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OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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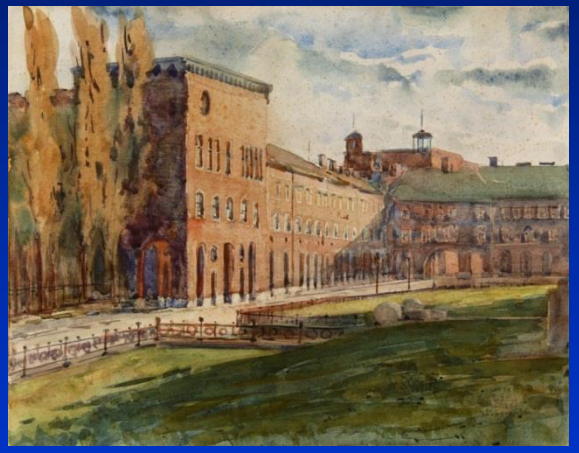
OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Atrial remodelling in permanent atrial fibrillation. Mechanism and implications

Garden view



Street view

Norbert Jost, PhD

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3rd International Conference on Clinical and Experimental Cardiology
April 15-17, 2013, Hilton Chicago/Northbrook

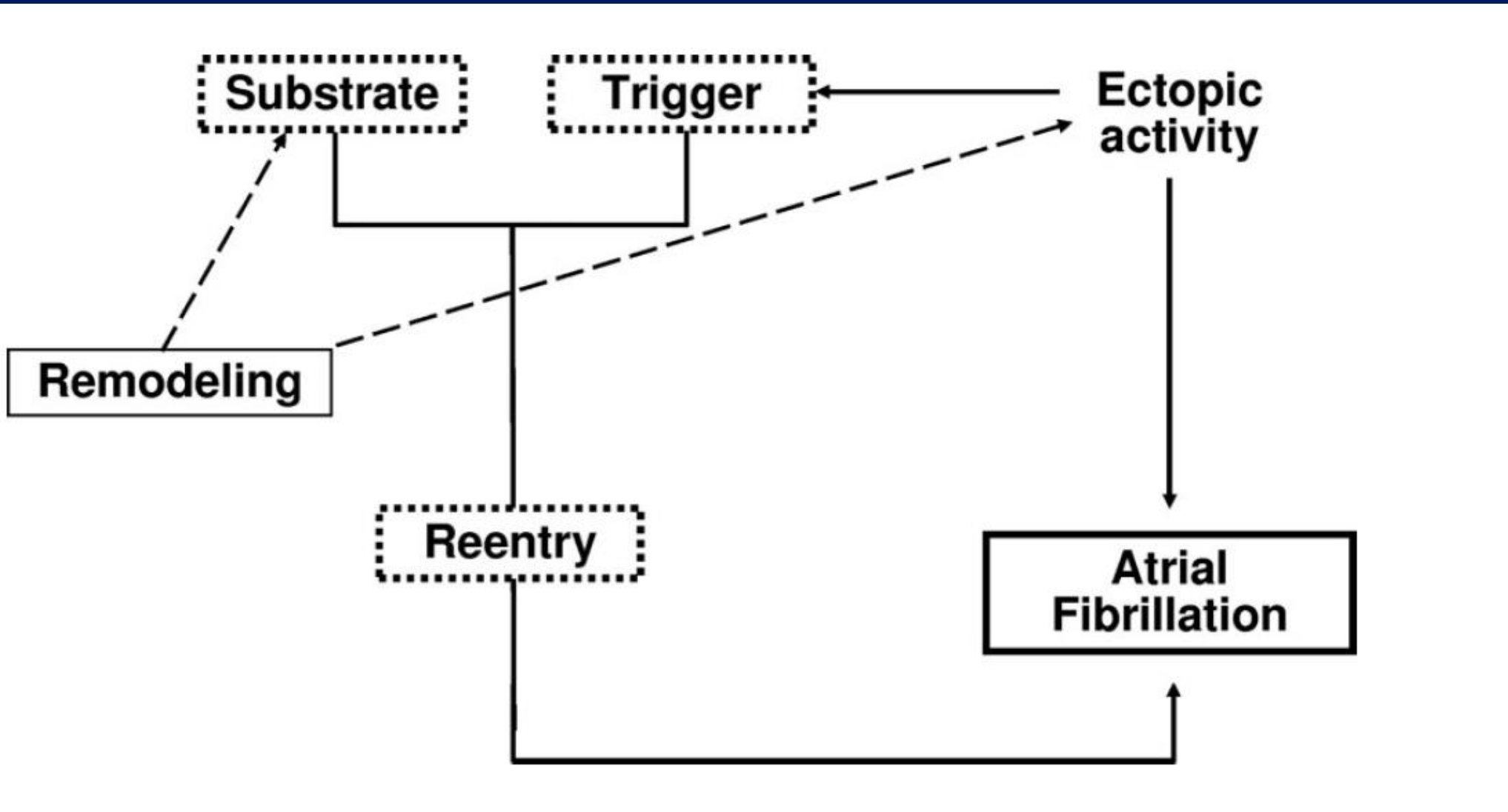
When the pulse strikes out in long beats and smoothly for a long time and then the beats of the pulse become smaller and hard on their own account, then a quick death will occur and no cure can be effected.

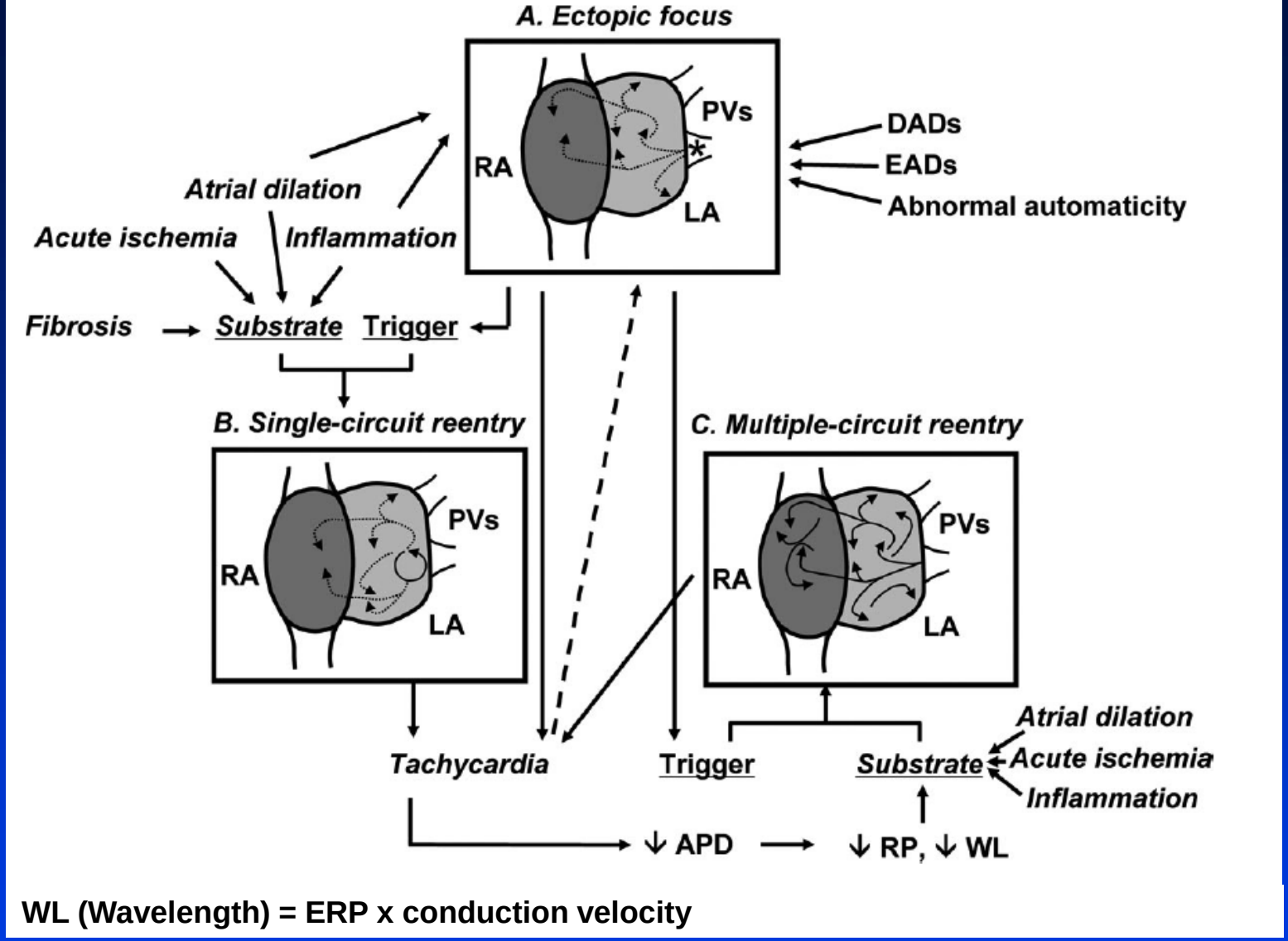
Huang Ti Nei Ching Su Wen, China ~ 2000 B.C.

Atrial fibrillation - AF

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It can occur at any age but becomes extremely common in the elderly, with a prevalence approaching 20% in patients 85 years of age. AF is characterized by disorganized, high-rate (300-500/min) atrial electrical activity and it is associated with shorter action potential duration (APD) and effective refractory period and a loss of rate-dependent APD adaptation that involve concomitant alterations in ion current activity.

General schema representing AF mechanisms and the role of remodeling



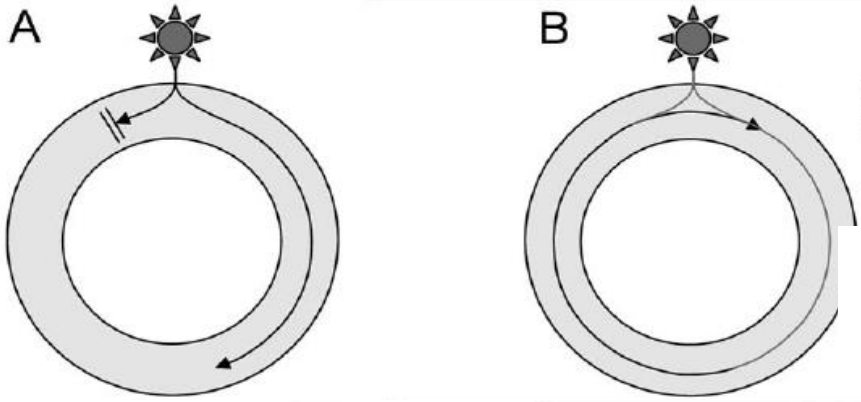


WL (Wavelength) = ERP x conduction velocity

Principal mechanisms that can produce AF. Reentry involves a vulnerable substrate, which requires a trigger for reentry initiation. Ischemia, inflammation, and dilation make atria more vulnerable to AF. AF that results from any mechanism causes tachycardia-induced remodeling. Even if AF is initially maintained by ectopic activity or single-circuit reentry in a given patient, ATR-induced spatially heterogeneous refractoriness abbreviation creates conditions favorable to multiple-circuit reentry, which may then become the AF-maintaining mechanism. Thus, multiple circuit reentry may be a final common pathway AF mechanism in many patients.

Principal mechanisms that can produce AF – *the reentry*.

