Neural Mechanisms of Paroxysmal Atrial Fibrillation

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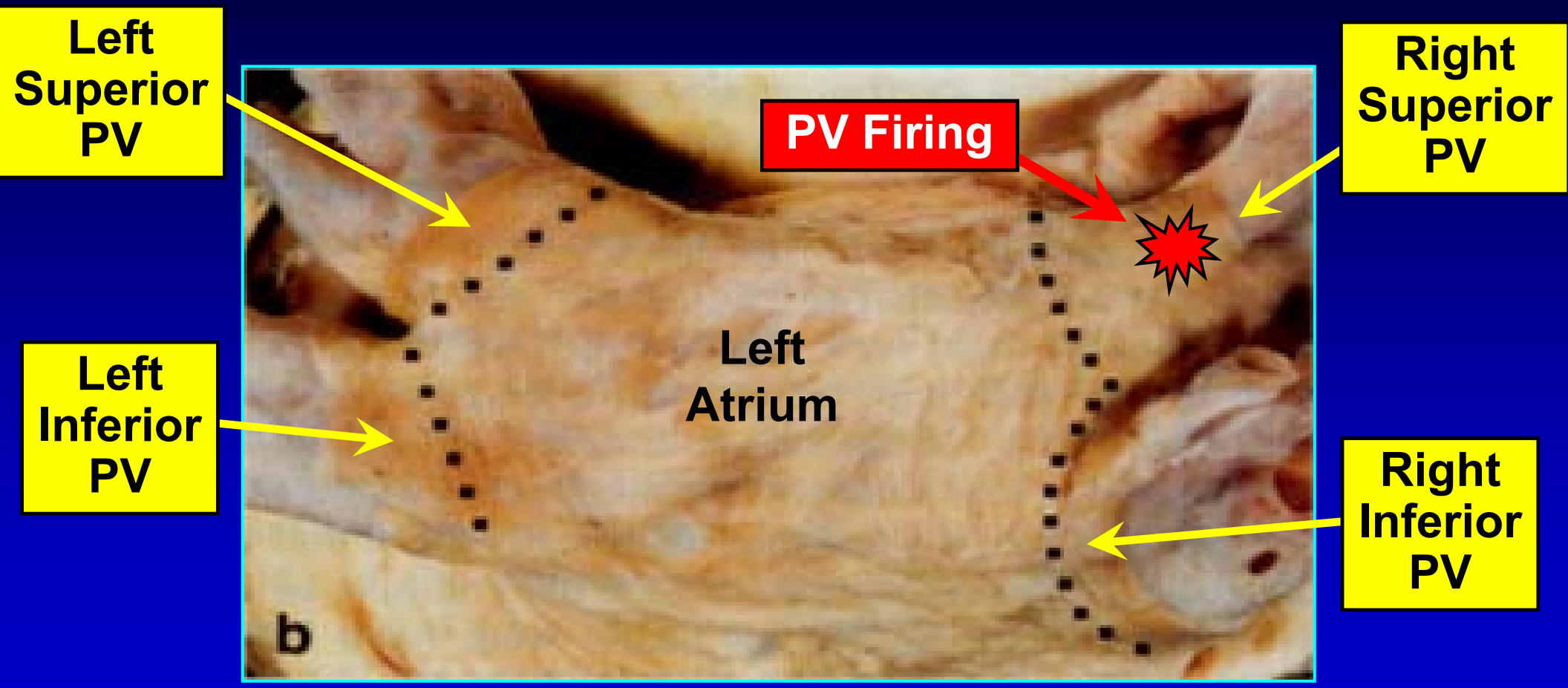
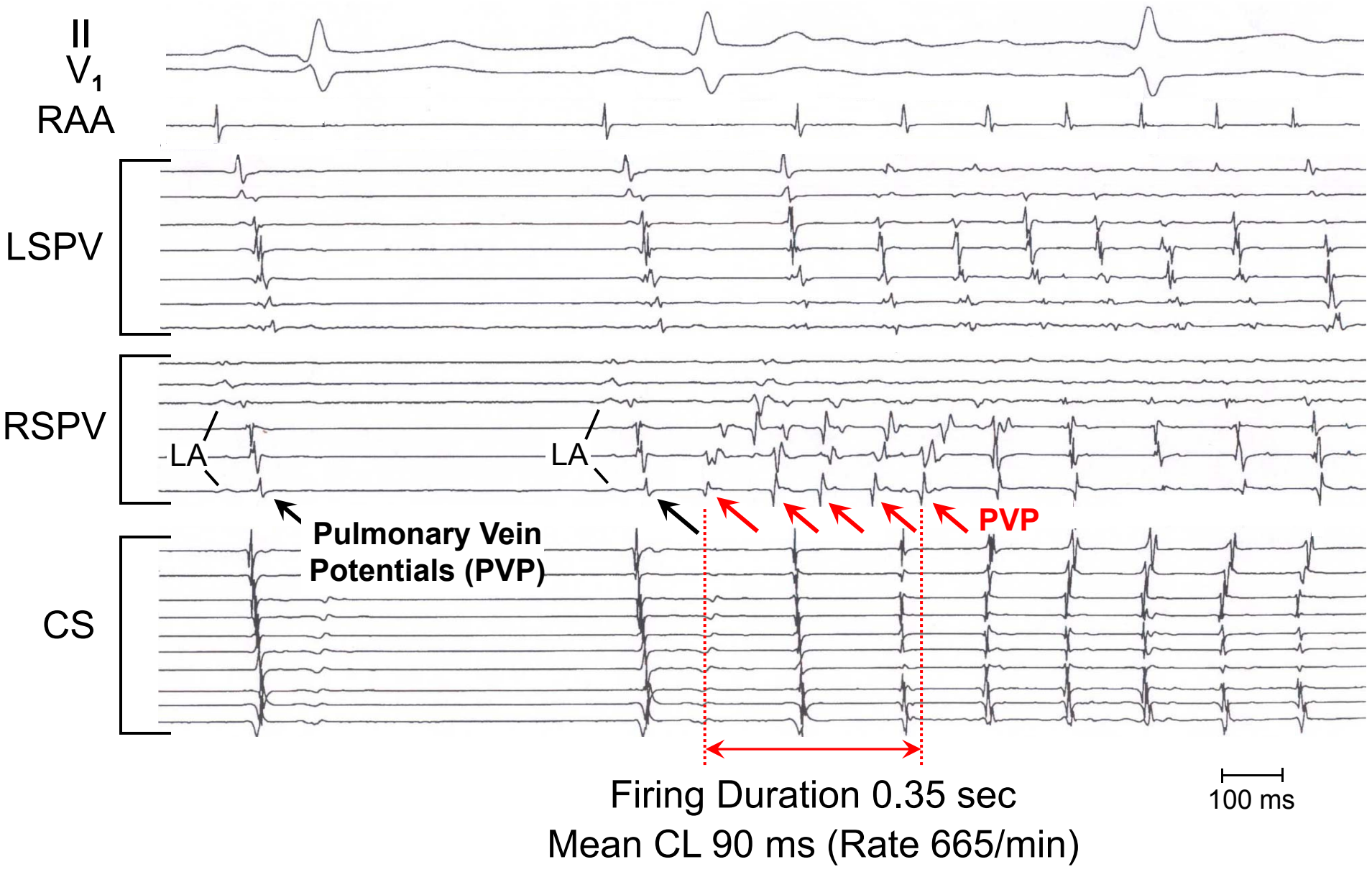
Paroxysmal AF Usually Begins With Firing in the Pulmonary Veins (PV)



