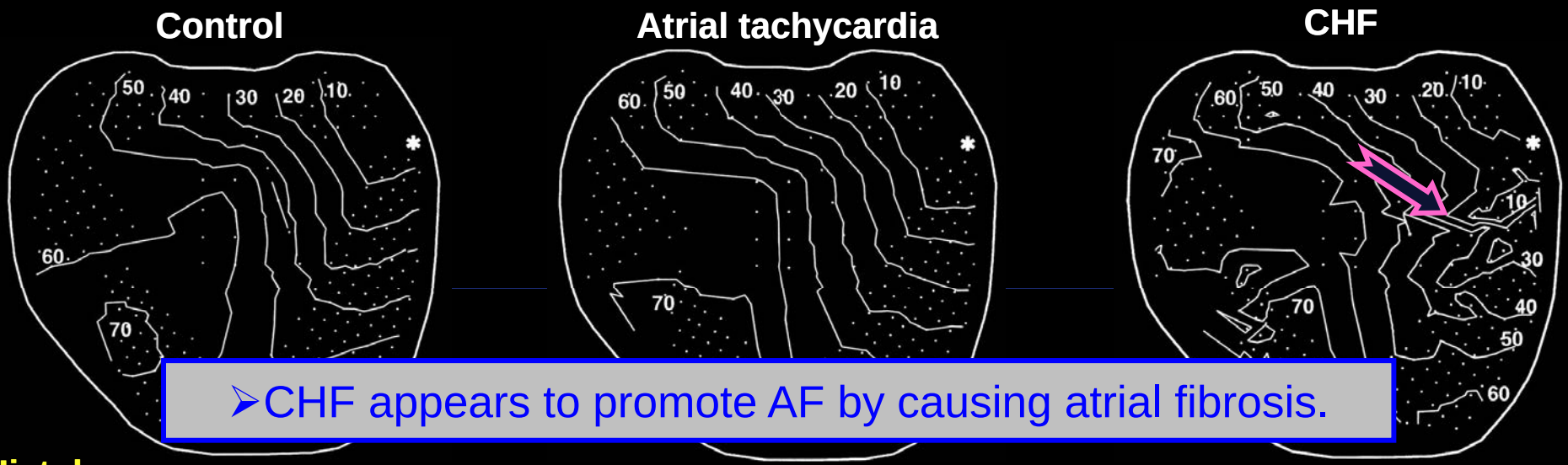




LI et al, *Circulation 1999, 100:87-95*

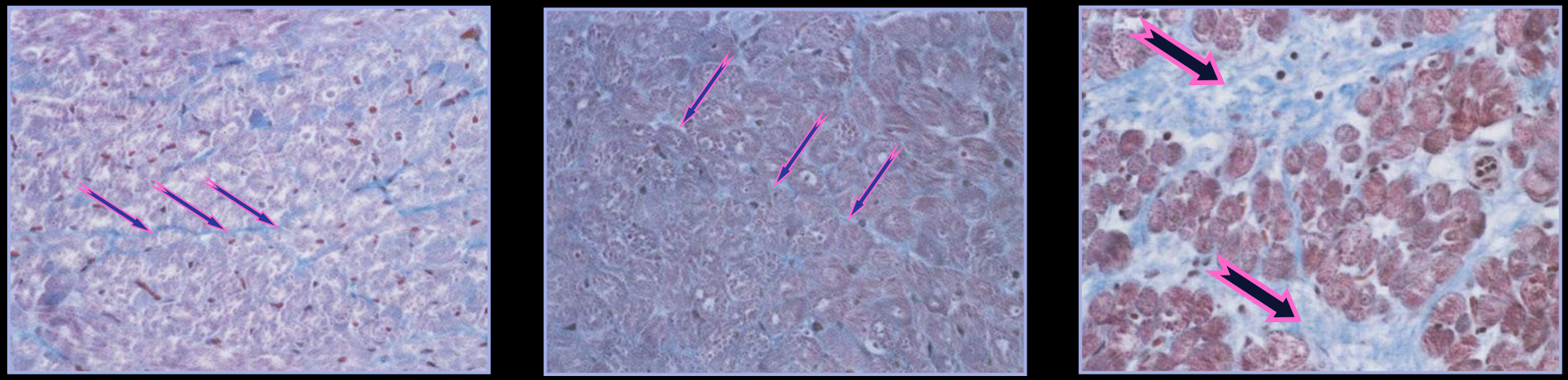
Conduction Abnormalities and Atrial Fibrosis in CHF (Structural remodeling)

Epicardial maps



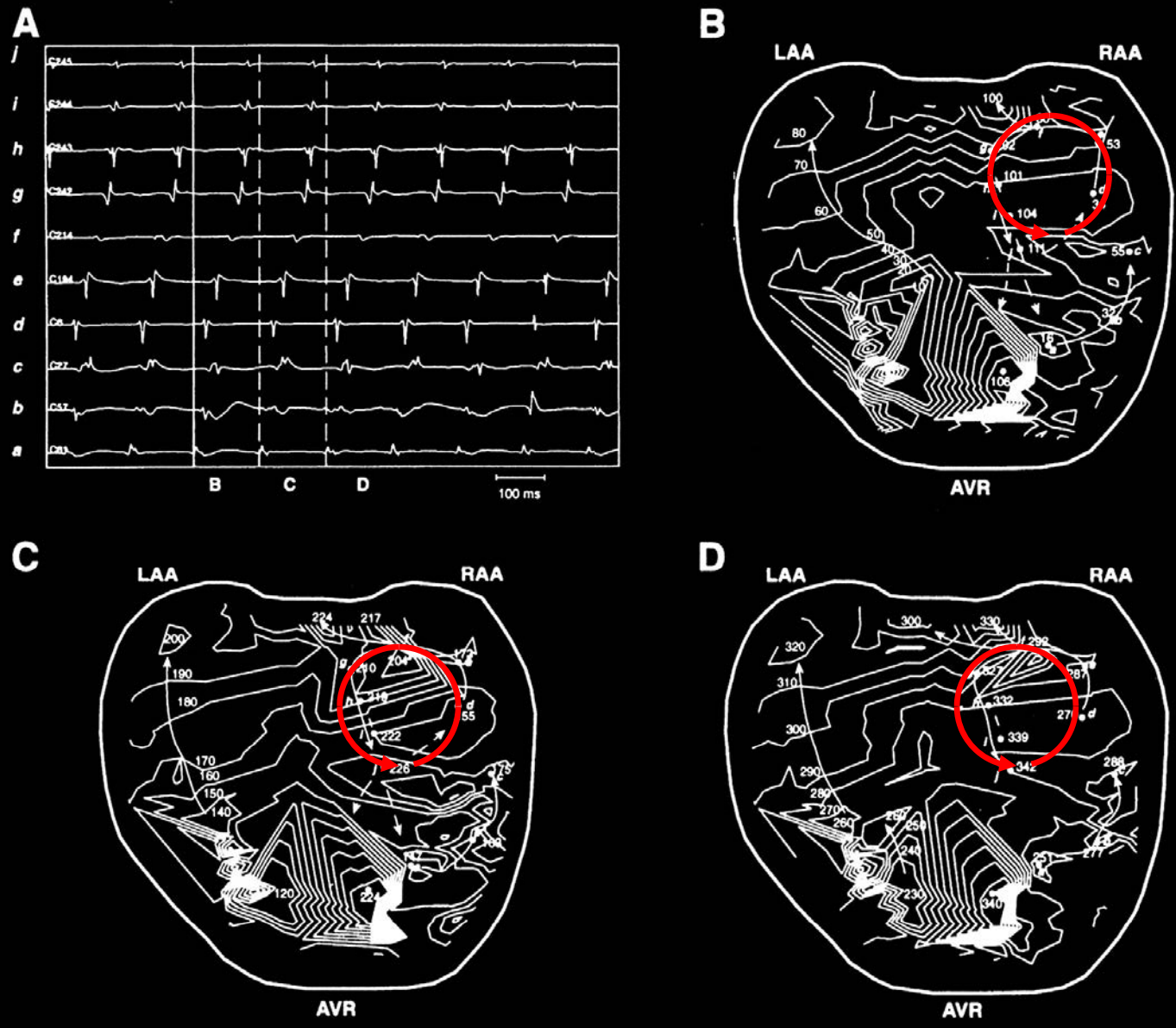
➢CHF appears to promote AF by causing atrial fibrosis.