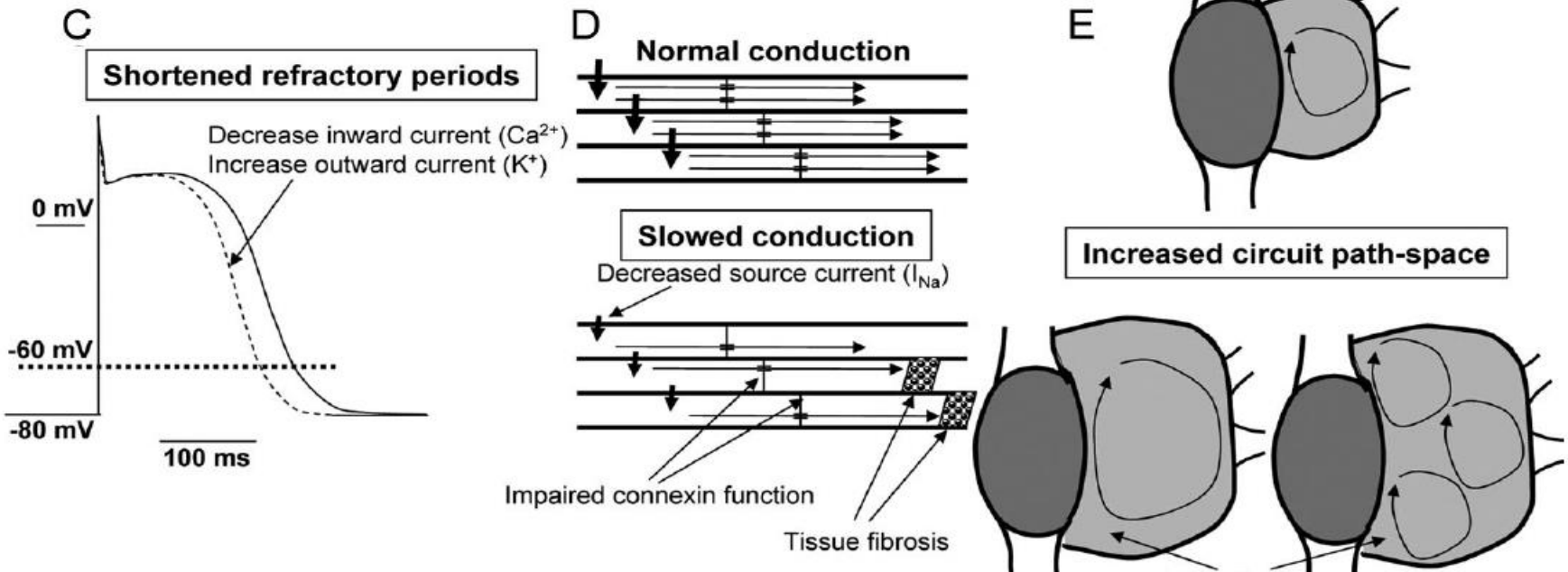
Fundamental determinants of reentry



Circuit time: has to be greater than RP.
Favored by:
- Short refractory periods
- Slow conduction
- Long pathways available

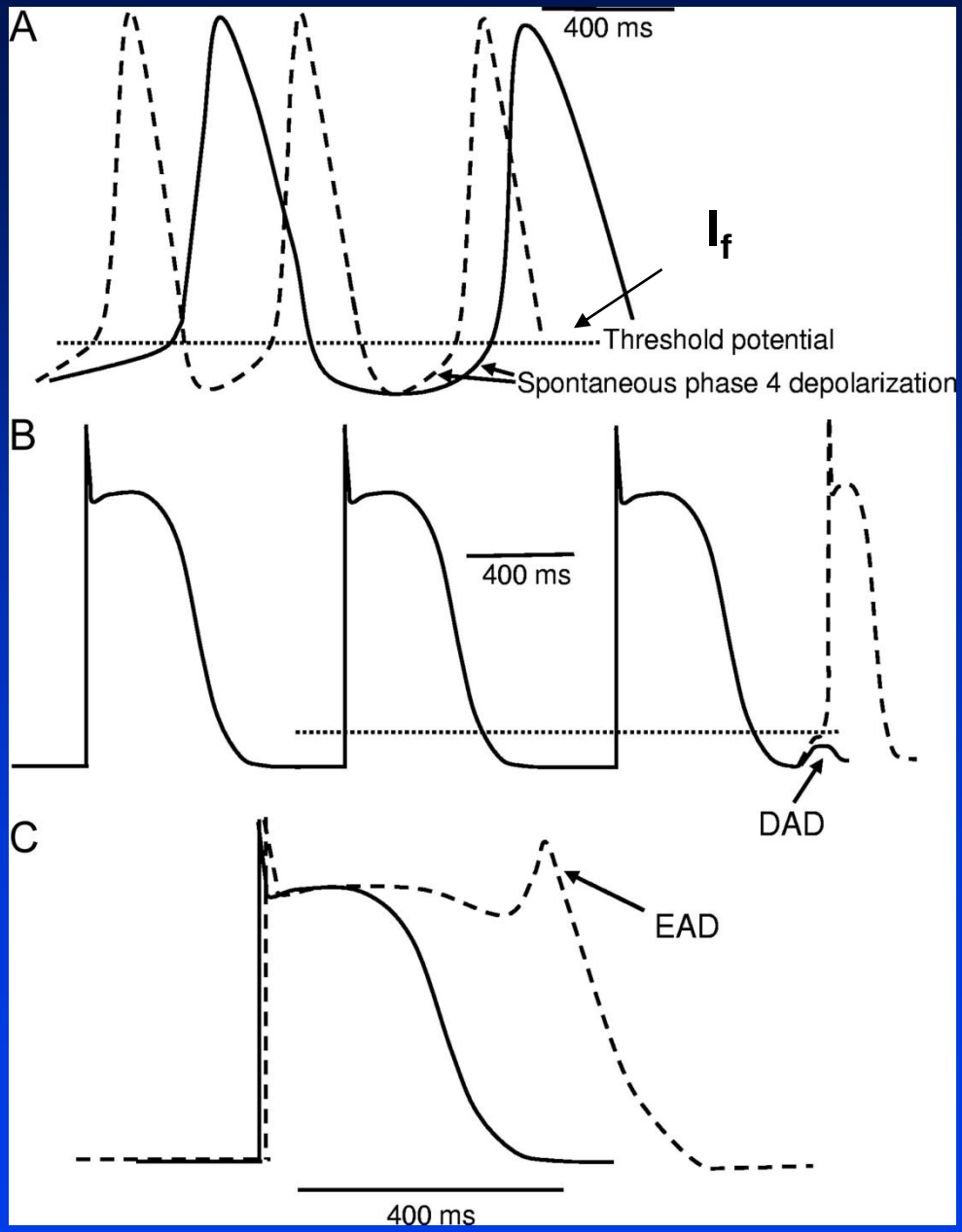
WL (Wavelength) = ERP x conduction velocity (*Allesie's* WL *theory*)
The main condition for maintaining of the AF is that WL to be smaller than the circuit time

How remodeling promotes reentry



The role of pulmonary veins

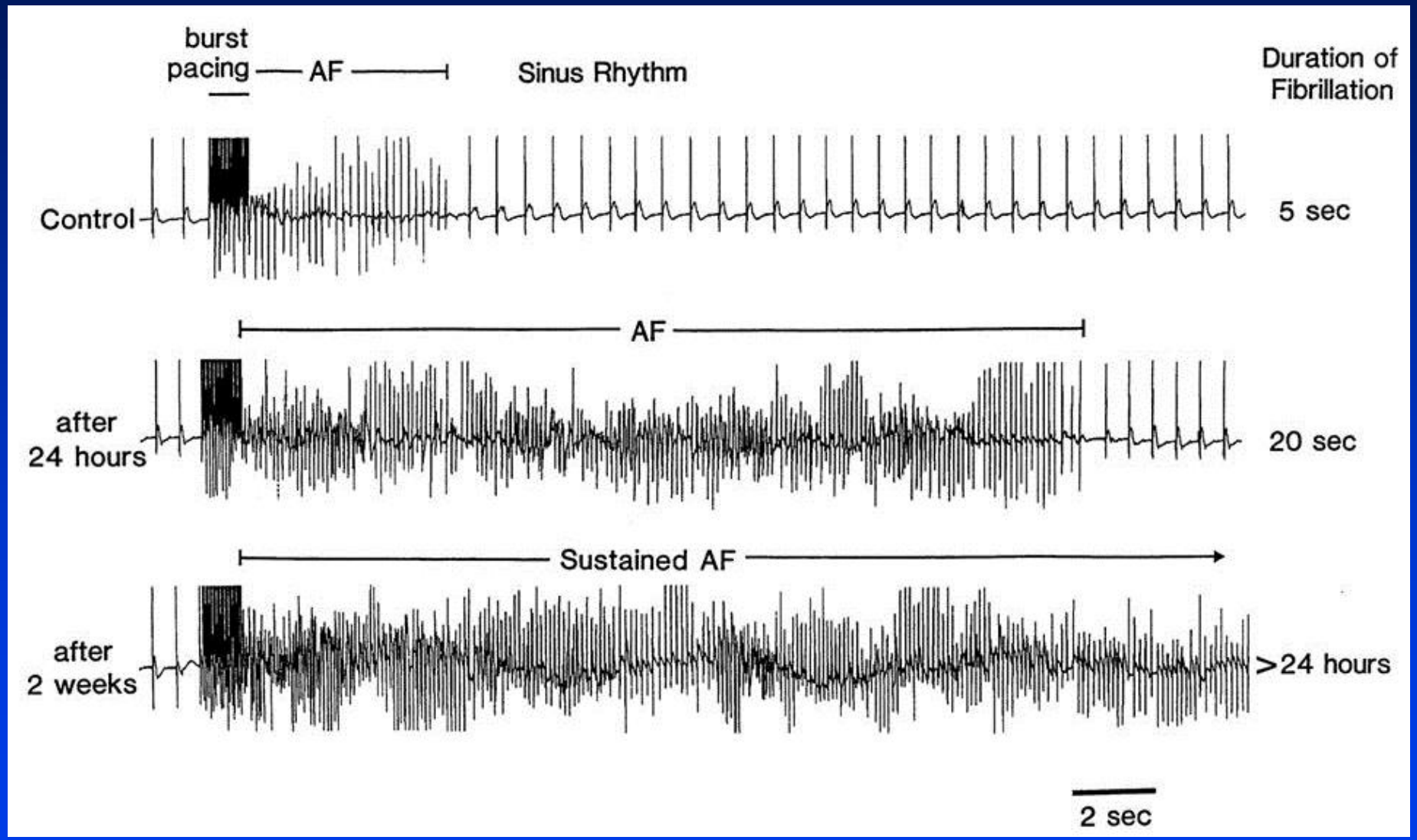
- The muscular sleeves of the pulmonary veins contains in large amount (40 %) myoycytes able for spontaneous diastolic depolarization (ectopic foci).
- The originating atrial systoles are the triggers of AFs. They can be suppressed by ablation.
- There were often observed spontaneous DADs or chatecholamine induced EADs.
- This PV-automaticity may be a thera-peutically relevant observation.



Atrial Fibrillation Begets Atrial Fibrillation

A Study in Awake Chronically Instrumented Goats

Maurits C.E.F. Wijffels, MD; Charles J.H.J. Kirchhof, MD, PhD;
Rick Dorland, BS; Maurits A. Allessie, MD, PhD



ERP 146 ms ⟶ 95 ms

Wijffels et al. Circulation 1995, 92: 1954-1968

Atrial fibrillation remodelling

AF is a progredient disease (paroxysmal → persistent → permanent)

(all changes, which are involved to initiate and maintain the AF)

Tachycardia (ATR)

Sarcolemmal ion channels

Signal transduction and „working" proteins

Gap-junctions, ECM

Neurohormonal systems,

Autonomic nervous system (RAAS)

etc.

1. Electrical remodelling
2. Contractile remodelling
3. Structural remodelling

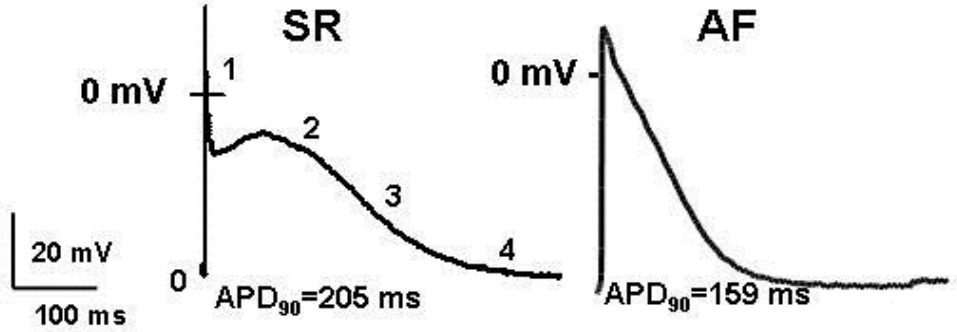
Congestive heart failure

Circulus vitiosus, which promote the initiation, renewal, stabilization and maintaing of the AF