PA View

Saito T, Becker AE et al, JCE 2000; 11:888

Rapid Firing From Right Superior Pulmonary Vein (RSPV) Initiates Atrial Fibrillation



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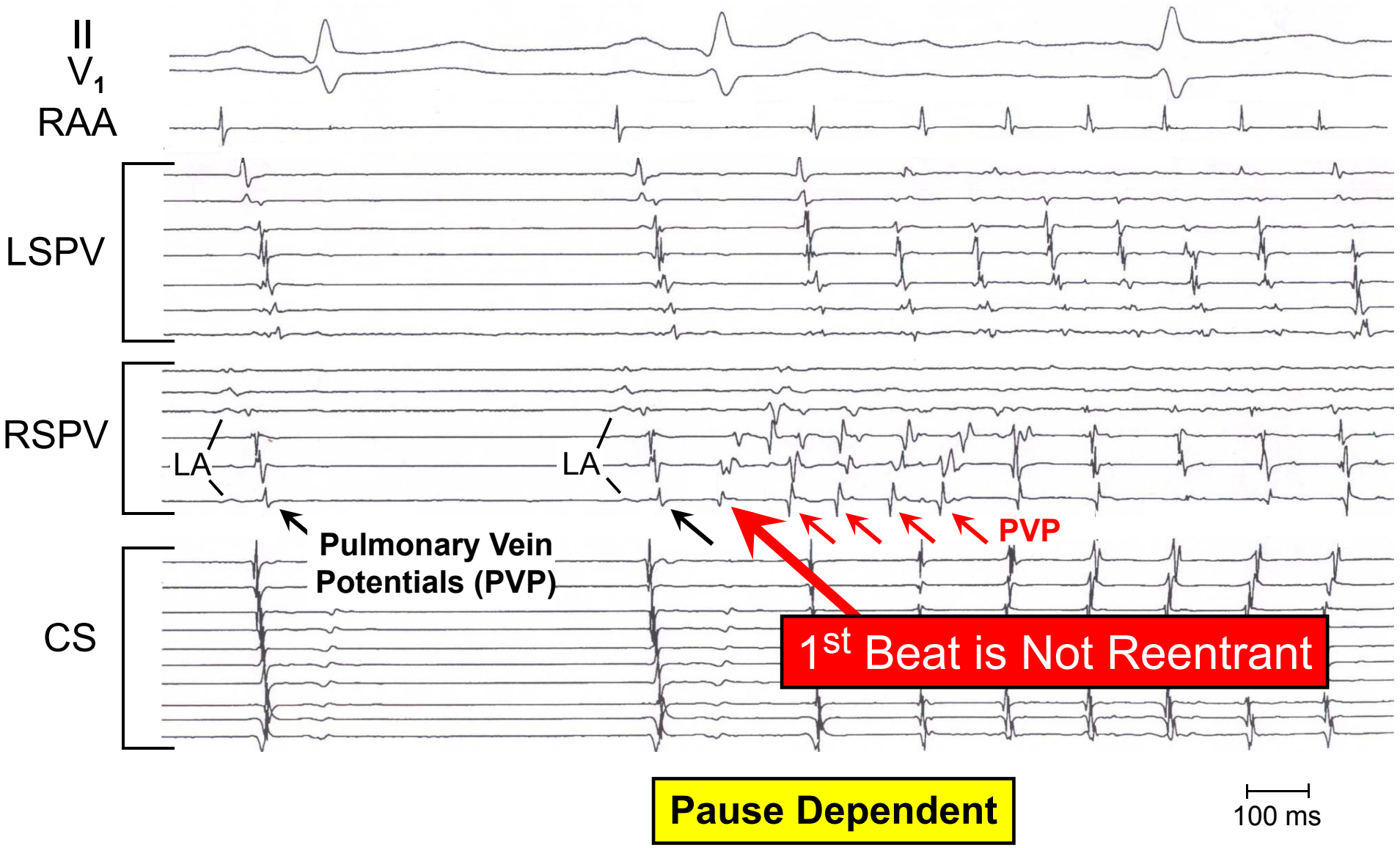
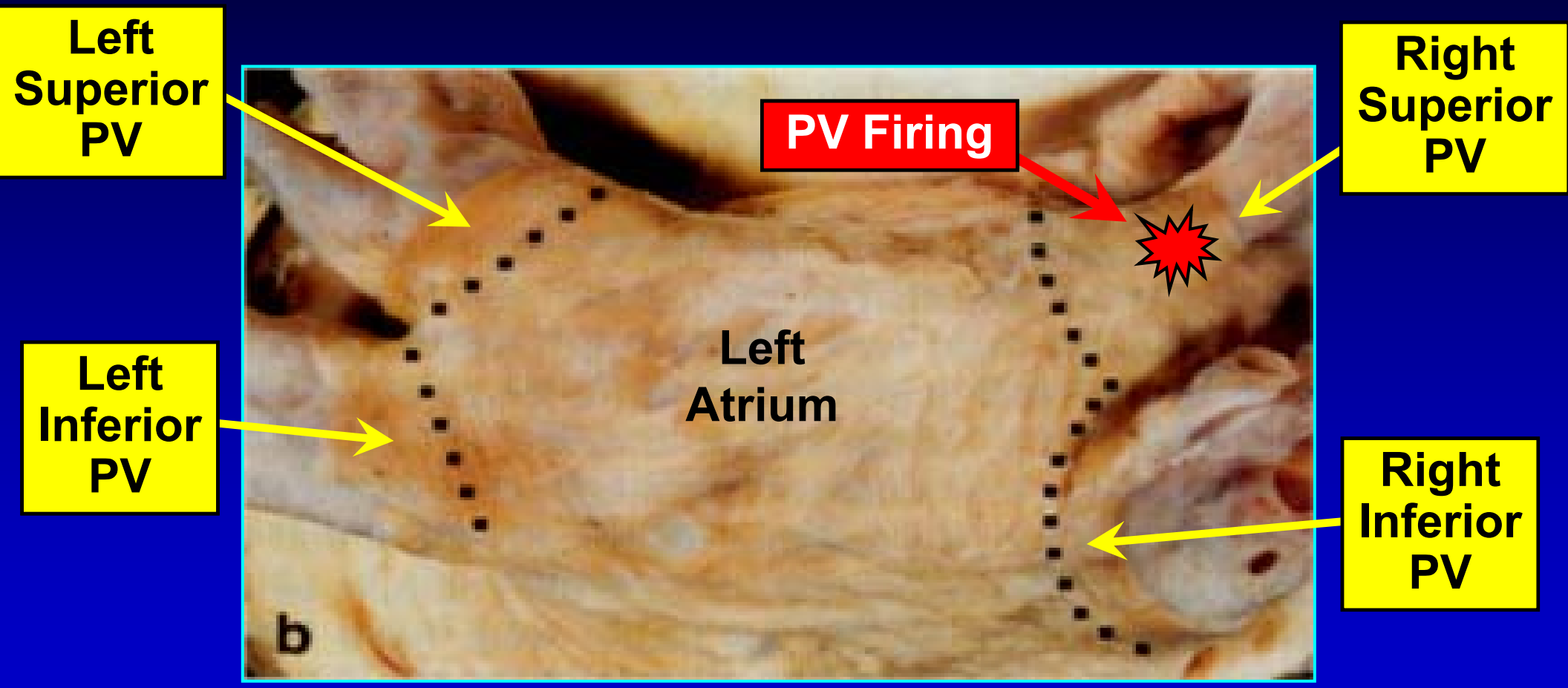
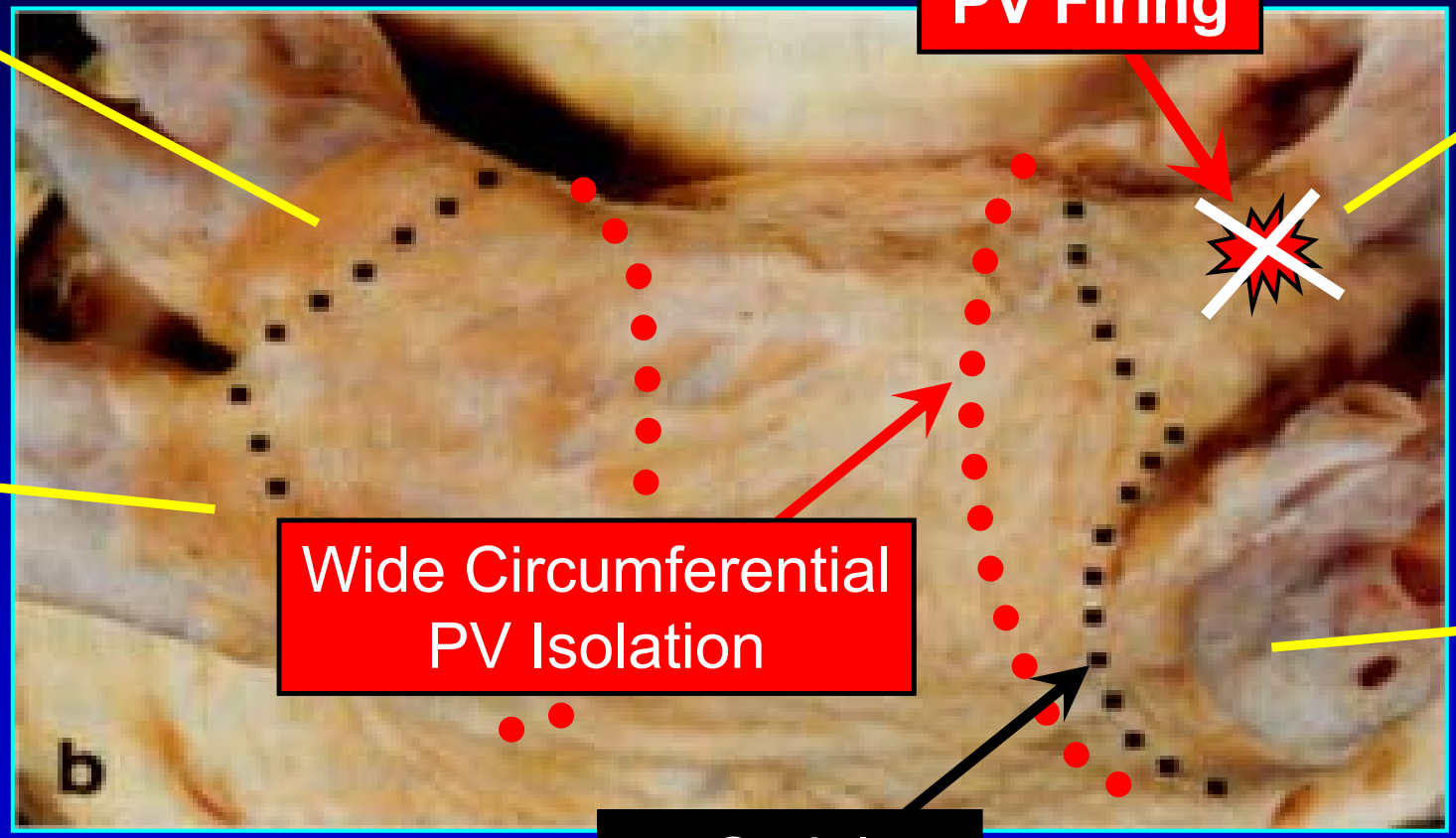