Histology



LI et al, *Circulation 1999; 100:87-95*

Mapping of Sustained AF in a Dog with CHF

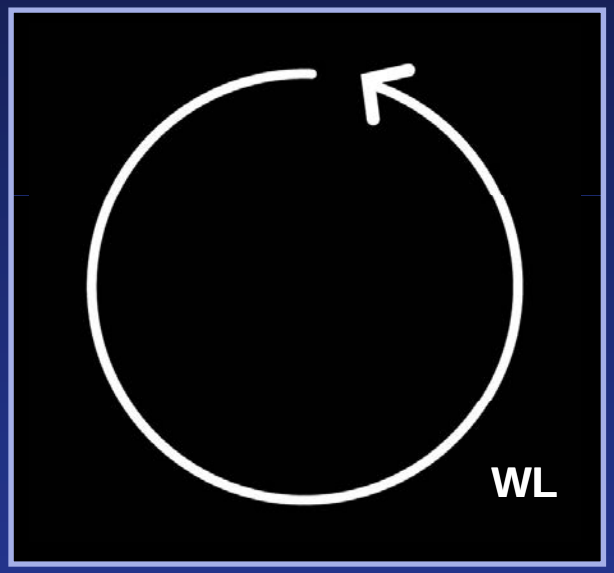


SN.2002

NATTEL et al, *Annu. Rev. Physiol. 2000; 62:51-77*

Reentry:
Stabilization by Conduction Abnormalities

A



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- minimal path length for reentry
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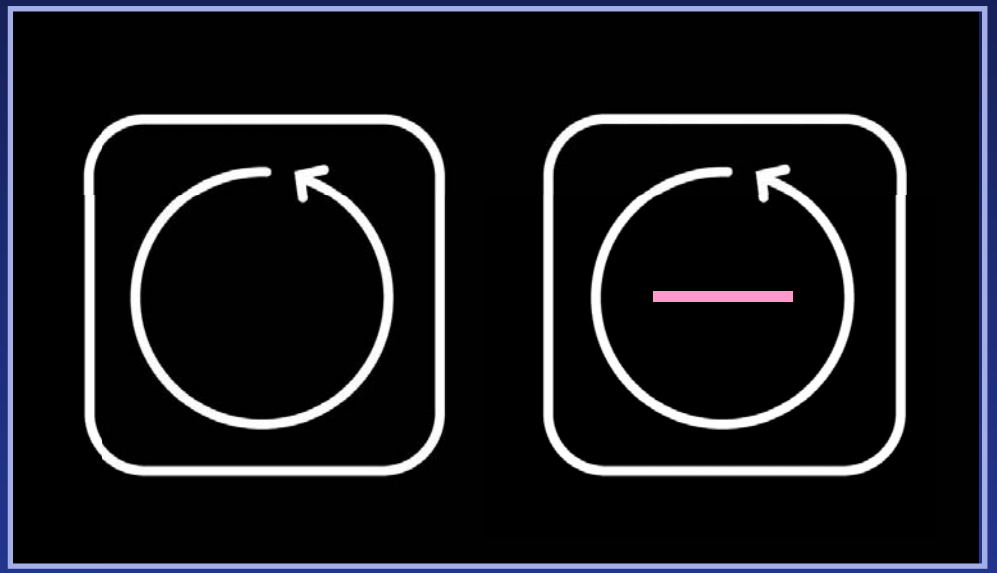


Normal atrial size
Normal WL

- reentry unstable
- AF not sustained

Normal atrial size
Normal WL

Local conduction abnormality

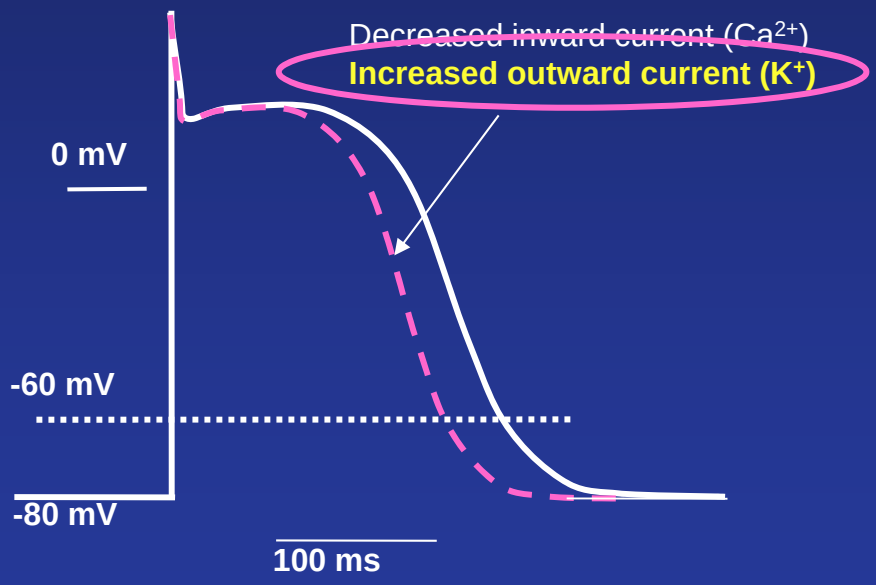
- **reentry stabilized**

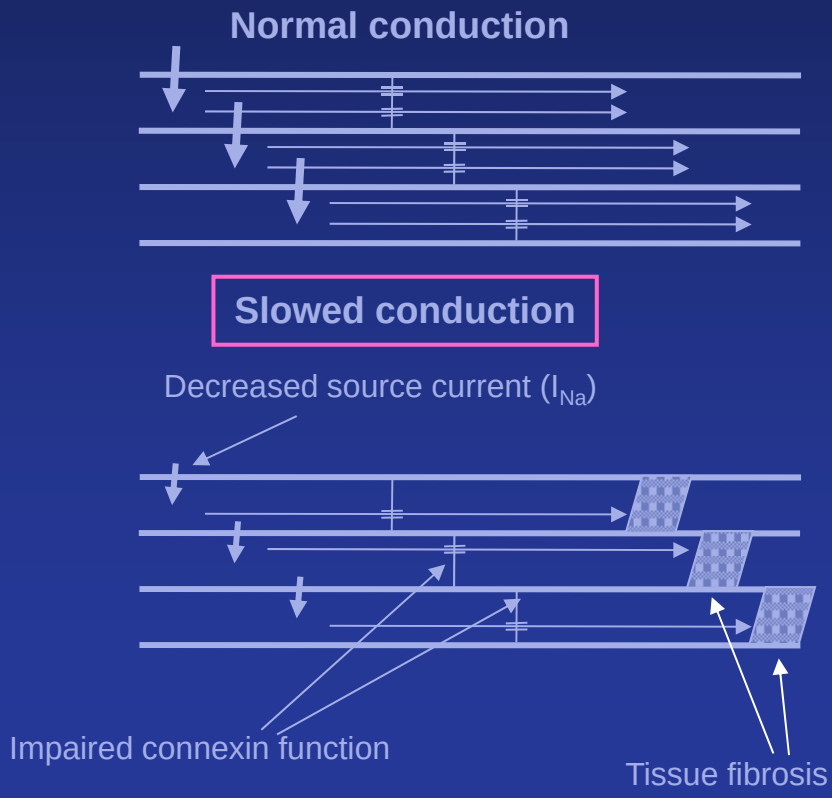
MicroRNAs implicated in AF via remodeling of APD/refractoriness