The legendary hydra of Hercules

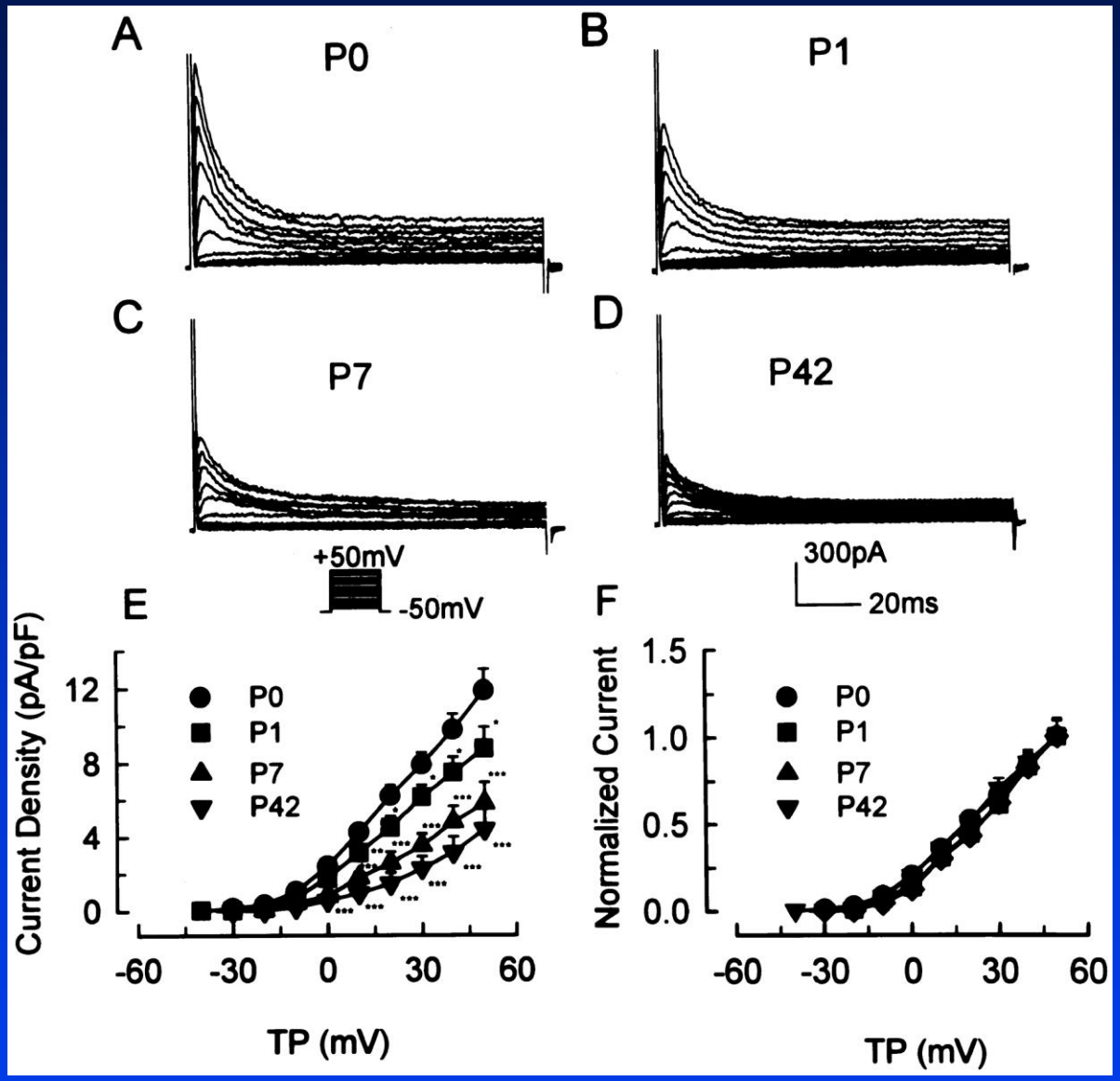
Lloyd and Langberg (*J Cardiov Electrophysiol,* 2006; 17: 236)

AF - electrical remodelling



Current		Main subunit (protein)		Gene
↔	I_{Na}	↔ Nav1.5	↔	*SCN5A*
60-70% ↓	I_{CaL}	40-60% ↓ α_{1C}	40-60% ↓	*CACNA1C*
60-70% ↓	I_{to}	40-50% ↓ Kv4.3	30-60% ↓	*KCND3*
40-50% ↓	I_{Kur}	50-60% ↓ Kv1.5	↔	*KCNA5*
↔	I_{Kr}	↔ HERG	↔	*KCNH2*
70-80% ↑	I_{Ks}	n.a. KvLQT1	70-80% ↑	*KCNQ1*
100-140 % ↑	I_{K1}	100-140% ↑ Kir2.1-2.3	100 % ↑	*KCNJ2/12/4*
!!! 50% ↓	I_{KACh}	50% ↓ GIRK1/4	50% ↓	*KCNJ3/5*
n.a	$I_{K(ATP)}$	n.a. Kir6.2	35% ↓	*KCNJ11*
n.a.	I_{NCX}	n.a. NCX1	60-70% ↑	NCX1

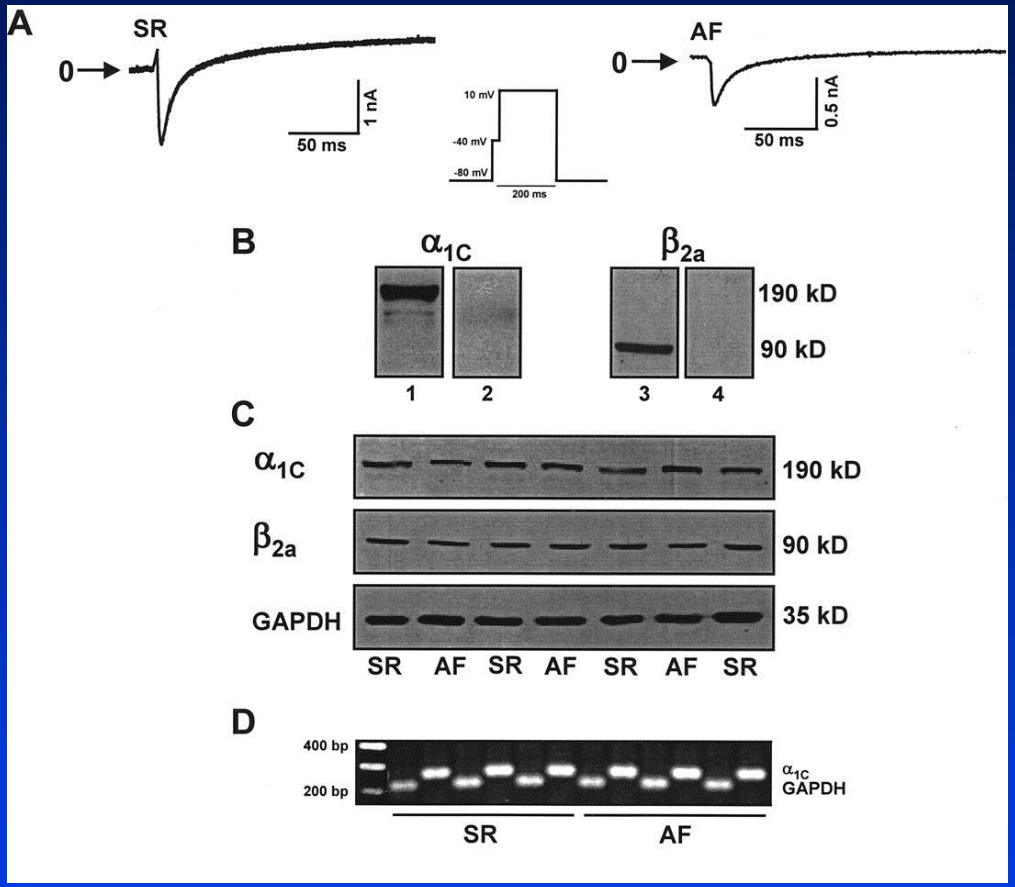
AF - electrical remodelling, transient outward current (I_{to})

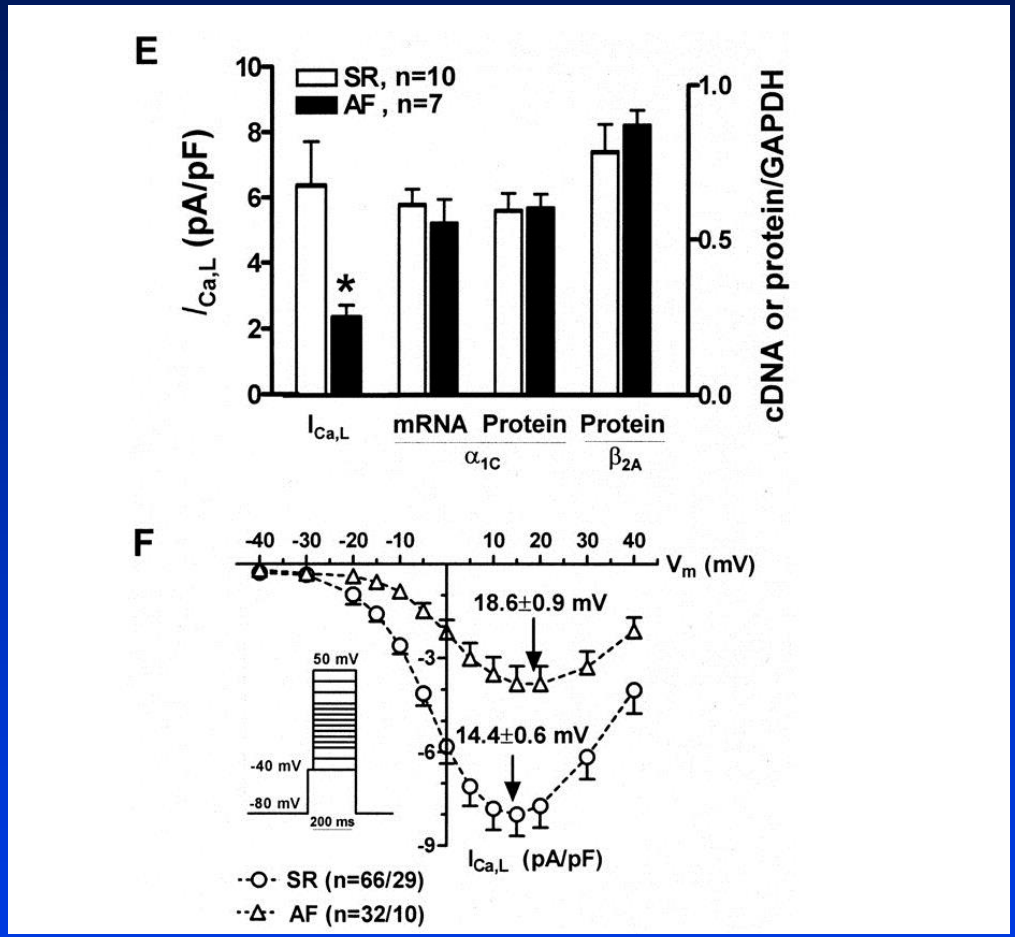


Recordings of I_{to} obtained with the voltage protocol shown in the inset at 0.1 Hz in representative cells obtained from a sham-operated dog (A) and dogs subjected to 1 (B), 7 (C), and 42 (D) days of rapid atrial pacing.

Yue et al. Circulation Research 1997, 81:512-525

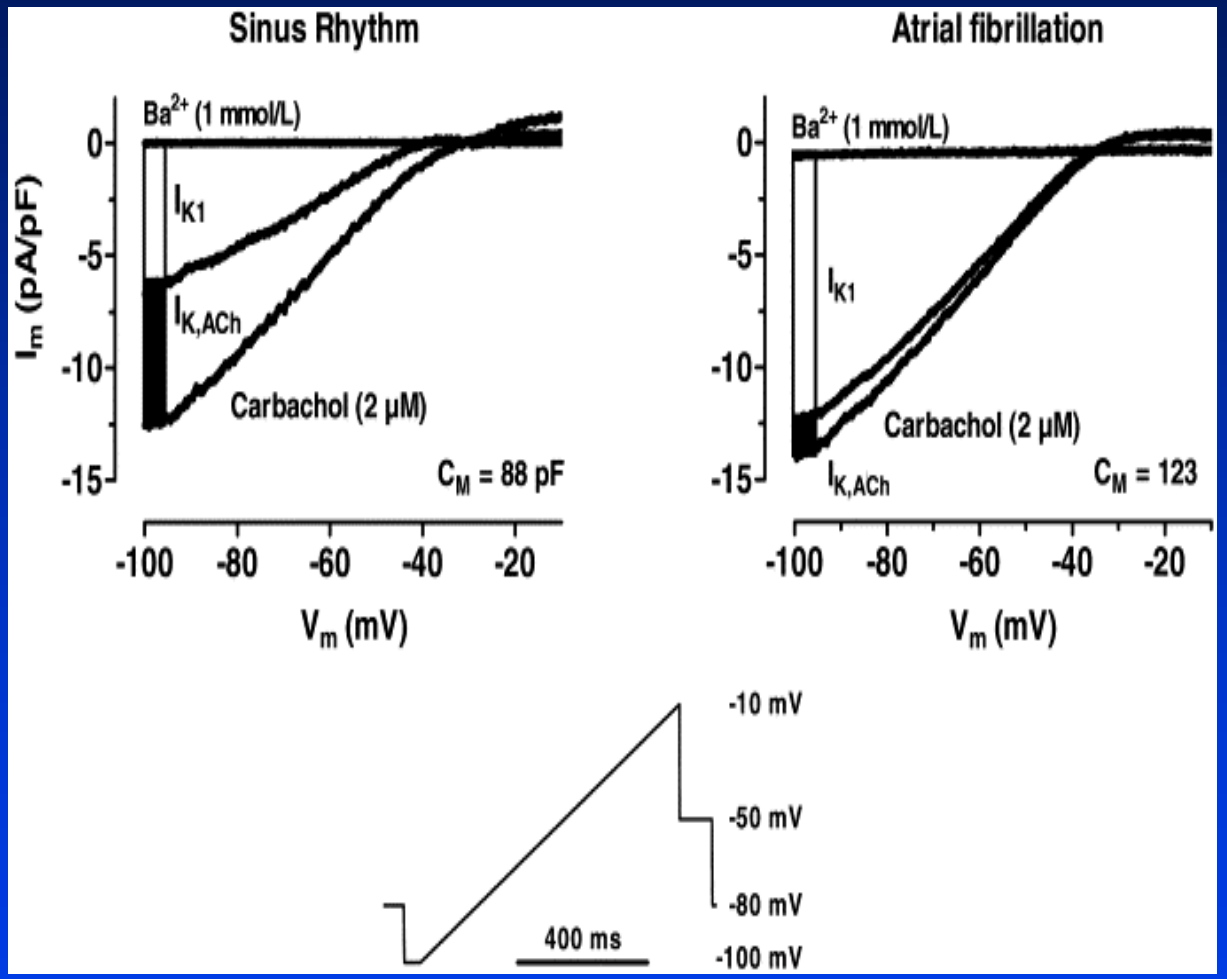
AF - electrical remodelling, L-type calcium current (I_{CaL})