Why is Firing Usually in the Pulmonary Veins (PV)?



PA View

Why Does PV Isolation Usually Stops Firing in PVs?



Left Superior PV

PV Firing

Right Superior PV

Left Inferior PV

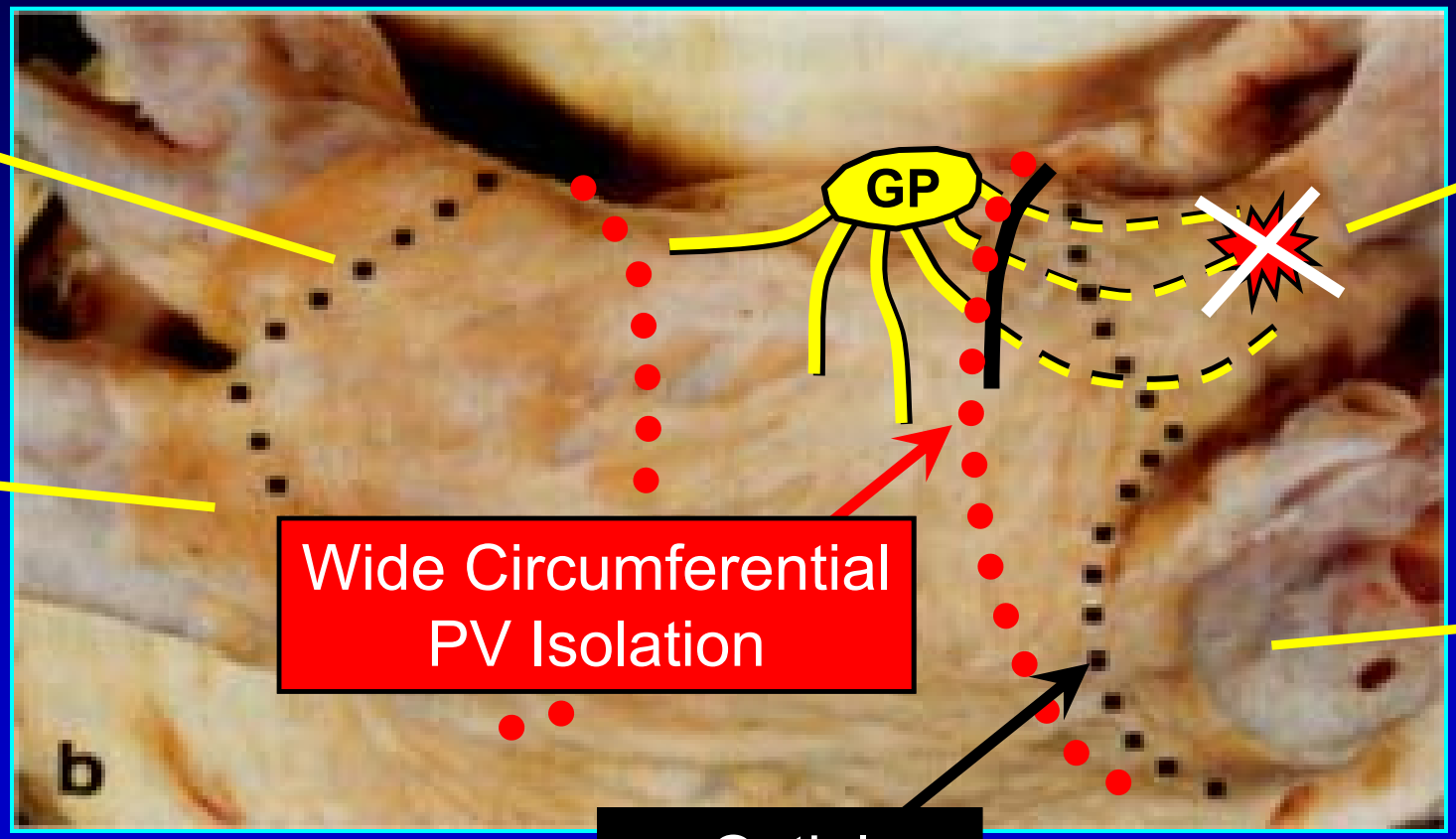
Wide Circumferential PV Isolation

Right Inferior PV

Ostial PV Isolation

Hypothesis

PV Isolation Stops Firing in PV by Blocking Autonomic Nerves from Ganglionated Plexi (GP) to PV