Substrate for Reentry in AF

How remodeling promotes reentry

Shortened refractory periods

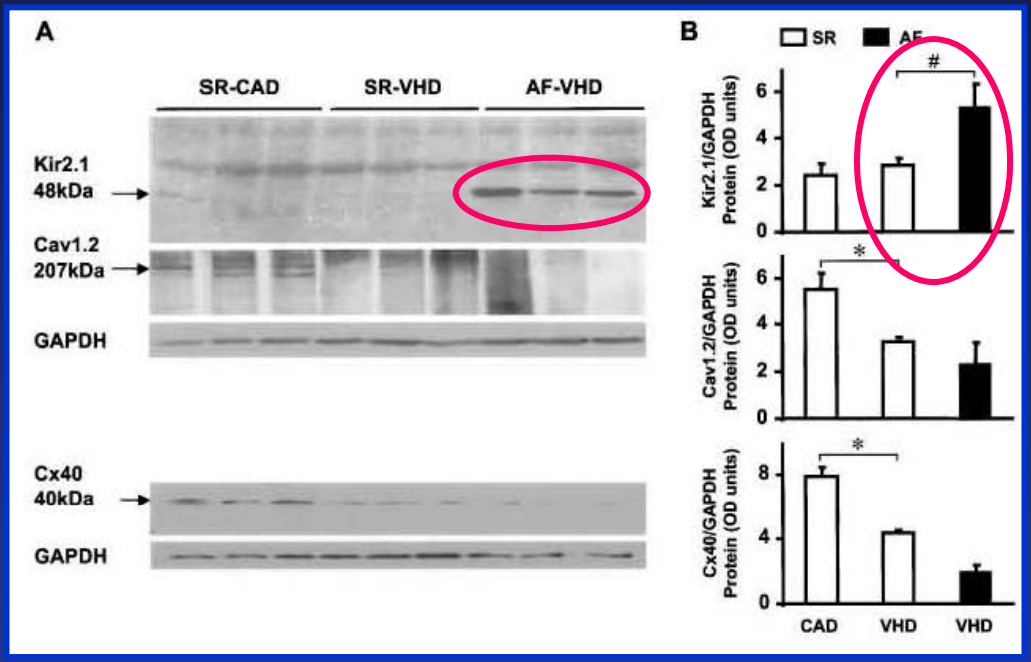




Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

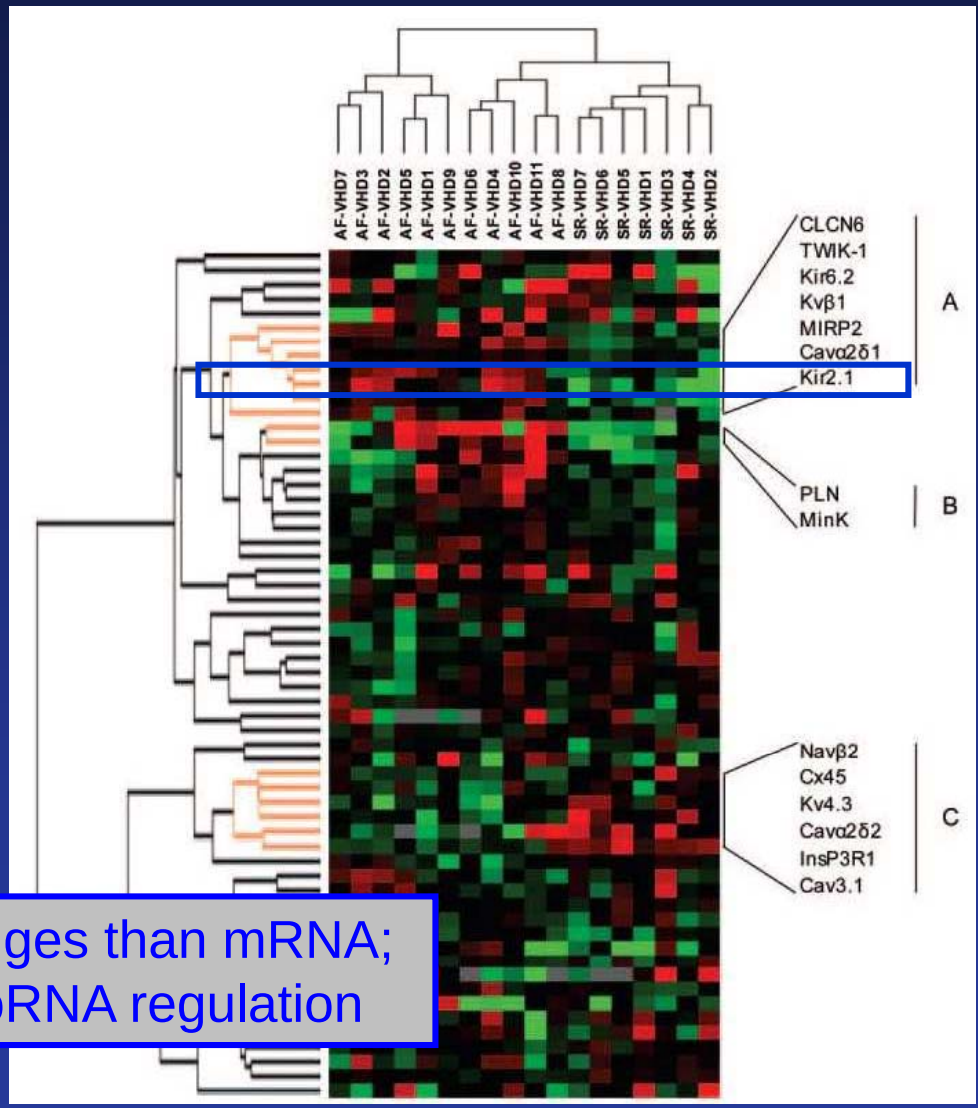
-Kir2.1 mRNA increased about 20-25% in AF

Molecular basis of I_{K1} upregulation?



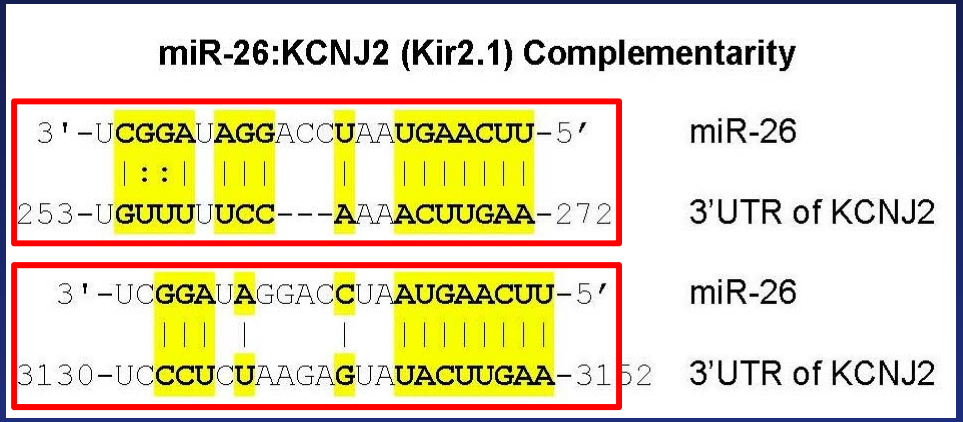
-Kir2.1 protein increased about 100% in AF
-similar change to I_{K1} upregulation

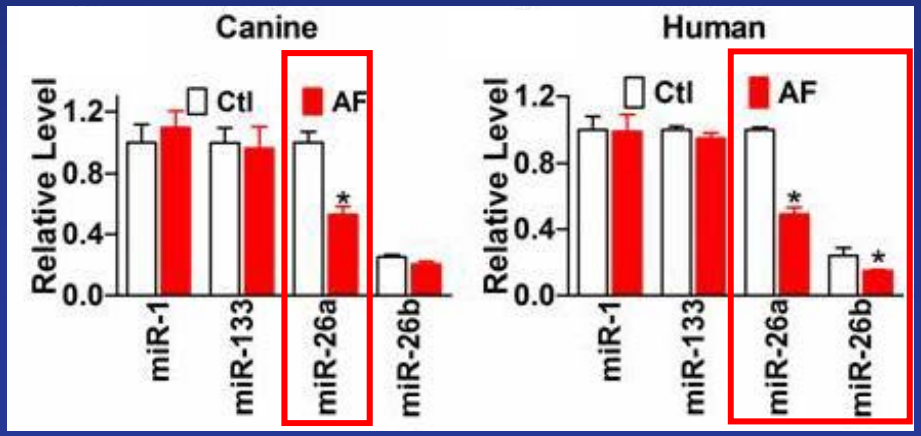
Greater protein changes than mRNA; suggestive of microRNA regulation