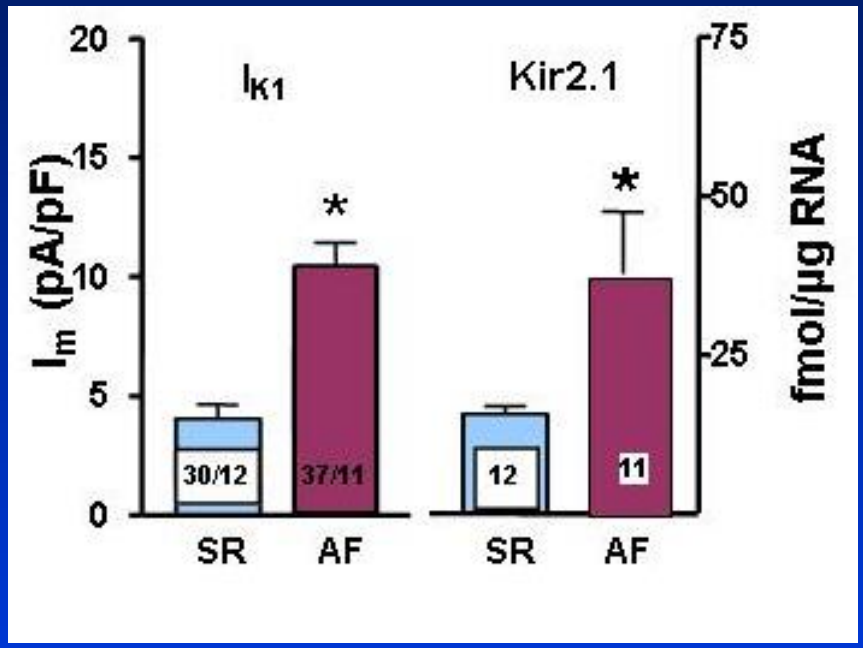




Christ et al. Circulation, 2004, 110(17):2651-2657

AF - electrical remodelling, inward rectifier potassium current (I_{K1})



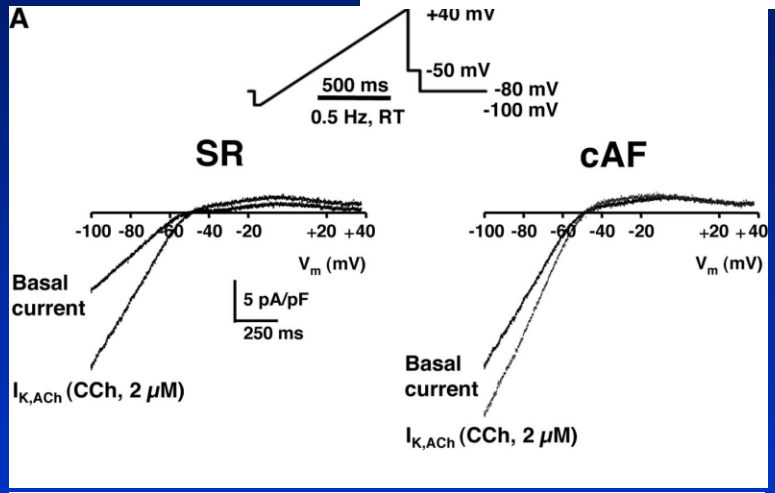


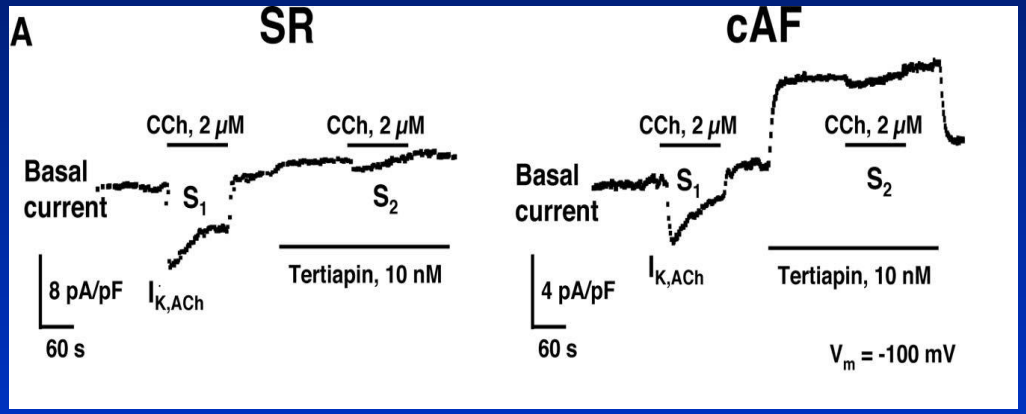
Dobrev et al. Cardiovasc. Res. 2002, 54: 397-404

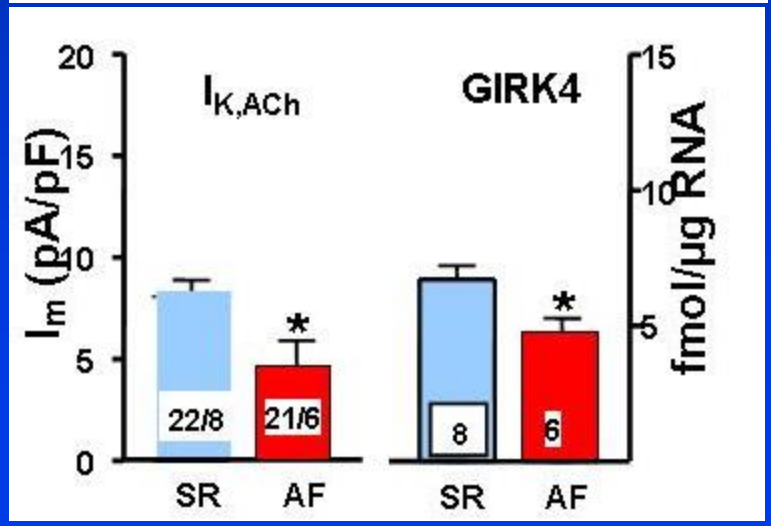
AF - electrical remodelling, acetylcholine sensitive potassium current ($I_{K,ACh}$)

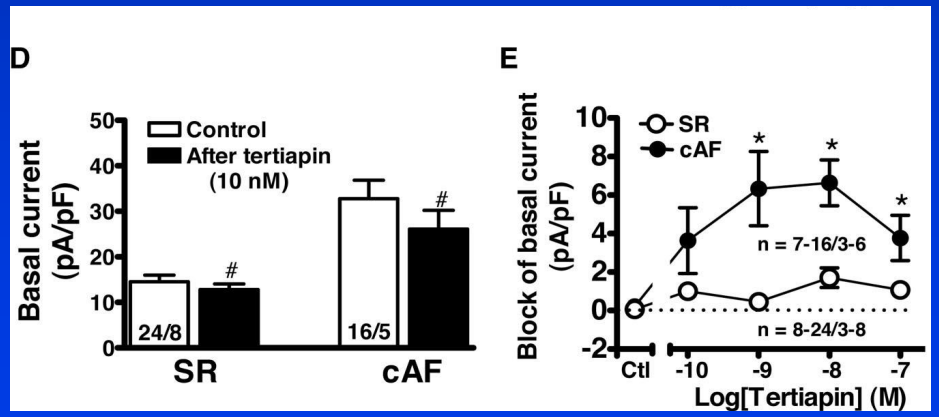
The G Protein–Gated Potassium Current $I_{K,ACh}$ Is Constitutively Active in Patients With Chronic Atrial Fibrillation

D. Dobrev, MD; A. Friedrich, CandMed; N. Voigt, CandMed; N. Jost, PhD; E. Wettwer, PhD; T. Christ, MD; M. Knaut, MD; U. Ravens, MD