Left Superior PV

Right Superior PV

Left Inferior PV

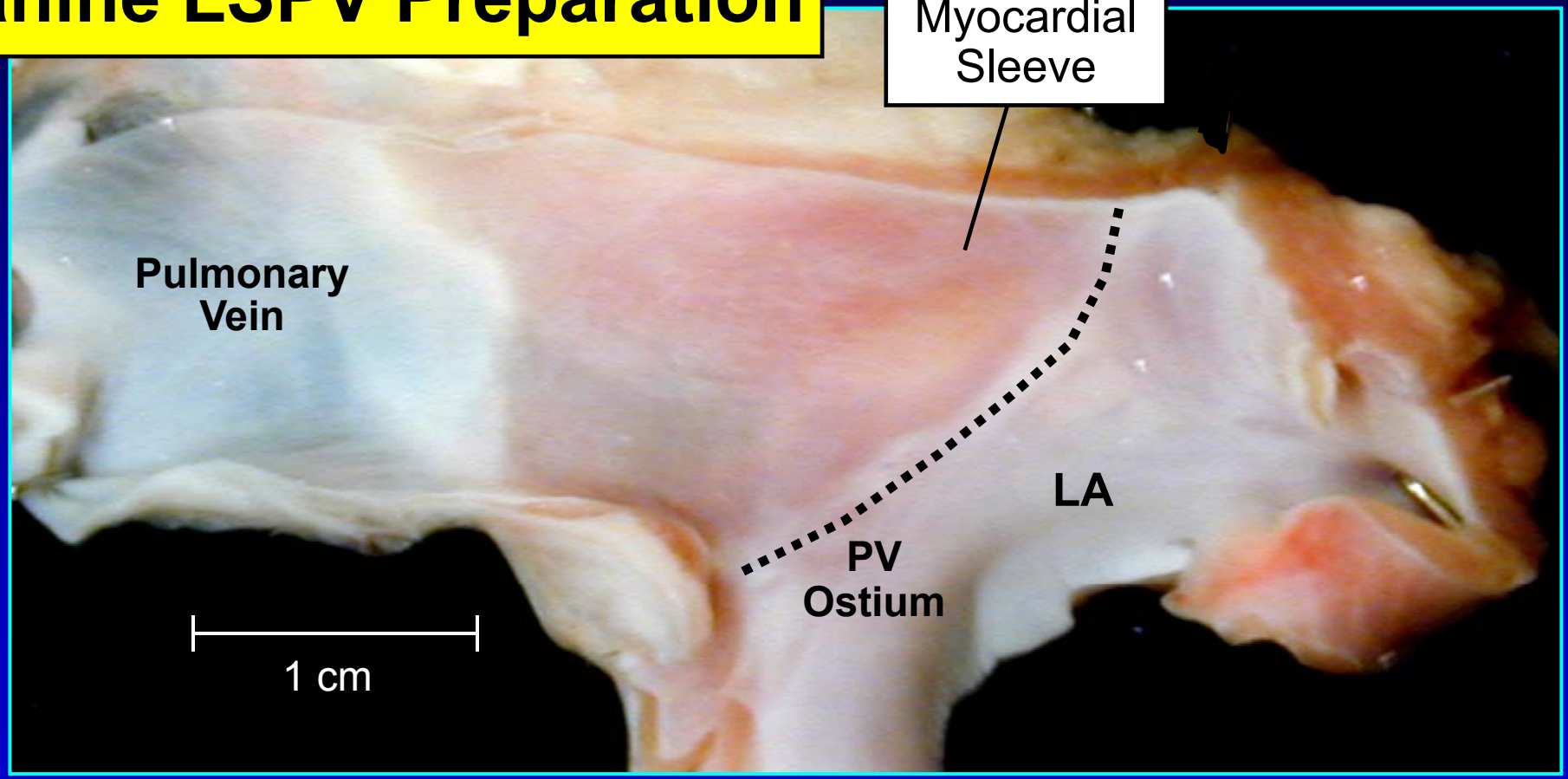
Right Inferior PV

Wide Circumferential PV Isolation

Ostial PV Isolation

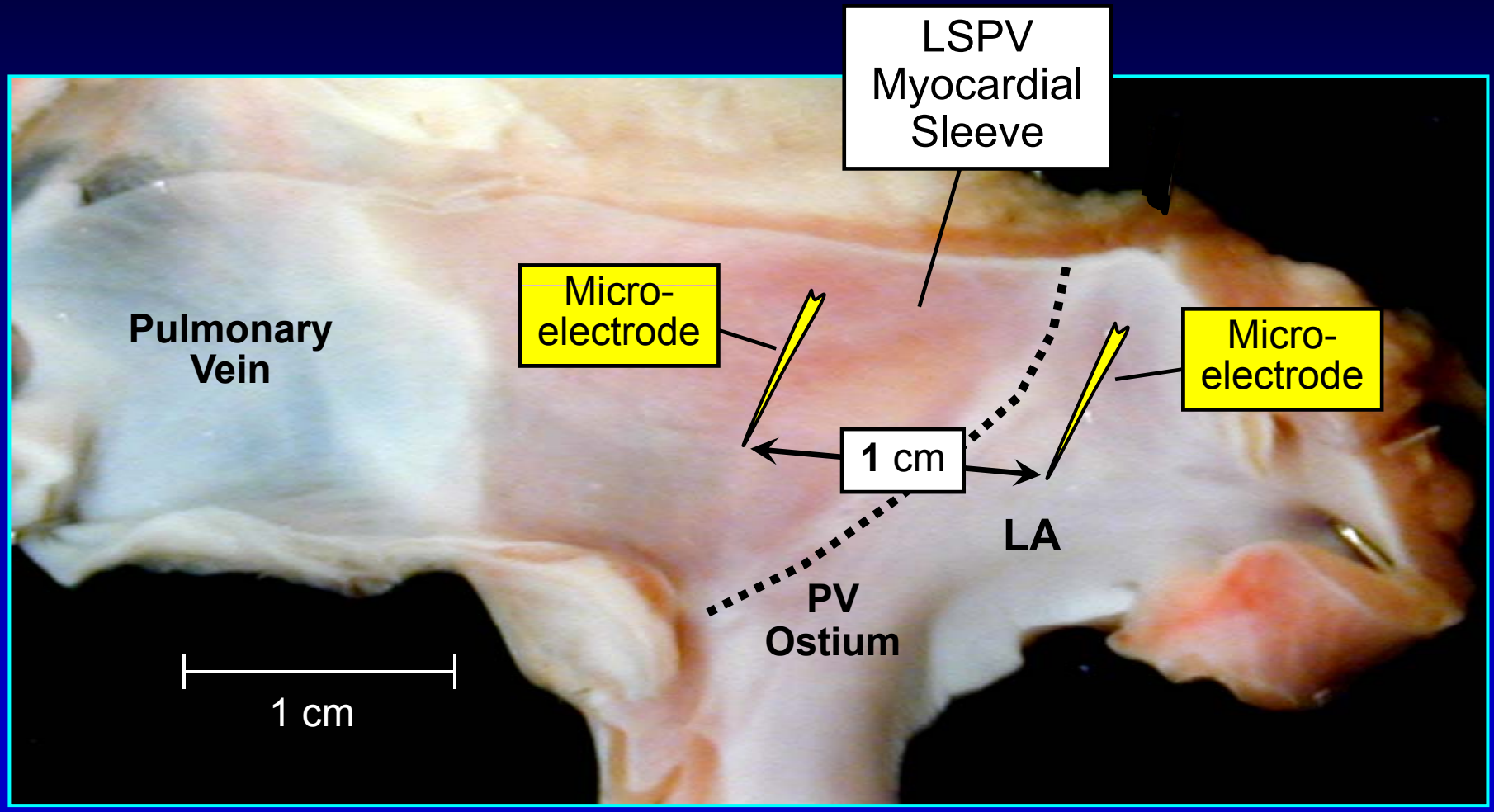
Difference in Response to GP Stimulation Between LA and PV Myocardium