GABORIT ET AL, *Circulation. 2005 Jul 26;112(4):471-81.*

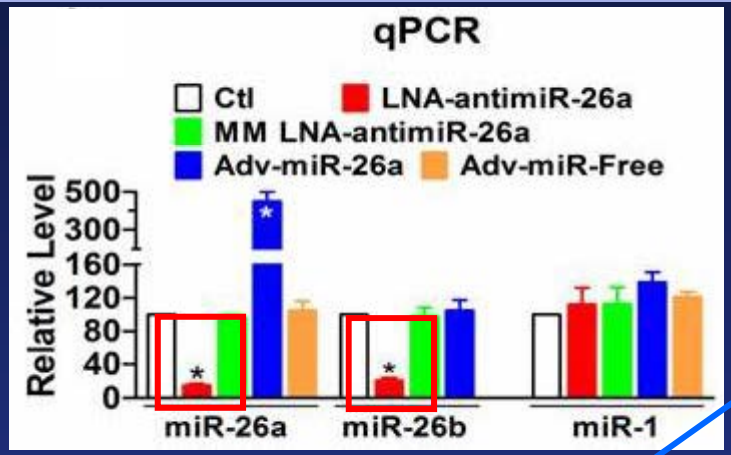
A miRNA potentially involved in I_{K1} upregulation in AF





Luo X et al, J Clin Invest 123:1939-51, 2013

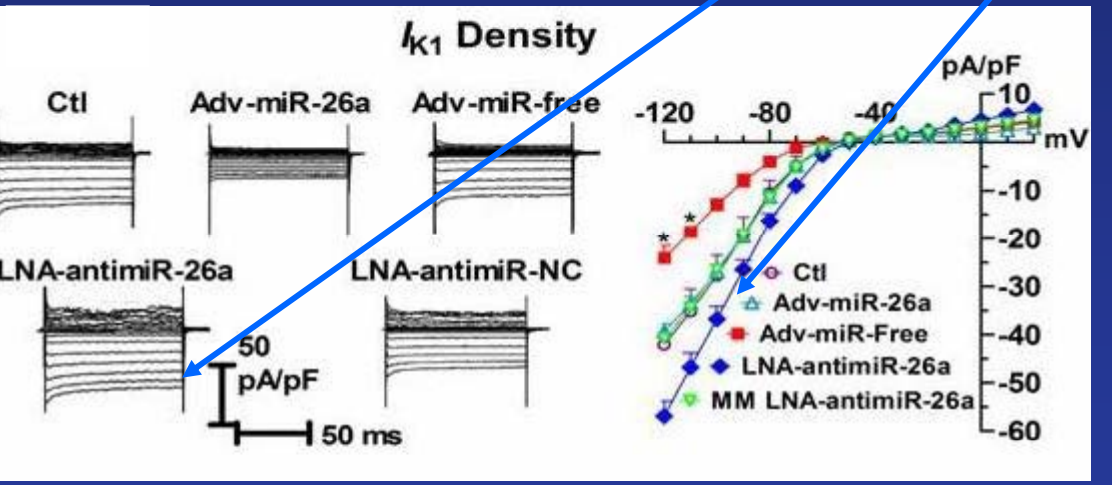
Manipulating miR-26 in vivo changes I_{K1} and profoundly regulates AF susceptibility

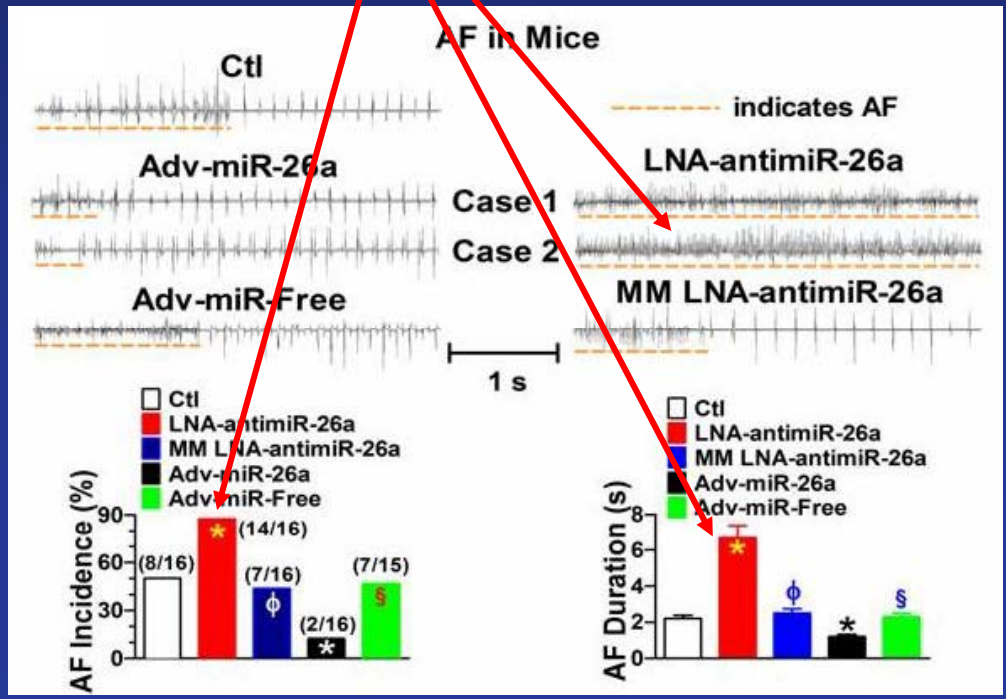


Mimicked AF-related miR-26 downregulation by tail vein injection of antimiR to mice

In vivo miR-26 downregulation upregulated IK1

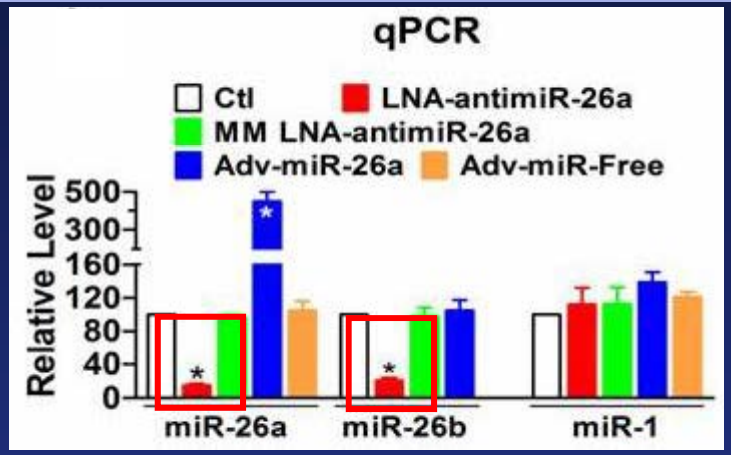
And promoted AF.