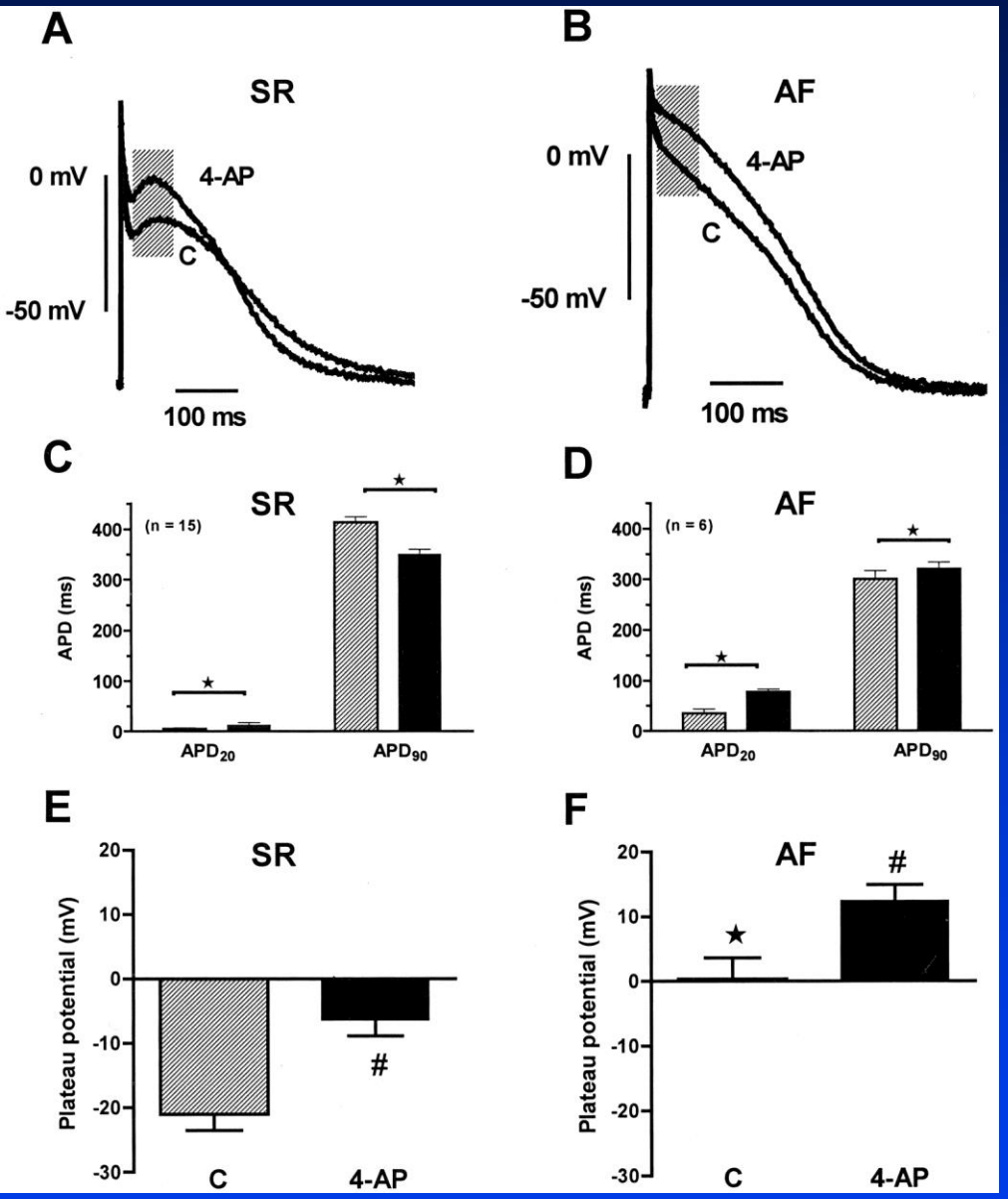


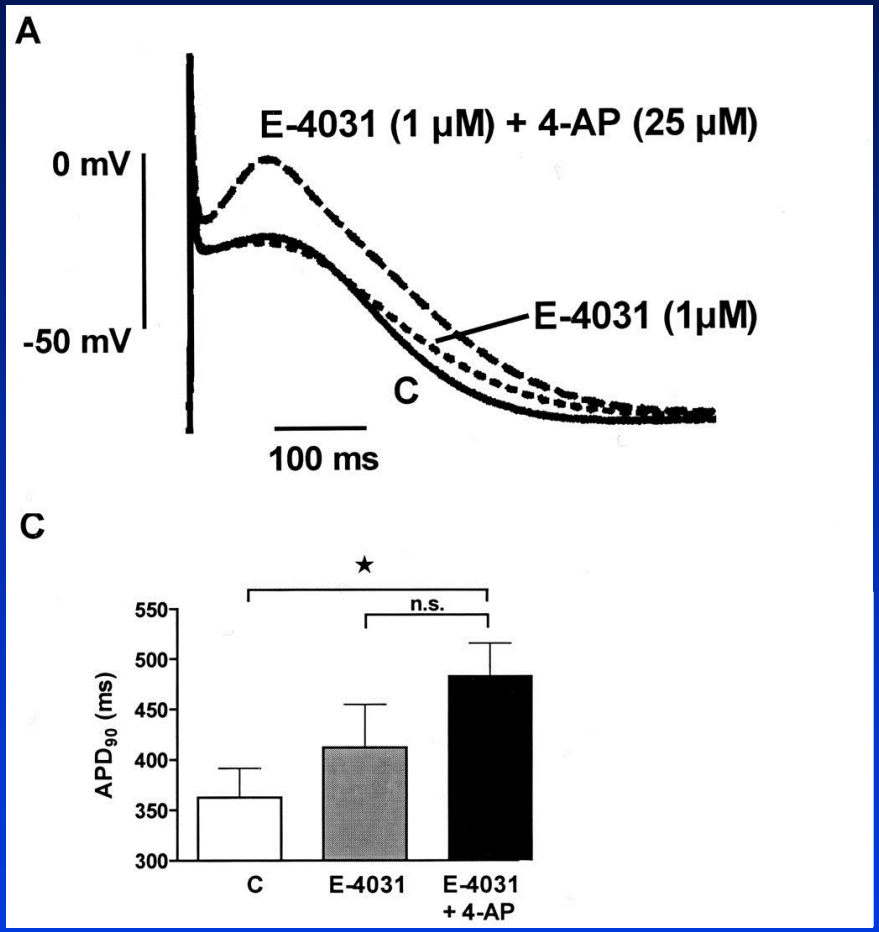




Circulation. 2005;112:3697-3706.

AF - electrical remodelling, ultrarapid delayed rectifier potassium current (I_{Kur})

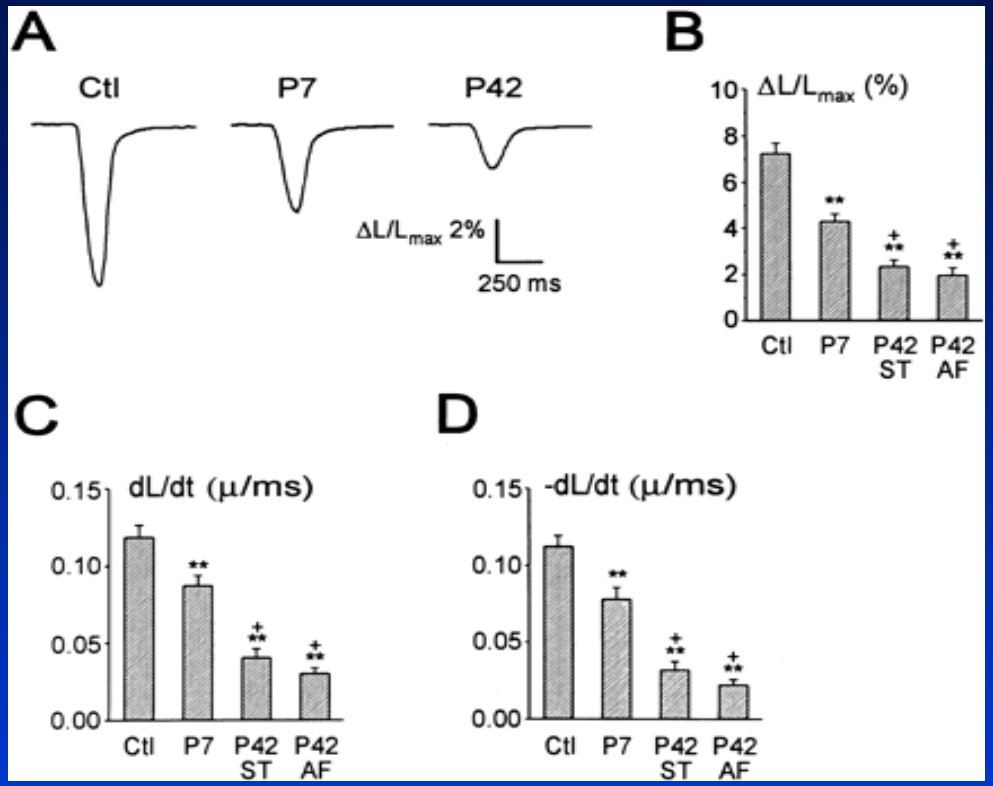


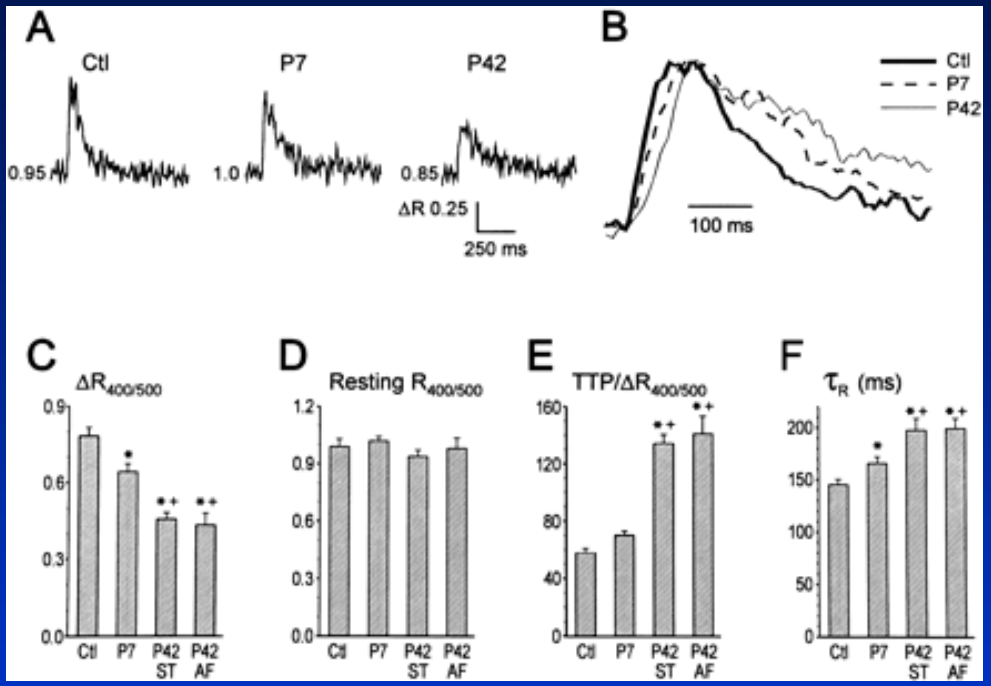


Wettwer et al Circulation, 110:2299-2306

I_{Kur} blockade in treating cAF ?

Contractile remodelling





Representative recordings of cell-shortenings (right) and calcium transients (left) obtained from a Ctl, a P7, and a P42 cells

Sun et al. Circulation 1998, 98: 719-727

The loss of contractile force of the myocardium, mainly due to I_{CaL} reduction (as a protective mechanism against Ca^{2+} overload) and consequently by the damage of the Ca^{2+}-homeostasis. Hipocontractility will increase the wall stretch, and thereby, causes atrial dilation (LAV ↑). ***Electrical and contractile remodelling go hand in hand !!!***

Structural remodelling (ASR)

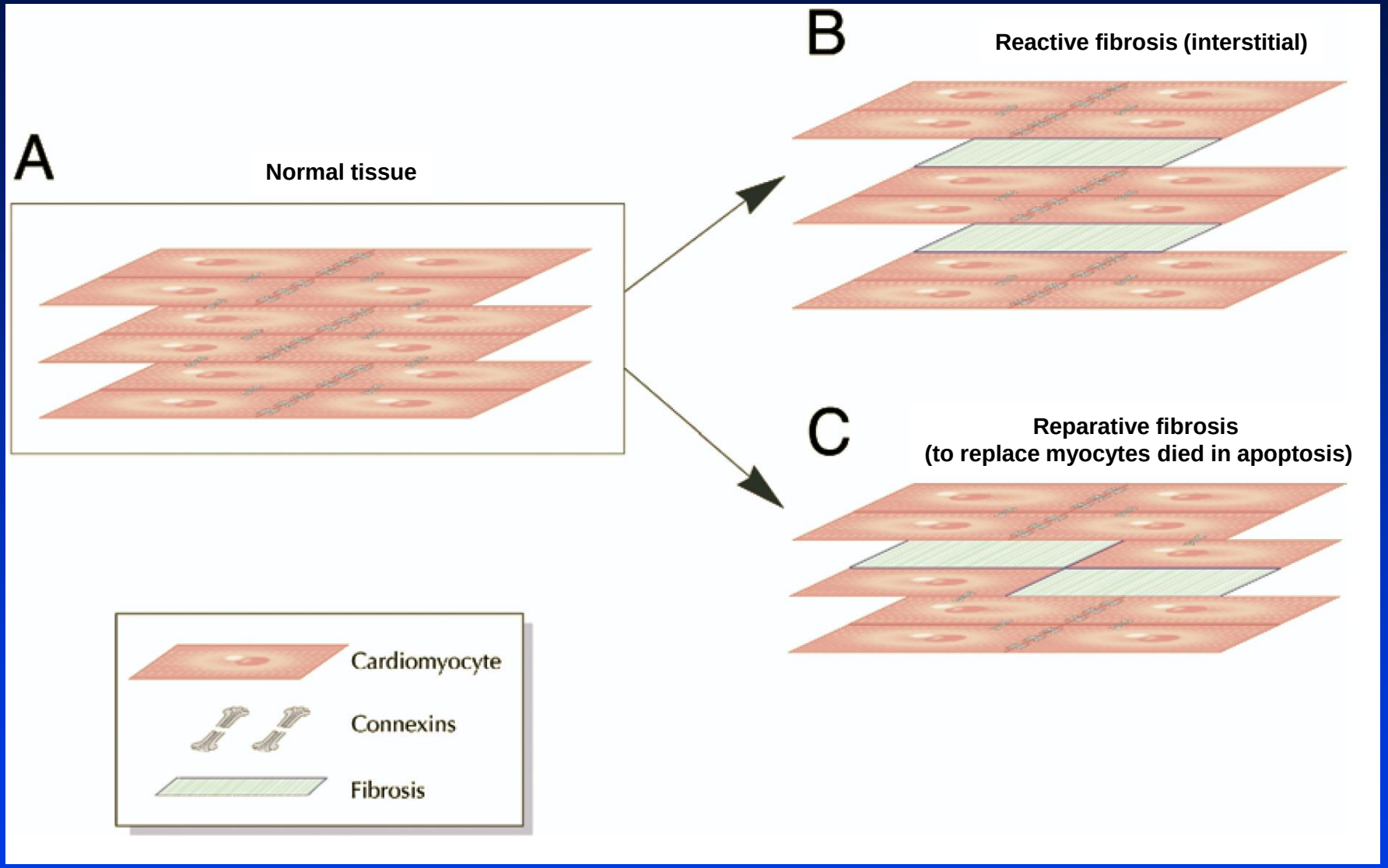
A paradigm shift in treatment af atrial fibrillation: from electrical to structural therapy ? (Heidbüchel, *Eur Heart J*, 2003; 24:2077-2078)

The importance of upstream/non channel treatment of AF !!!