Canine LSPV Preparation



Patterson et al, Heart Rhythm 2005;2:624

Difference in Response to GP Stimulation Between LA and PV Myocardium



Canine LSPV Preparation

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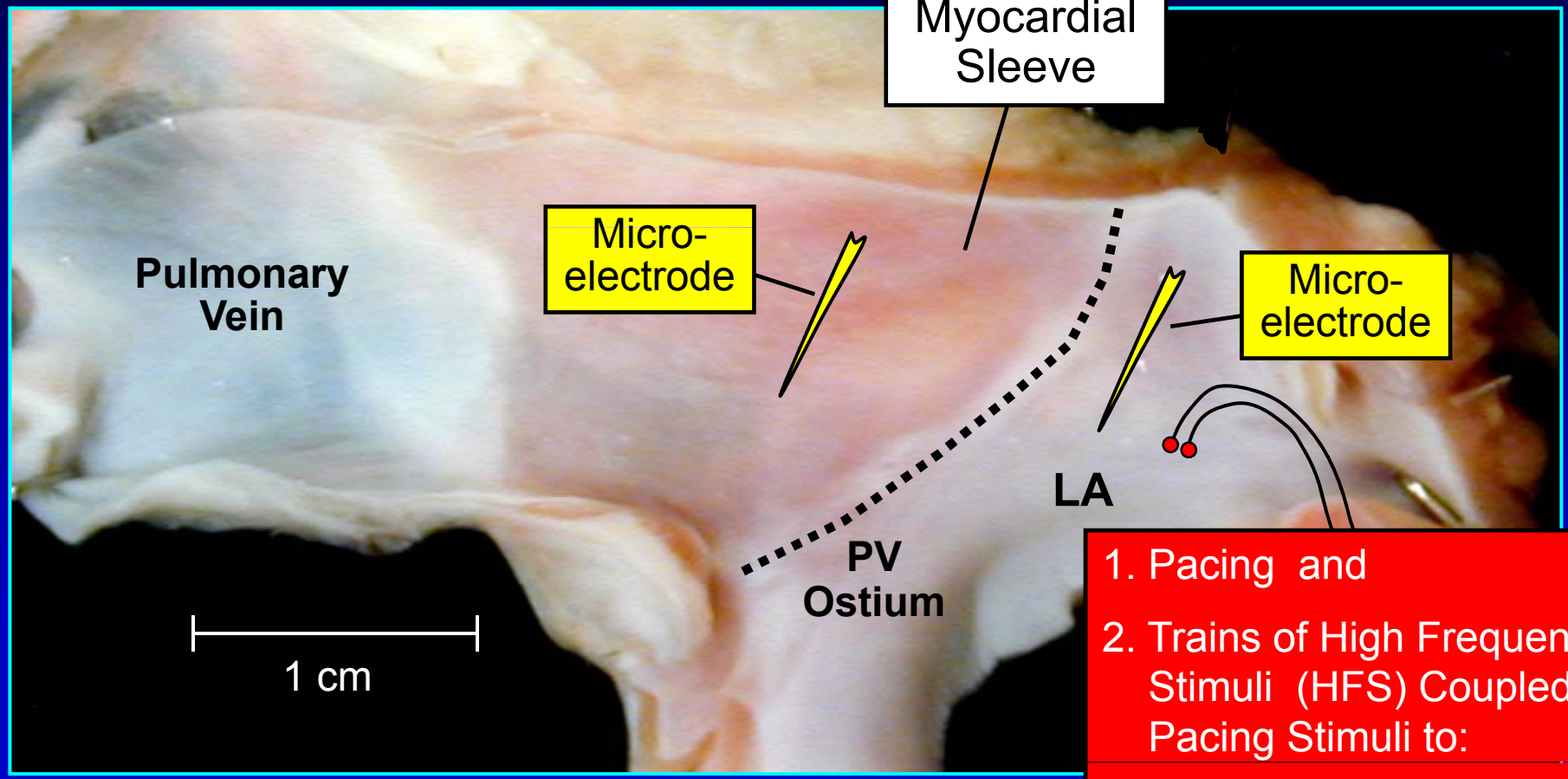
Difference in Response to GP Stimulation Between LA and PV Myocardium