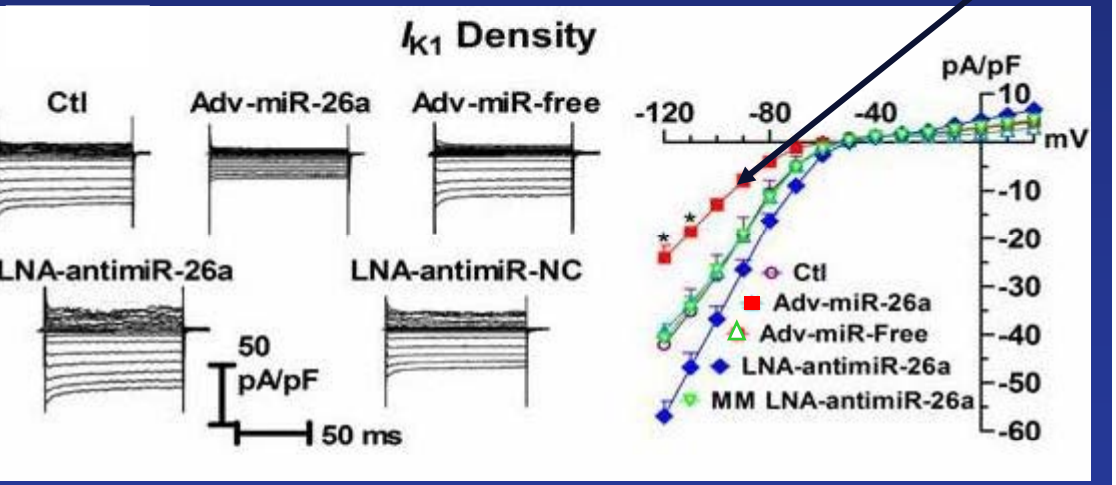


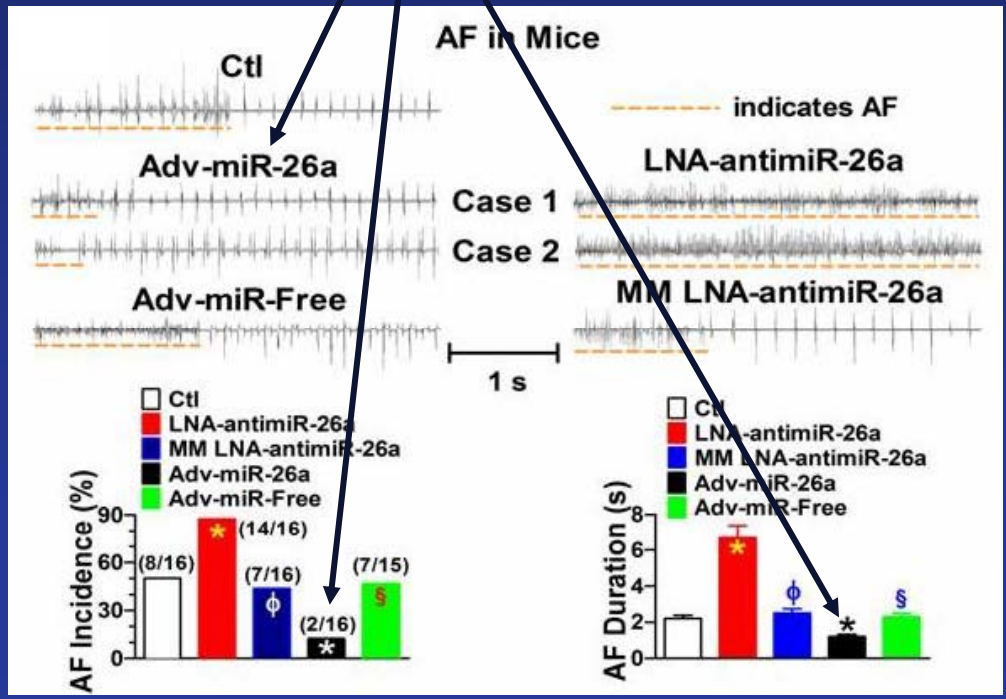
Luo X et al, JCI, J Clin Invest 123: 1939-1951, 2013 .

Manipulating miR-26 in vivo changes I_{K1} and profoundly regulates AF susceptibility



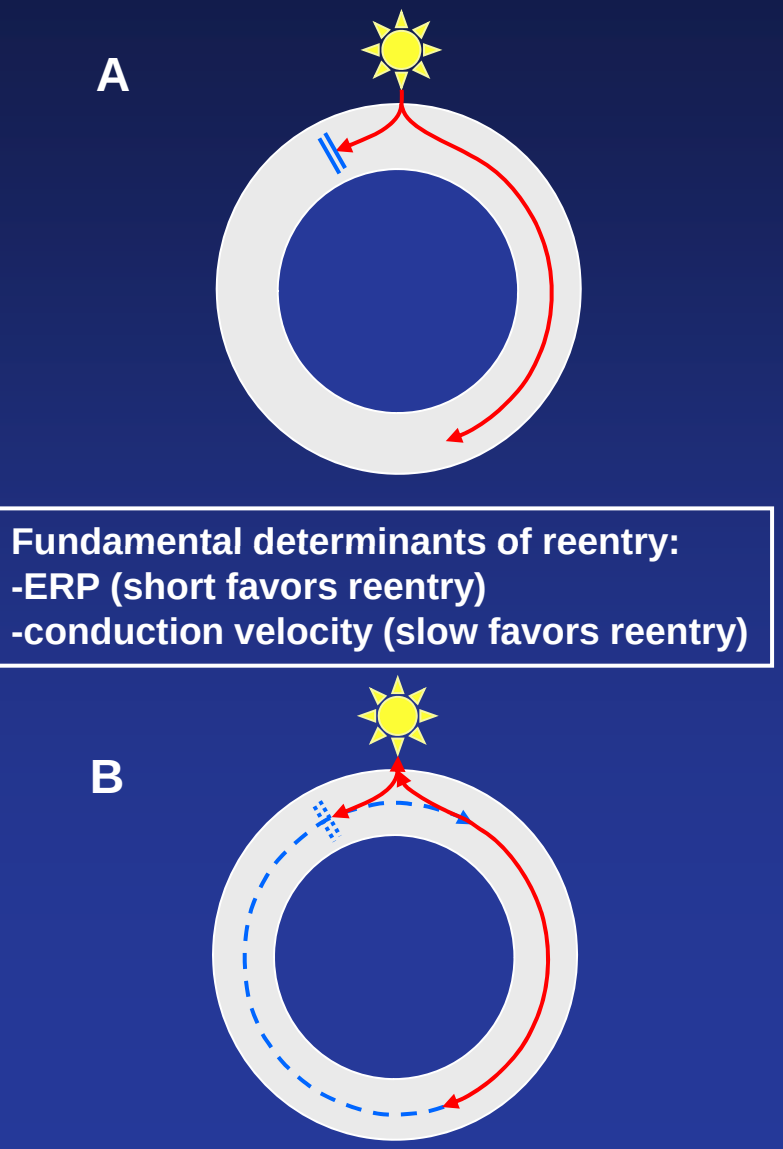
In vivo miR-26 overexpresssion reduced I_{K1} and suppressed AF.



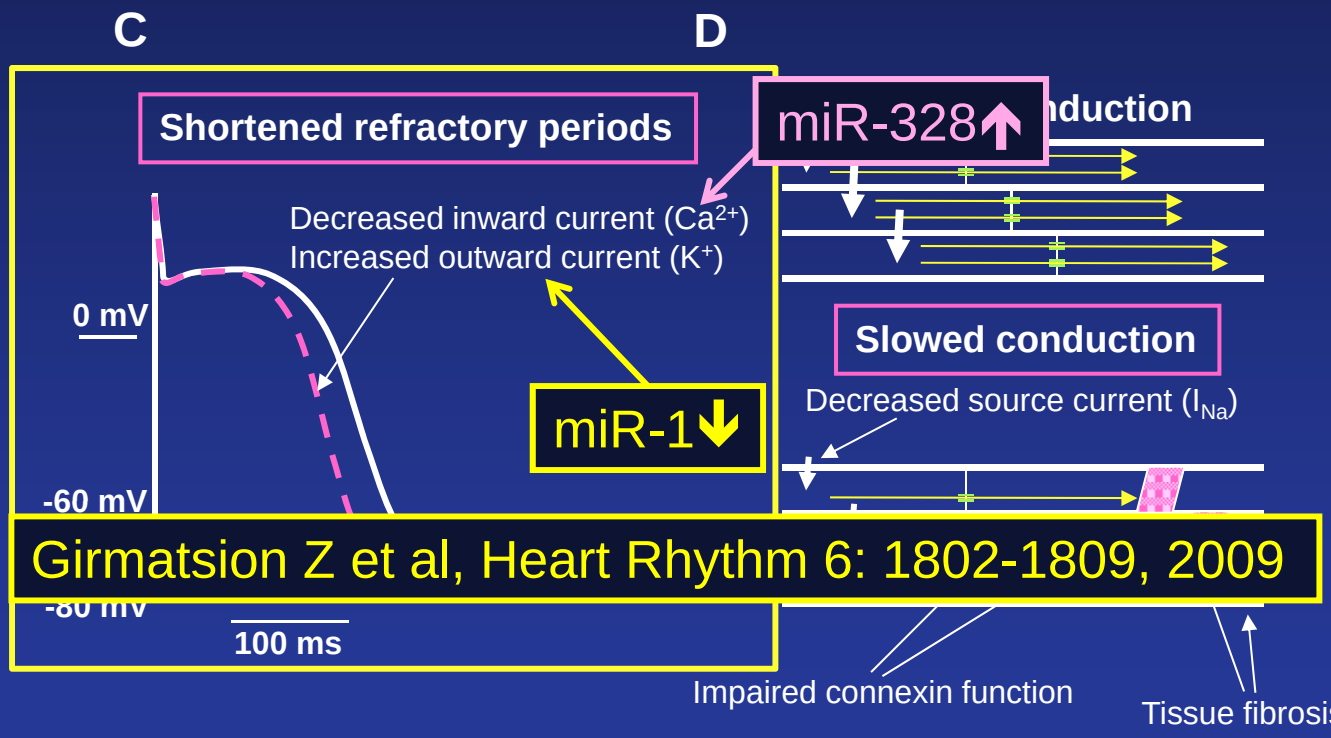


Luo X et al, *JCI, J Clin Invest 123: 1939-1951, 2013 .*

Reentry substrate in AF: Changed refractoriness: Other miRs



Lu Y et al, Circulation 122: 2378–2387, 2010.