The structural remodelling is the main cause for the progredient behaviour of the AF (paroxysmal → perzistent → permanent). In long lasting AF the following „*low flow ischaemia*" –type structural changes occur:

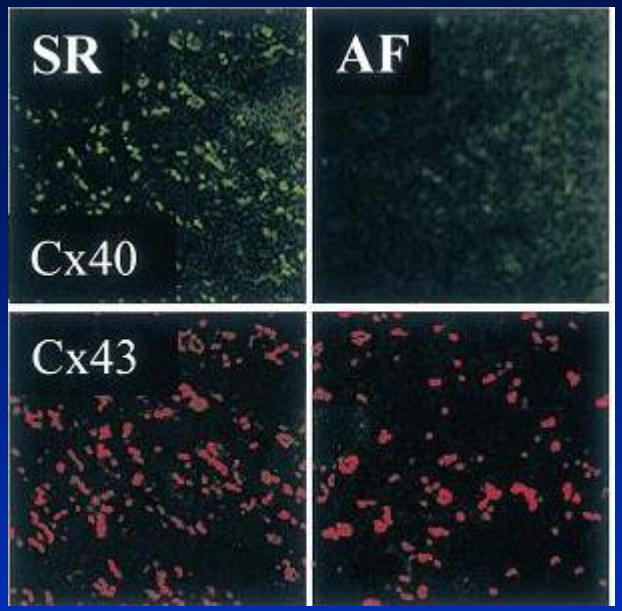
- **increase in cell size**
- **perinuclear accumulation of glycogen**
- **central loss of sarcomeres (myolysis)**
- **alterations in connexin expression (gap-junctions)**
- **changes in mitochondrial shape**
- **fragmentation of sarcoplasmic reticulum**
- **homogeneous distribution of nuclear chromatin**
- **changes in quantity and localization of structural cellular proteins**
- **fibrosis !!!**

Schematic illustrating how fibrosis disrupts myocyte coupling



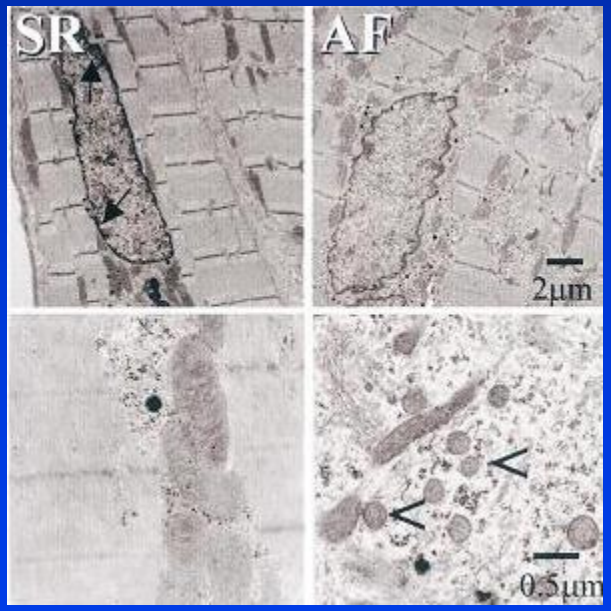
Cardiomyocytes in normal myocardial tissue are electrically coupled primarily in an end-to-end fashion by intercellular gap-junctional complexes. Reactive fibrosis results in extracellular matrix expansion between bundles of myocytes while reparative fibrosis replaces degenerating myocytes. Both patterns of collagen distribution become exaggerated during structural remodeling.

Structural remodelling of atrial myocytes after 4 months of AF in the goat 2.



Connexins

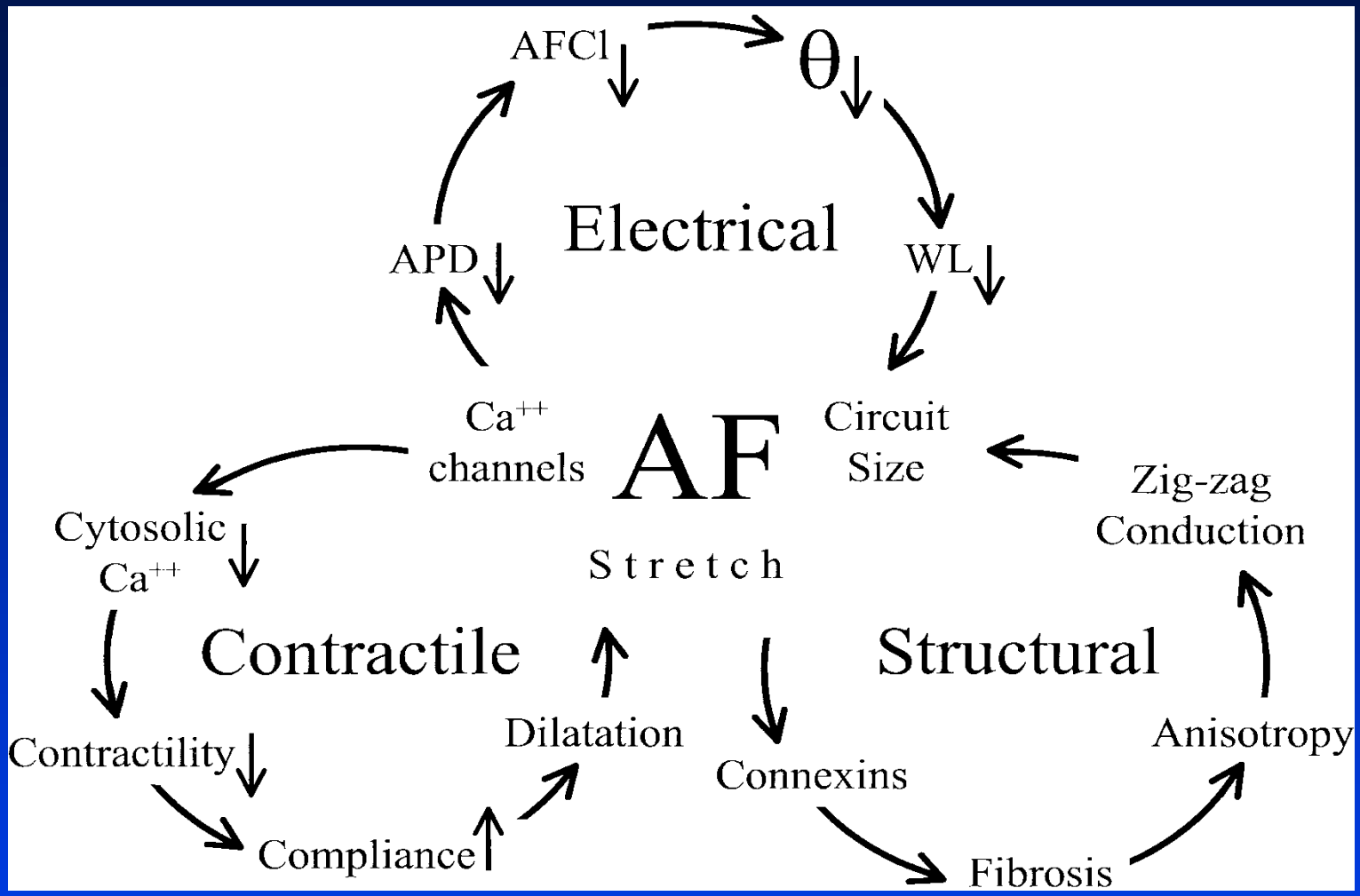
Labeling of Cx40 (green) and Cx43 (red) revealed a clear reduction in Cx40 and no change in Cx43 expression



Ultrastructure during AF the atrial nuclei get a more homogeneous distribution of chromatin. For comparison the normal clustering of chromatin at the nuclear membrane is indicated by arrows in the upper left panel. During AF many small donut shaped mitochondria can be found (arrowheads right lower panel)

van der Velden et al. *J Cardiovasc Electrophysiol* 1998; 9:596-607

The positive feedback correlation between the three types of atrial remodellings



Allessie et al. Cardiovasc Res, 2002, 54: 230-246

Electrical and contractile remodelling may occur in minutes, hours and days – reversible after conversion

Structural remodelling develops within 3-4 months, and is hardly or even nonreversible

Therapeutic implications

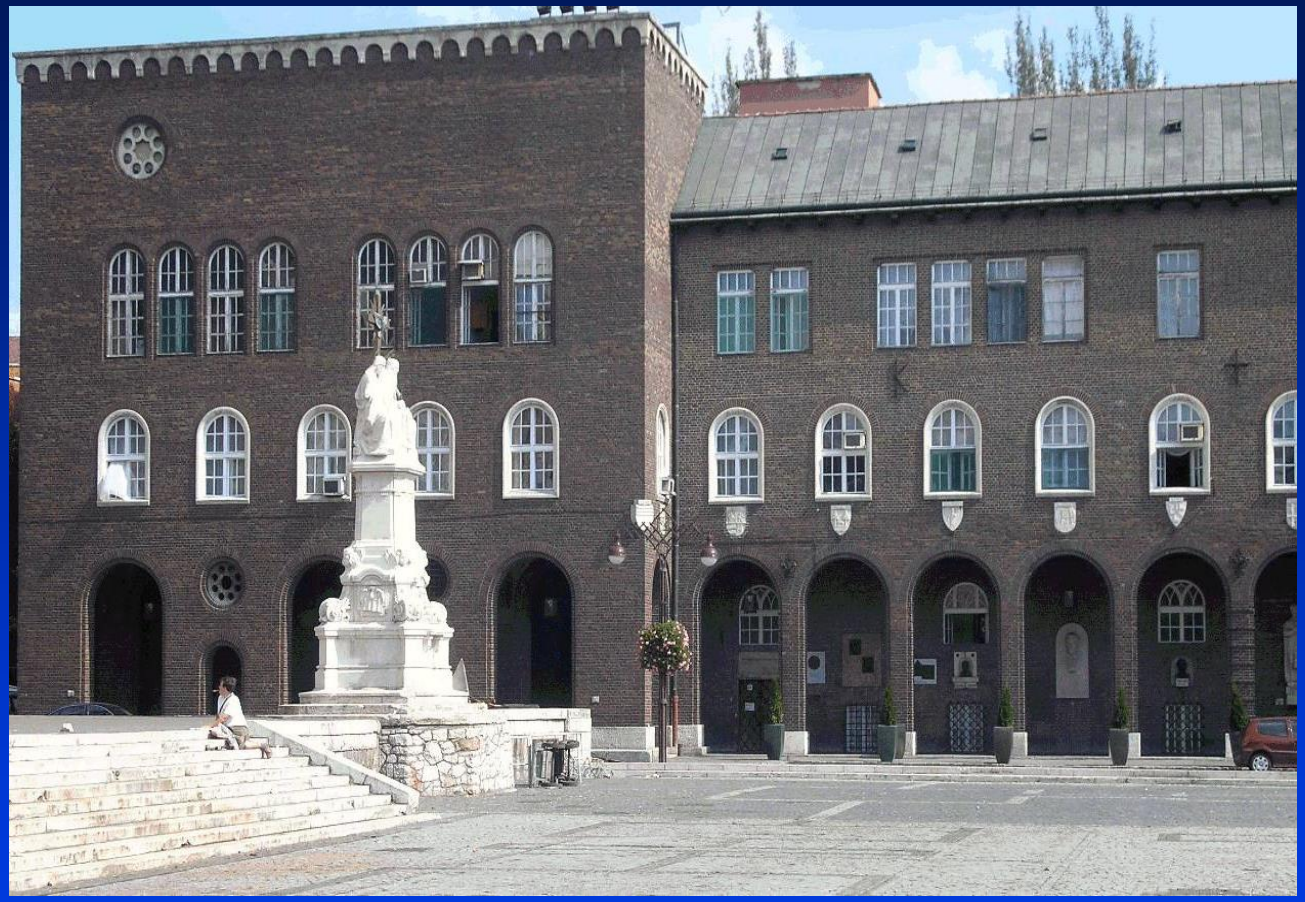
Therapeutic consequences of ATR

- To develop atria-selective antiarrhythmic drugs
- Repolarization lenghtening - I_{Kr} blockade ??
- I_{CaL} blockade – to prevent Ca^{2+} -overload
- ~~I_{CaT} blockade – mibefradil~~
- ~~I_{Kur} blockade (I_{Kur} + I_{Kr} ?)~~
- I_{K1} blockade (?)
- $I_{K,ACh}$ blockade (NIP-142, NIP-151) !!!
- amiodarone

Therapeutic consequences of ASR

- Drugs to prevent against fibrosis
- „Gap-junction therapy”- rotigaptide (GAP-486)
- nonselective stretch-sensitive cation channels blockers

Thank you for your attention !!