1. Pacing and
2. Trains of High Frequency Stimuli (HFS) Coupled to Pacing Stimuli to:

Stimulate Neurons

Canine LSPV Preparation

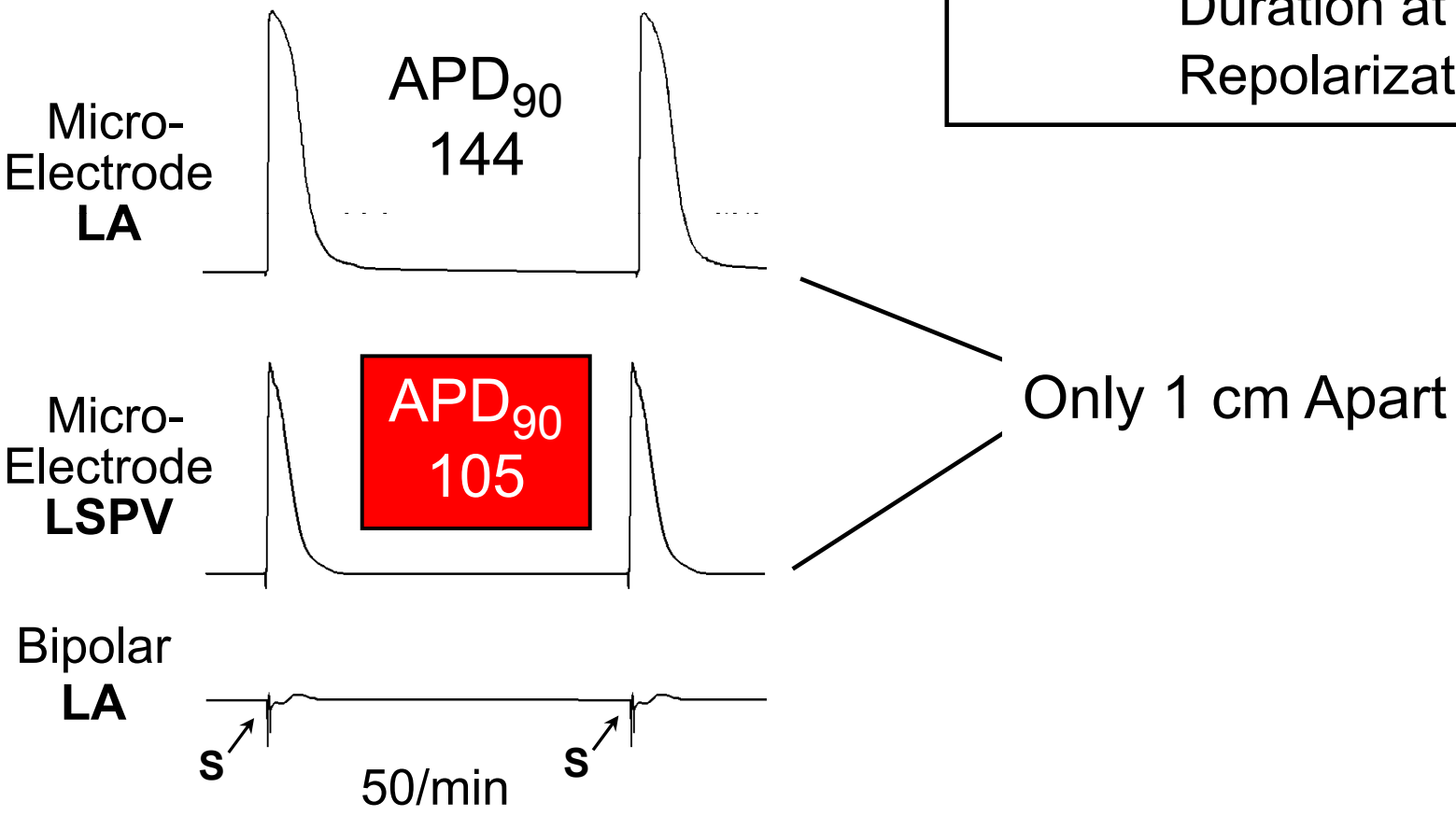
Patterson et al, Heart Rhythm 2005;2:624