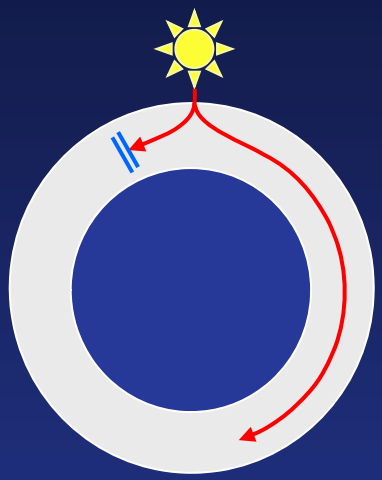


Girmatsion Z et al, Heart Rhythm 6: 1802-1809, 2009

Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

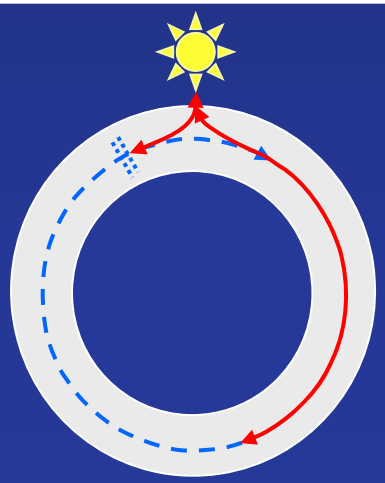
Substrate for Reentry in AF

A



Fundamental determinants of reentry:
-ERP (short favors reentry)
-conduction velocity (slow favors reentry)