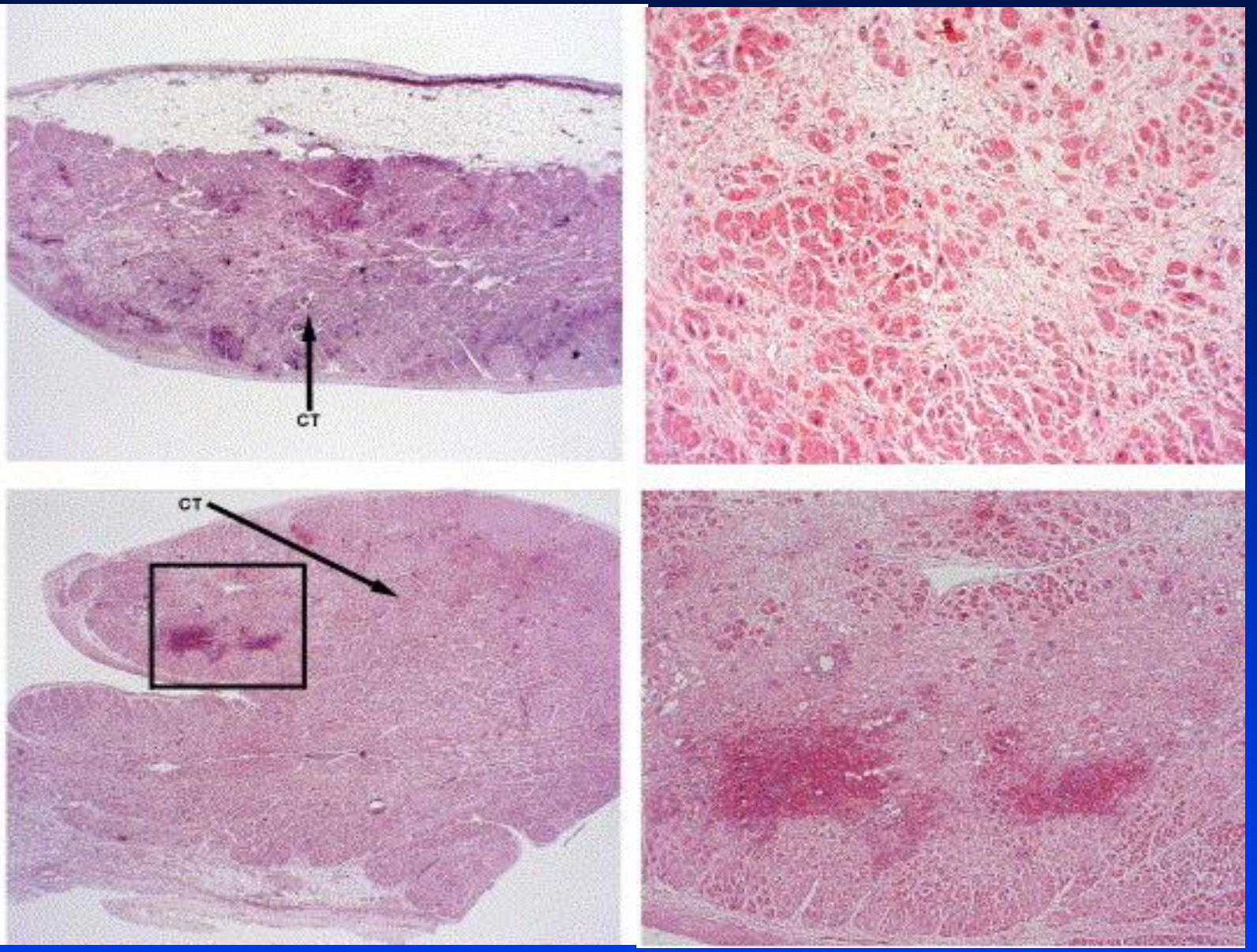


Department of Pharmacology & Pharmacotherapy, University of Szeged; Szeged, Hungary

Profibrotic factors

- Angiotenzin II (presence of fibrosis in transgenic ACE overexpressed mice; Xiao et al, Am J. Phatol, 2004; 165: 1019-1032)
- Transforming grown factor-β1 (TGF-β1) (in spite of normal structural heart an increased atrial conduction heterogeneity and AF prvelance was observed in TGF-β1 overexpressed mice; Verheule et al, Circ Res; 94:1458-1465)
- Platelet-derived growth factor
- Connective tissue growth factor
- Oxidative stress
- inflammation

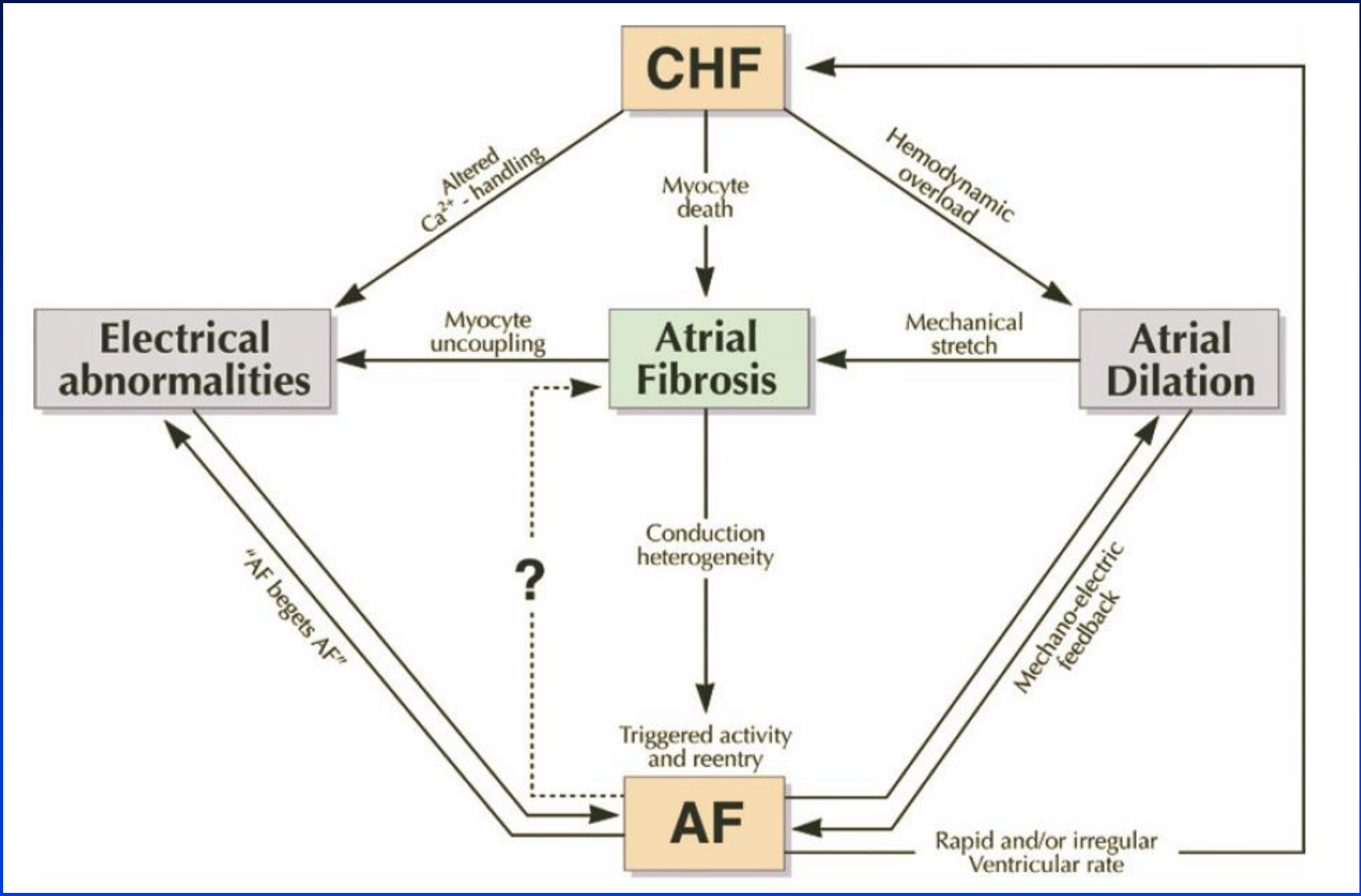
Extensive replacement fibrosis (scarring) in the inferior part of the terminal crest



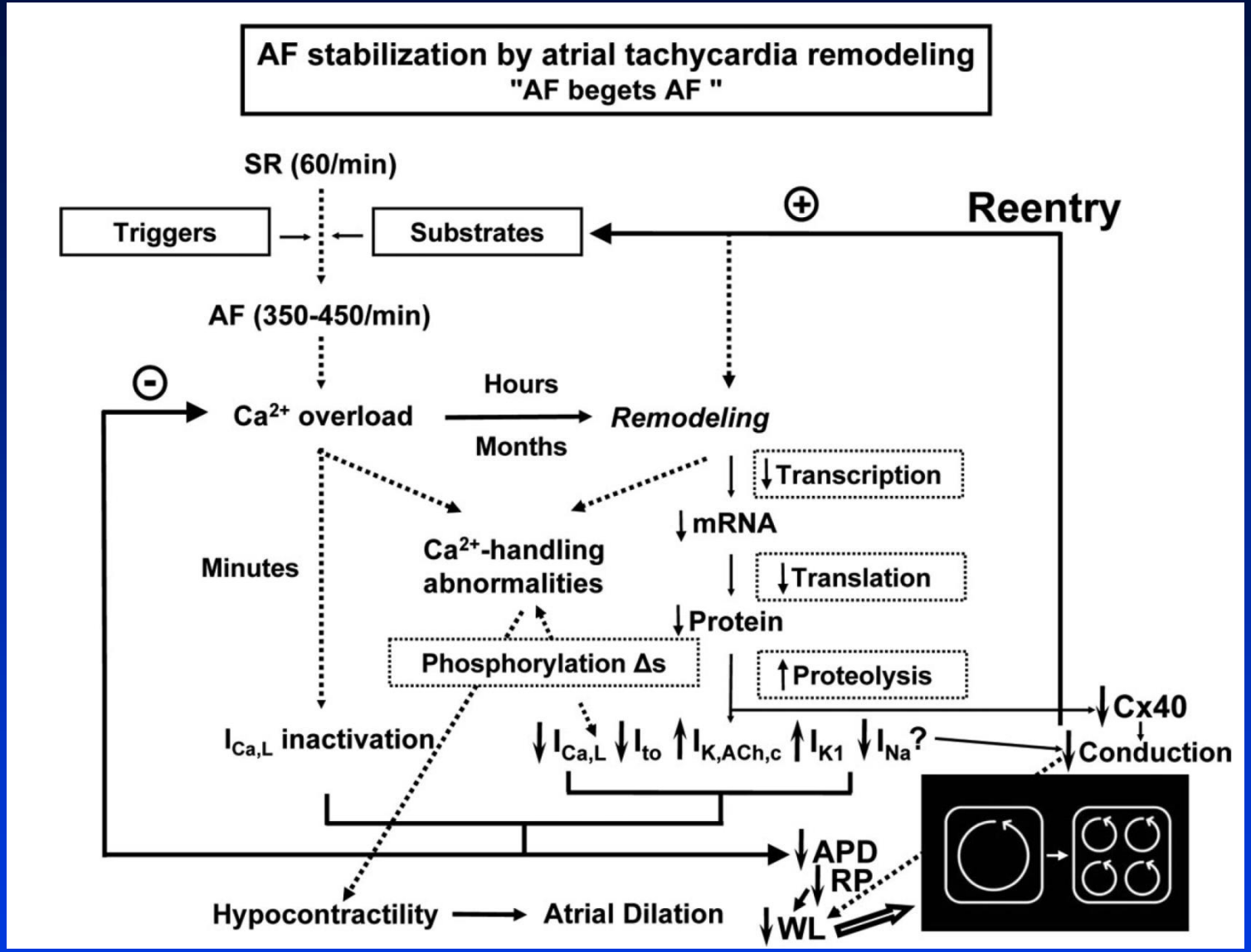
Recent hemorrhagic micro-infarcts and extensive replacement fibrosis

Becker AE. *Heart Rhythm*, 2004; 1:627-631.

Mechanism by which CHF leads to AF (in turn, AF causes changes that can impair cardiac function, leading to potentially deleterious positive feedback systems



„Another sort of …. remodelling" (Cha et al, *Circulation*, 2004; 110: 1520-1526)



Mechanisms underlying ATR. Rapid atrial rates increase potentially cytotoxic Ca^{2+} loading. Autoprotective I_{CaL} reductions occur via rapidly developing functional changes (I_{CaL} inactivation) and more slowly developing changes in gene and protein expression. Decreased I_{CaL} reduces Ca^{2+} loading but decreases APD. Diminished APD shortens refractoriness and reduces the wavelength (WL), which allows for smaller and more atrial reentry circuits, thus making AF unlikely to terminate. Atrial tachycardia also increases inward-rectifier currents such as I_{K1} and I_{KACh}, which further reduces APD and promotes AF.