B

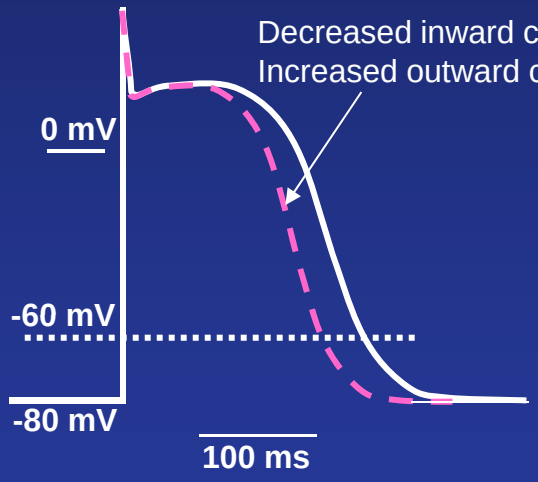


How remodeling pro

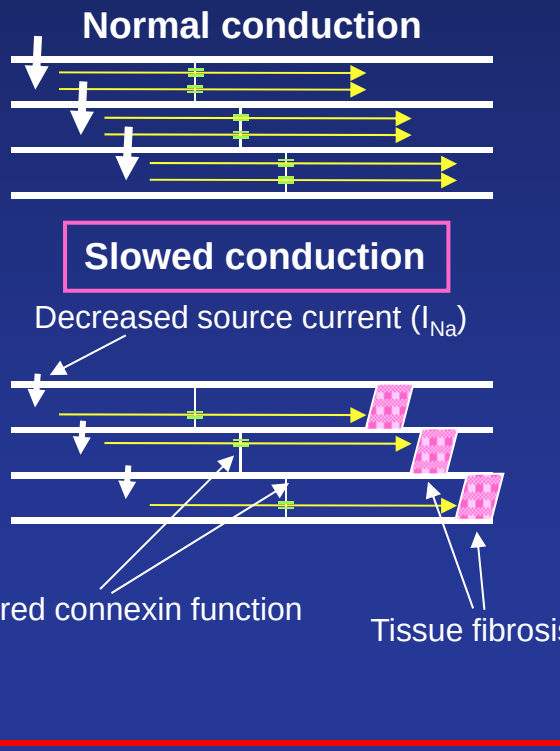
Impaired conduction and dilated atria

C

Shortened refractory periods

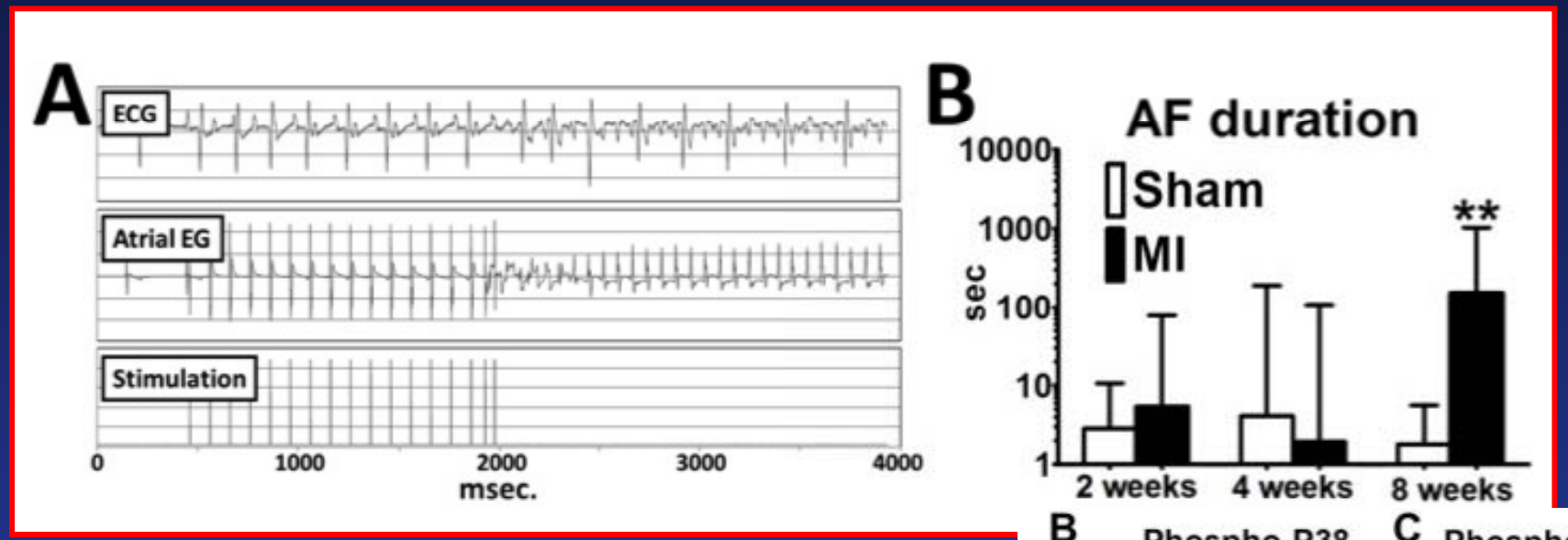


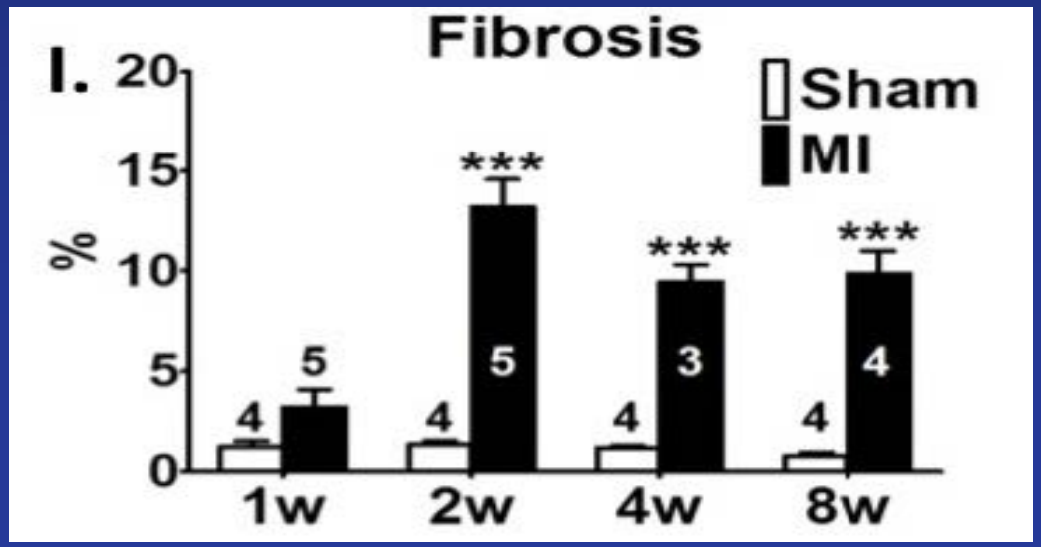
D

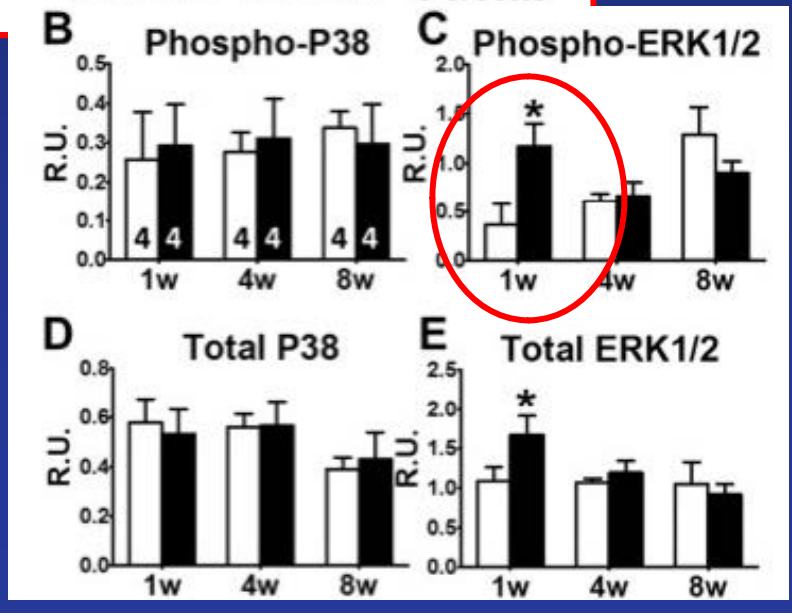


Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

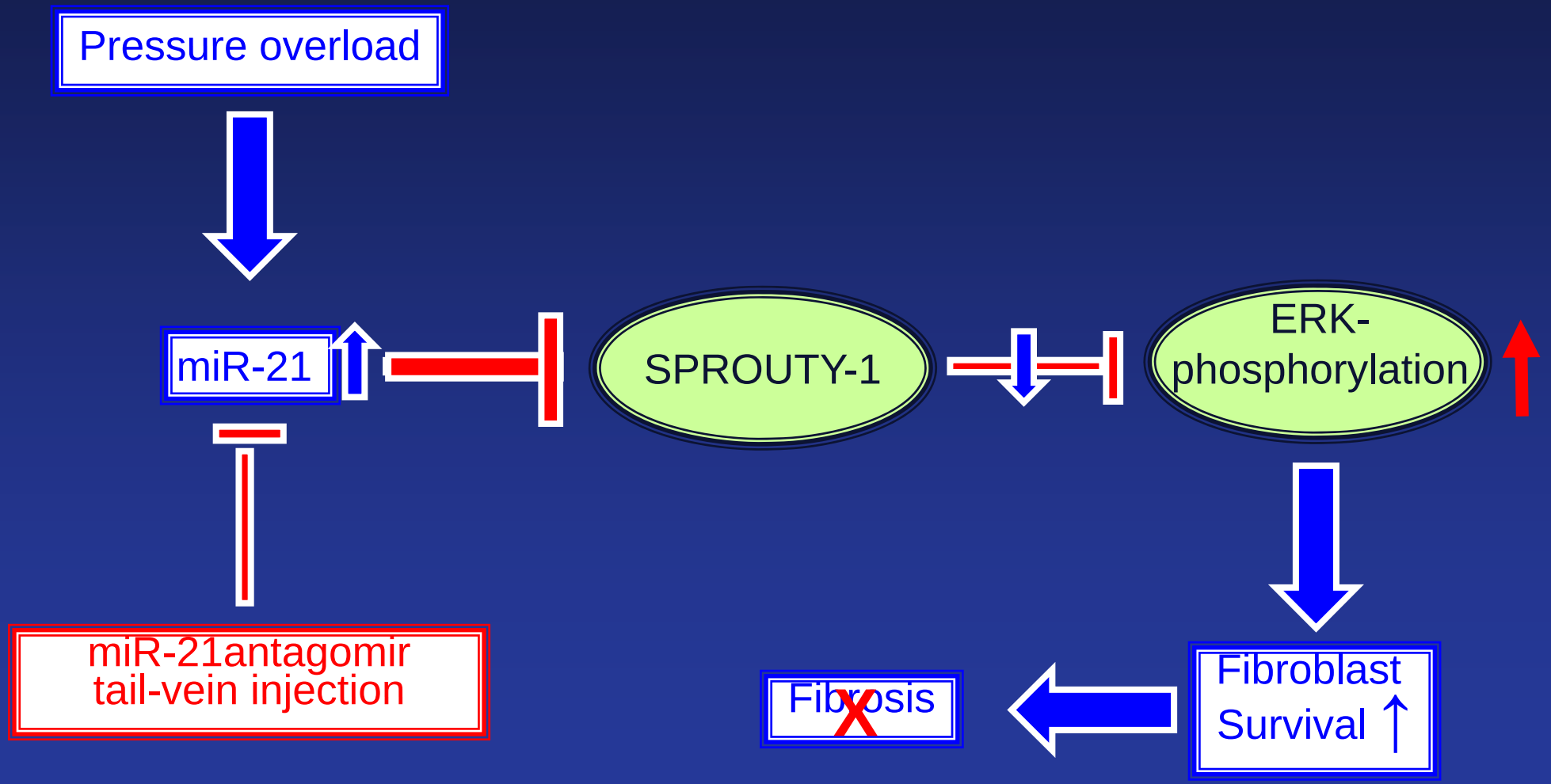
Rat model of post-myocardial infarction CHF with which to test molecular mechanisms





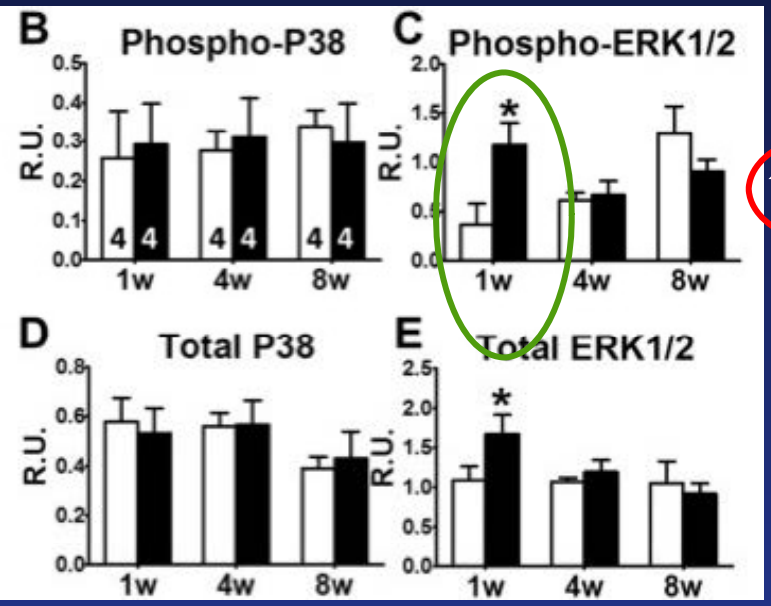


A MicroRNA (miR-21) controls ventricular fibrosis in TAC mouse model via ERK-phosphorylation