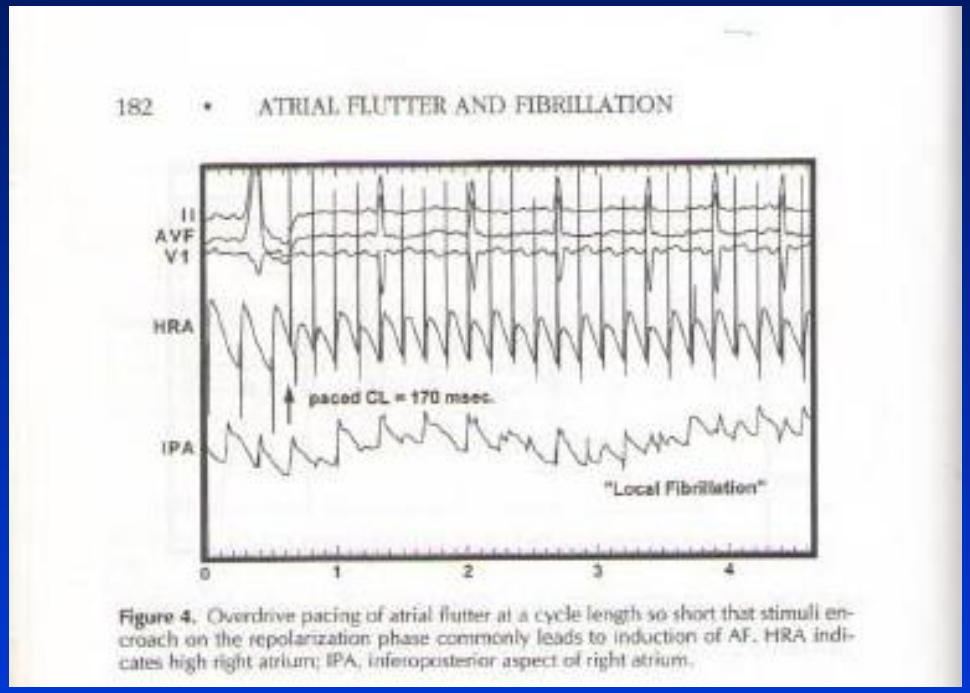


Figure 4. Overdrive pacing of atrial flutter at a cycle length so short that stimuli encroach on the repolarization phase commonly leads to induction of AF. HRA indicates high right atrium; IPA, inferoposterior aspect of right atrium.

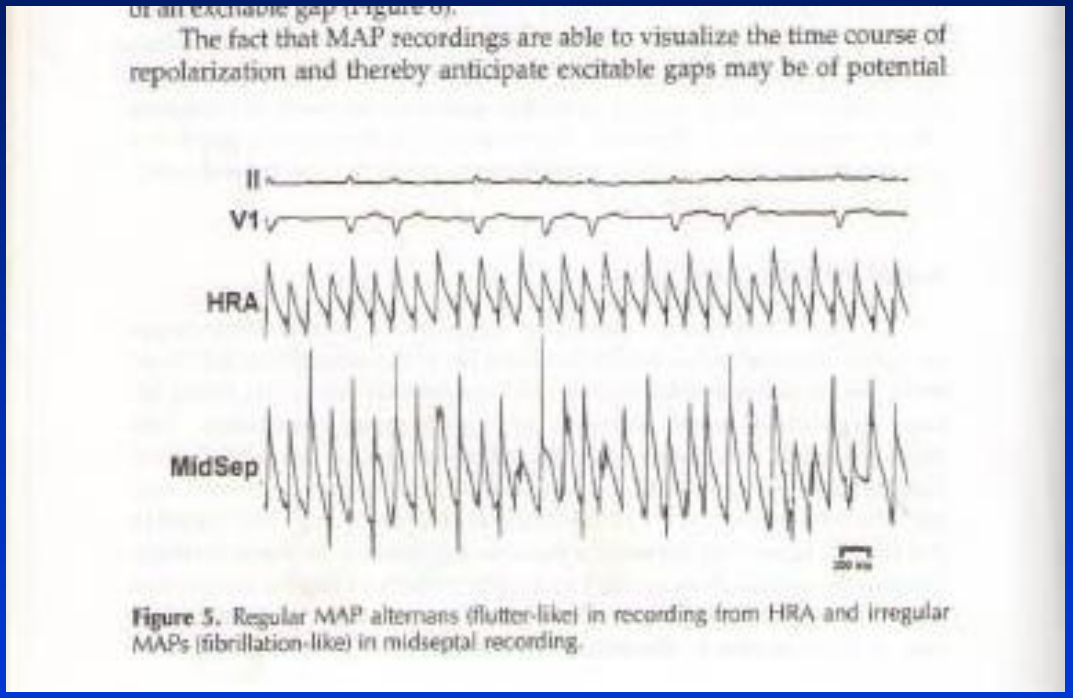
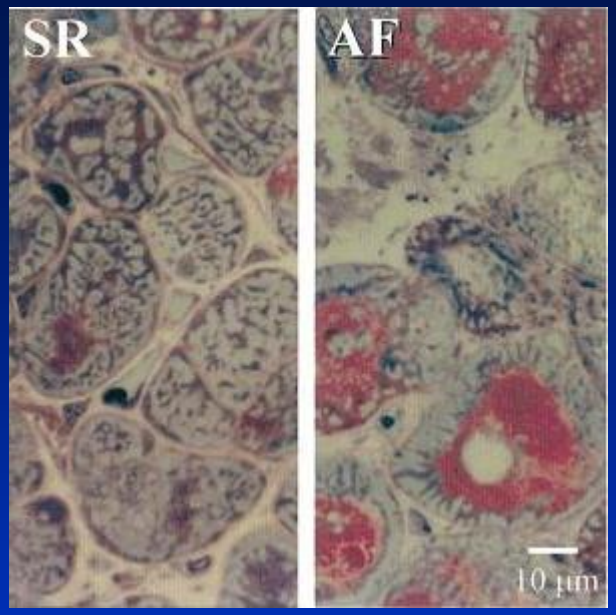


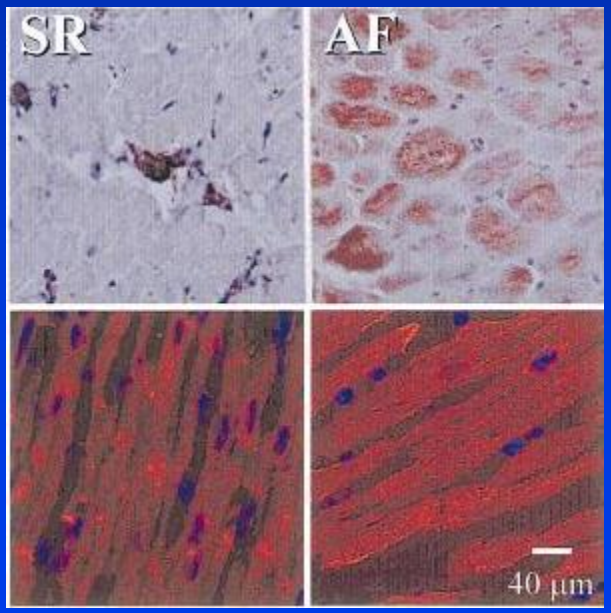
Figure 5. Regular MAP alternans (flutter-like) in recording from HRA and irregular MAPs (fibrillation-like) in midseptal recording.

Franz MR. Atrial fibrillation and atrial flutter seen through the "eye" of monophasic action potential recordings. In *Atrial flutter and fibrillation. From basic to clinical apllications.* Saoudi N, Schoels W, El-Sherif N (eds), Futura Publishing Co., Inc, Armonk, New York, 1998, p. 177-191.

Structural remodelling of atrial myocytes after 4 months of AF in the goat 1.



Severe myolysis (loss of sarcomeres: blue staining) and accumulation of glycogen (red)

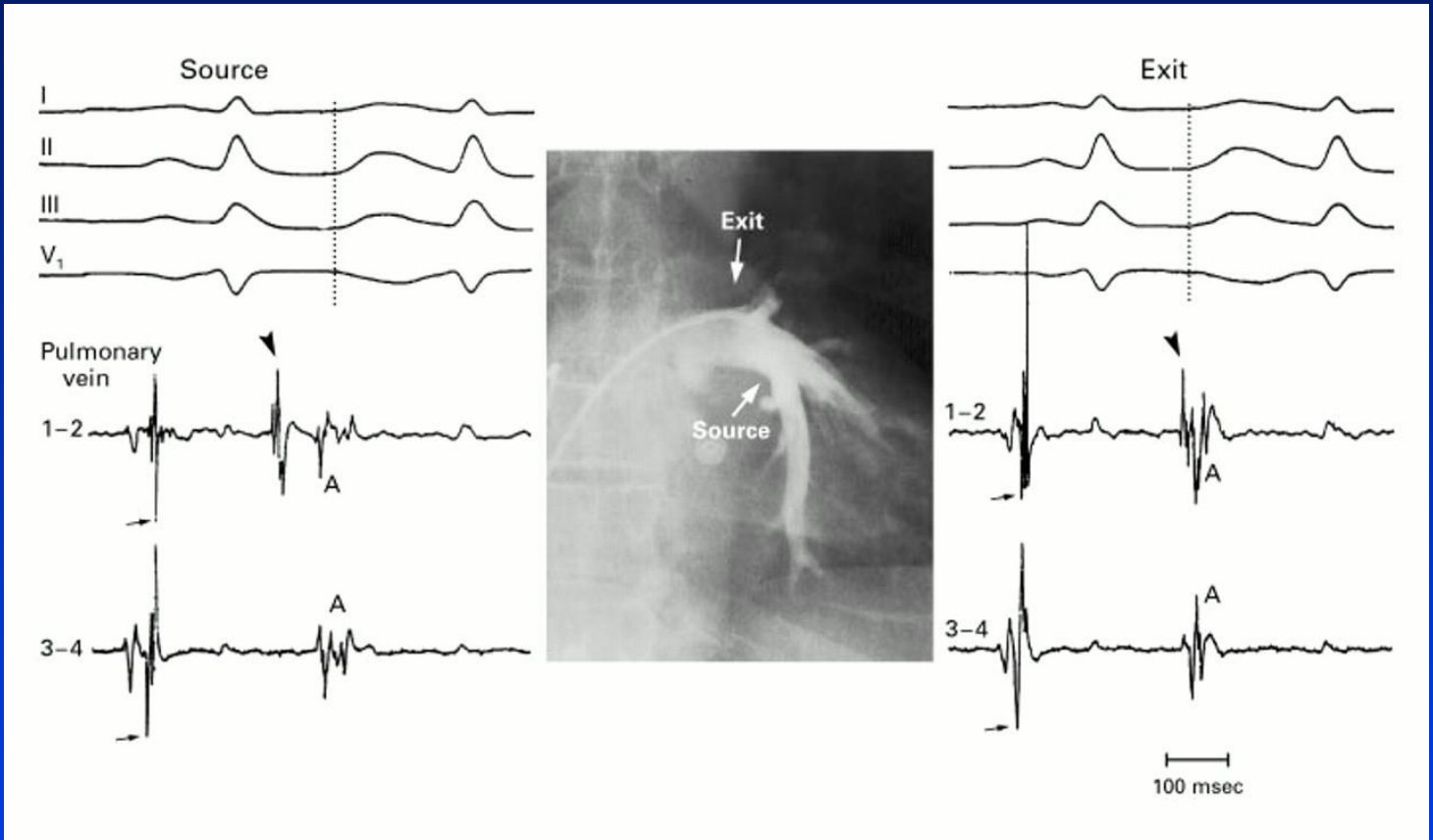


Fetal phenotype dedifferentiation of the atrial myocardium by a clear increase in fetal α-smooth muscle actin (red staining in upper pictures). In the lower pictures of this panel the myocytes are stained for desmin (red). The nuclei are stained by blue DAPI. During AF desmin looses its cross-striated pattern in the cytoplasm and at the intercalated disks the intensified desmin staining is no longer present.

Ausma et al. Circulation 1997; 96:3157-3163

The role of pulmonary veins

The pulmonary veins (PV) may be sources of ectopic beats, which may cause paroxismal AF.



Angiogram of a left inferior pulmonary vein depicting the source and axit of actopic activity

Haissaquerre et al. N.Engl. J Med. 1998 339:659

Thanks' for your kind attention!!!!!!

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