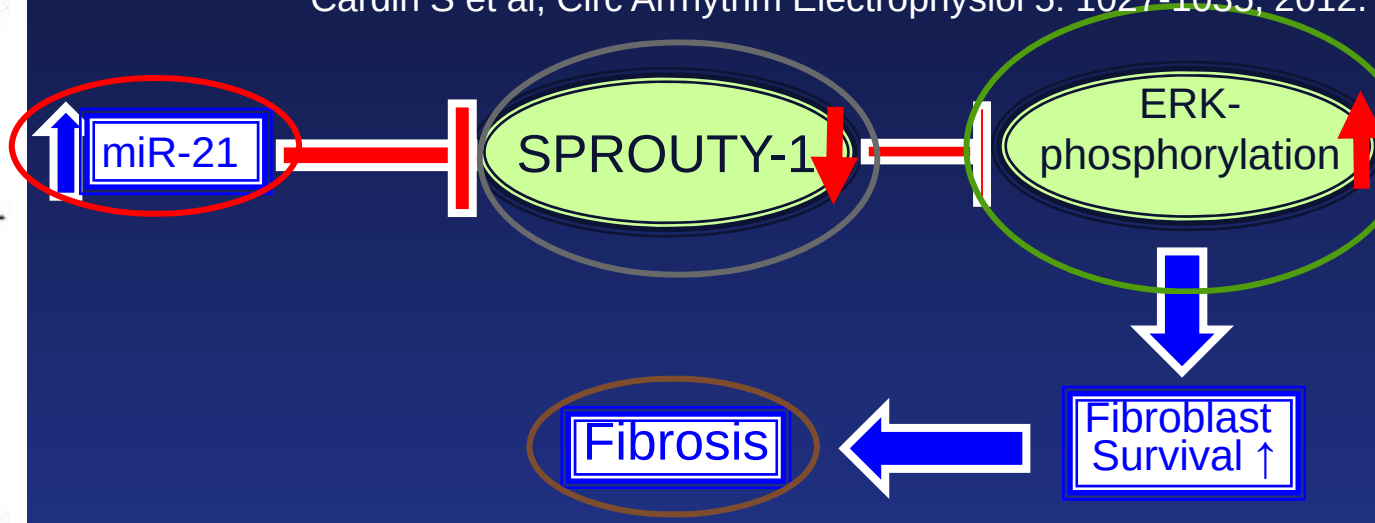


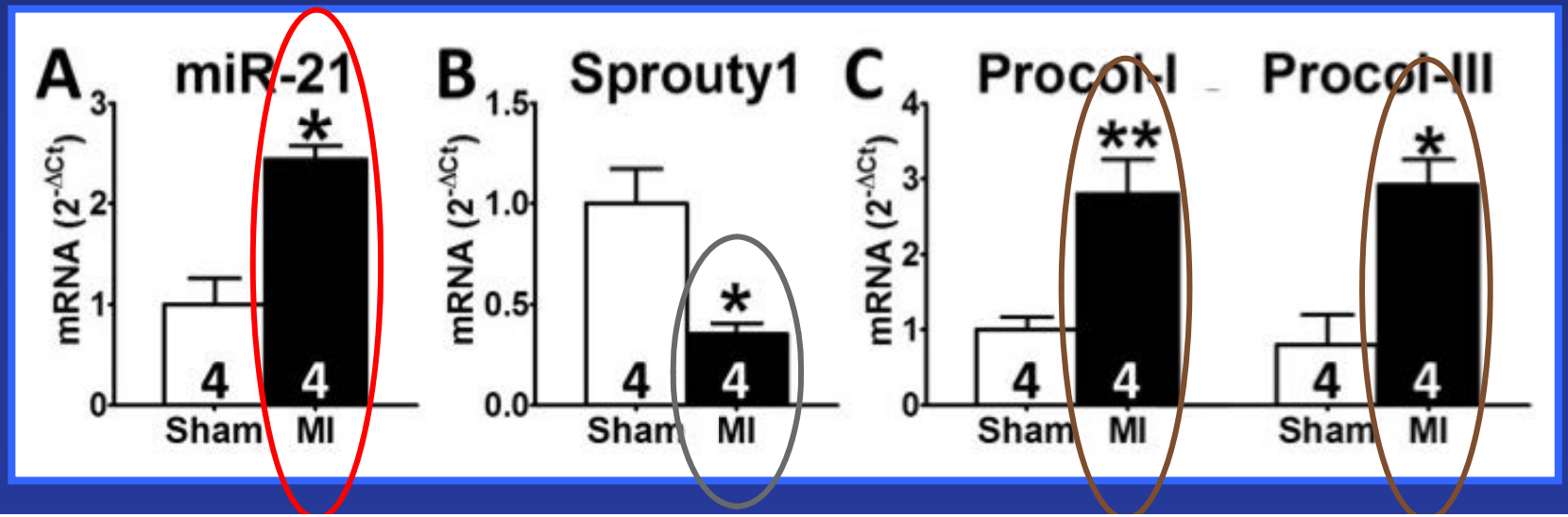
Thum T et al, *Nature, 456:18-256,2010.*

Is miR-21 involved in atrial fibrosis/AF of rats with post-MI CHF? Indirect Evidence

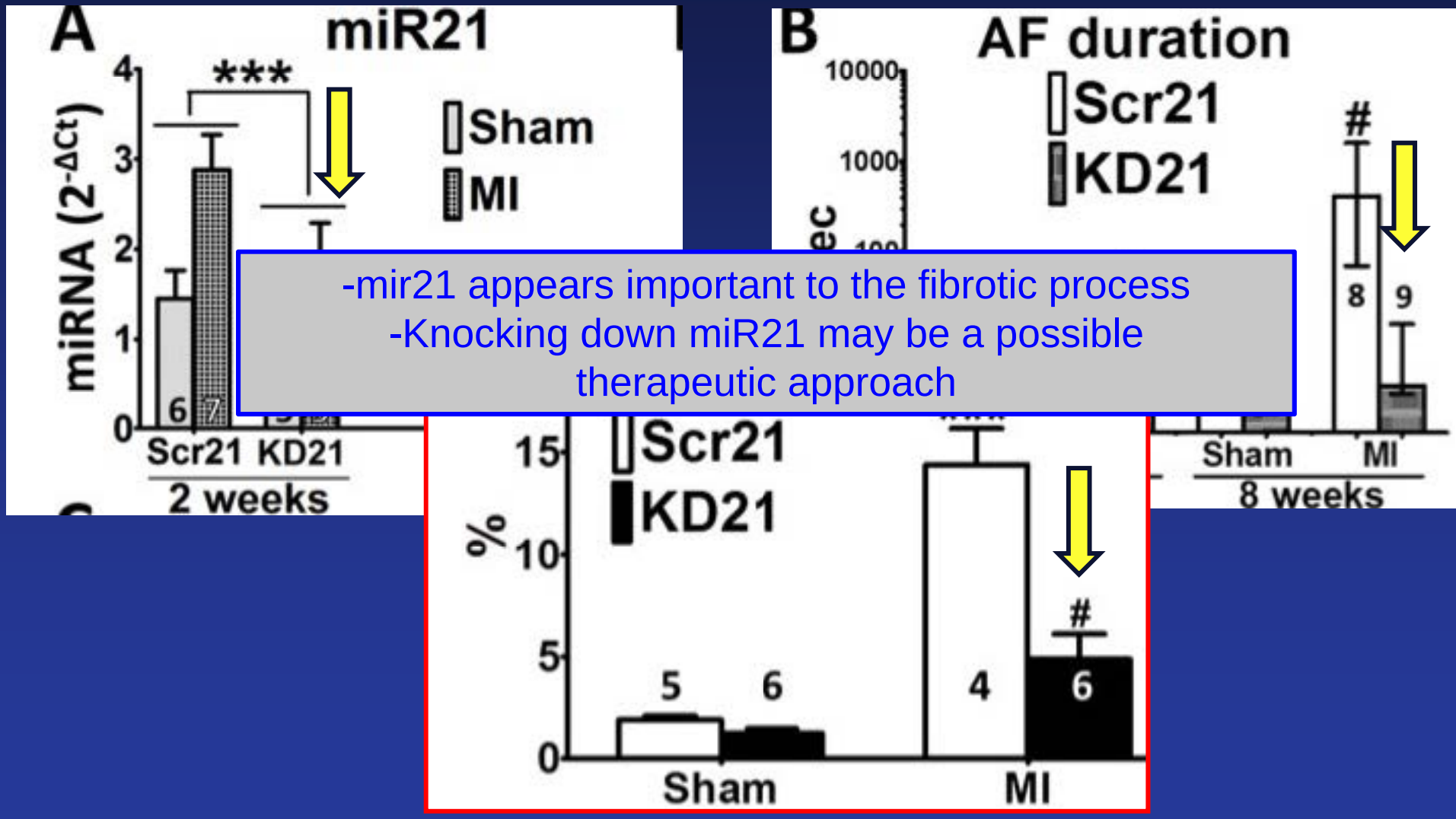


Cardin S et al, Circ Arrhythm Electrophysiol 5: 1027-1035, 2012.





Effects of miR-21 knockdown on atrial fibrosis and AF



-mir21 appears important to the fibrotic process
-Knocking down miR21 may be a possible therapeutic approach

Cardin S et al, Circ Arrhythm Electrophysiol 5: 1027-1035, 2012.