Shorter Action Potential Duration in PV Myocardium

Canine LSPV Preparation

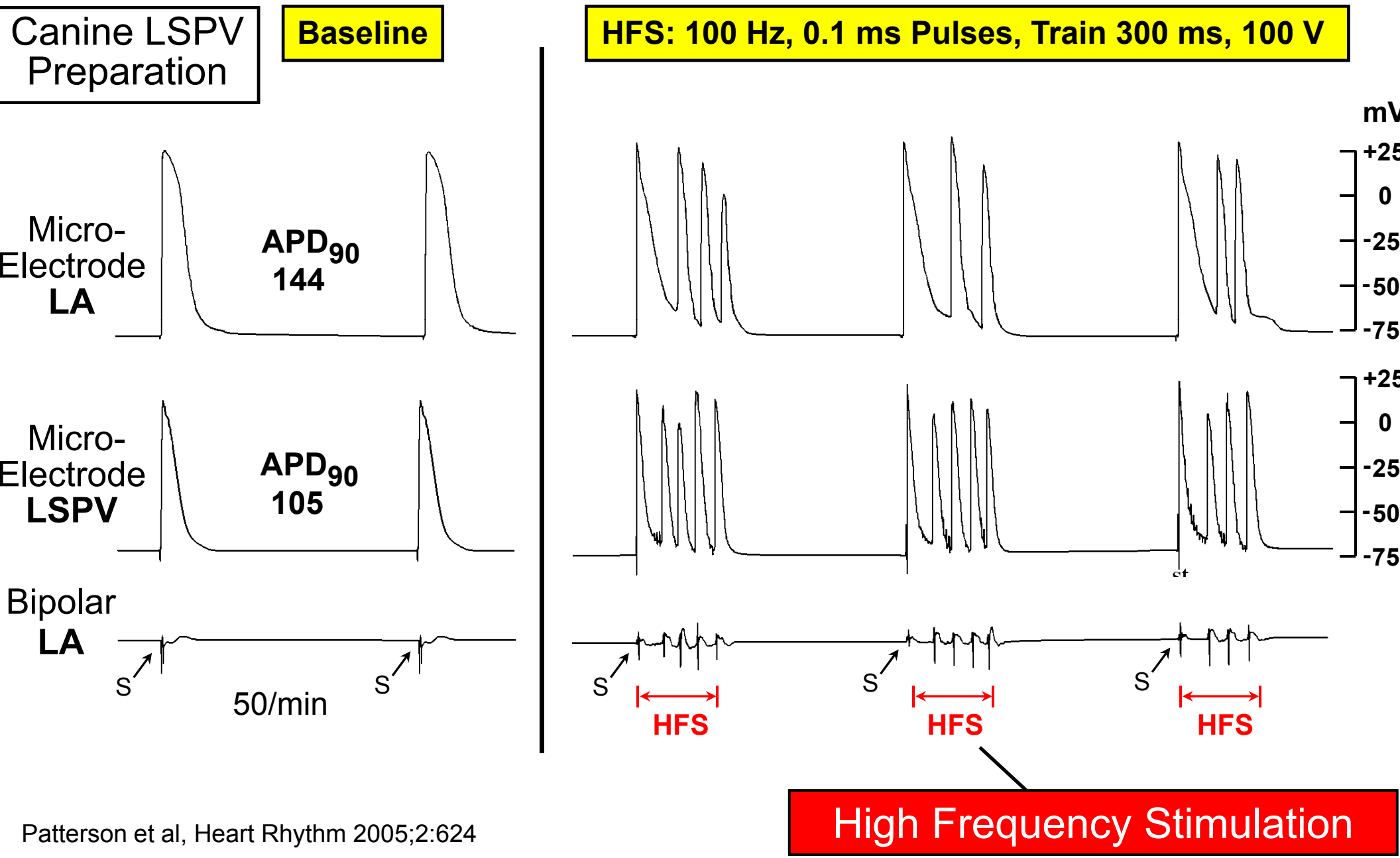
Baseline No HFS

APD_{90} - Action Potential Duration at 90% Repolarization



Patterson et al, Heart Rhythm 2005;2:624

Different Response to High Frequency Stimulation (HFS)



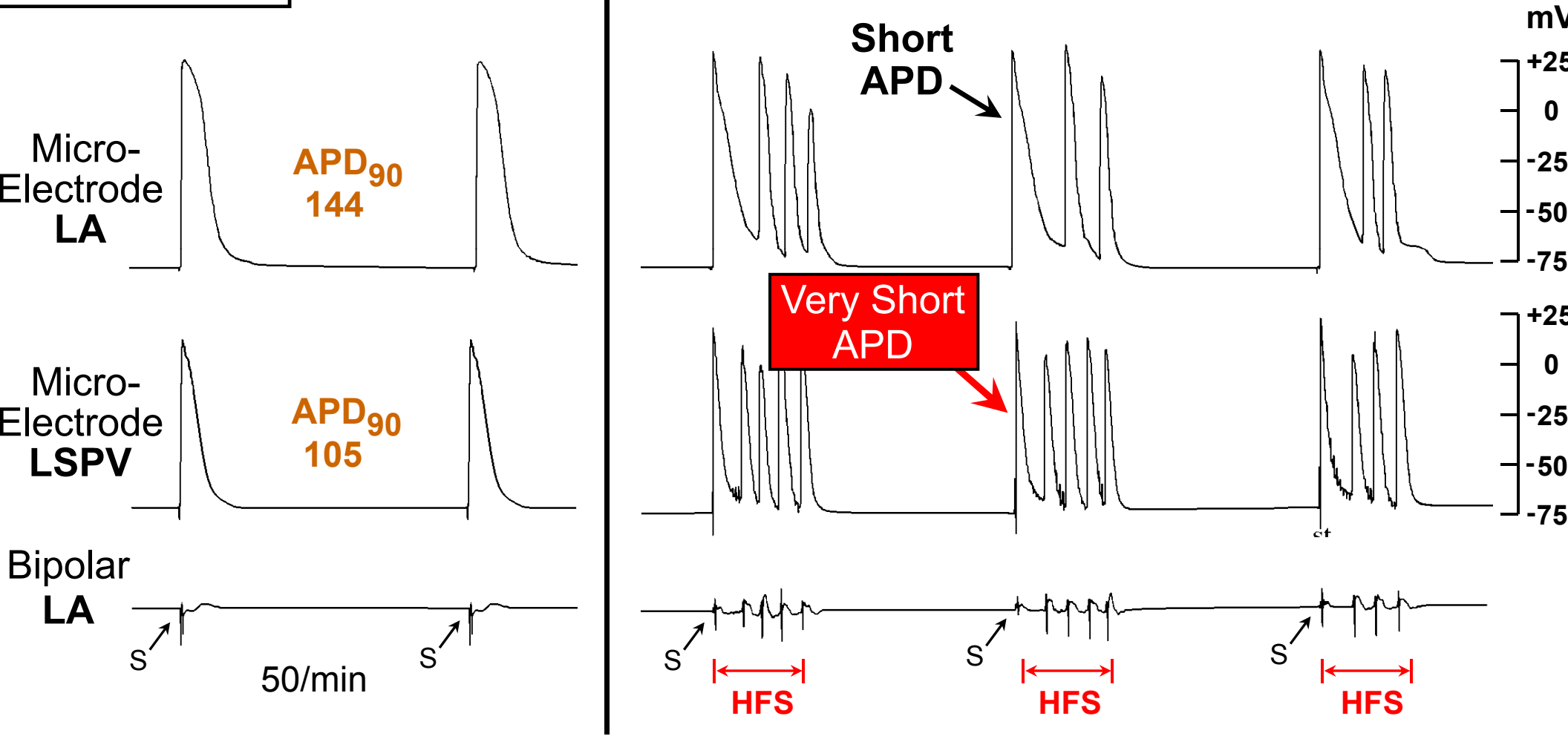
Patterson et al, Heart Rhythm 2005;2:624

Different Response to High Frequency Stimulation (HFS)

Canine LSPV Preparation

Baseline

HFS: 100 Hz, 0.1 ms Pulses, Train 300 ms, 100 V



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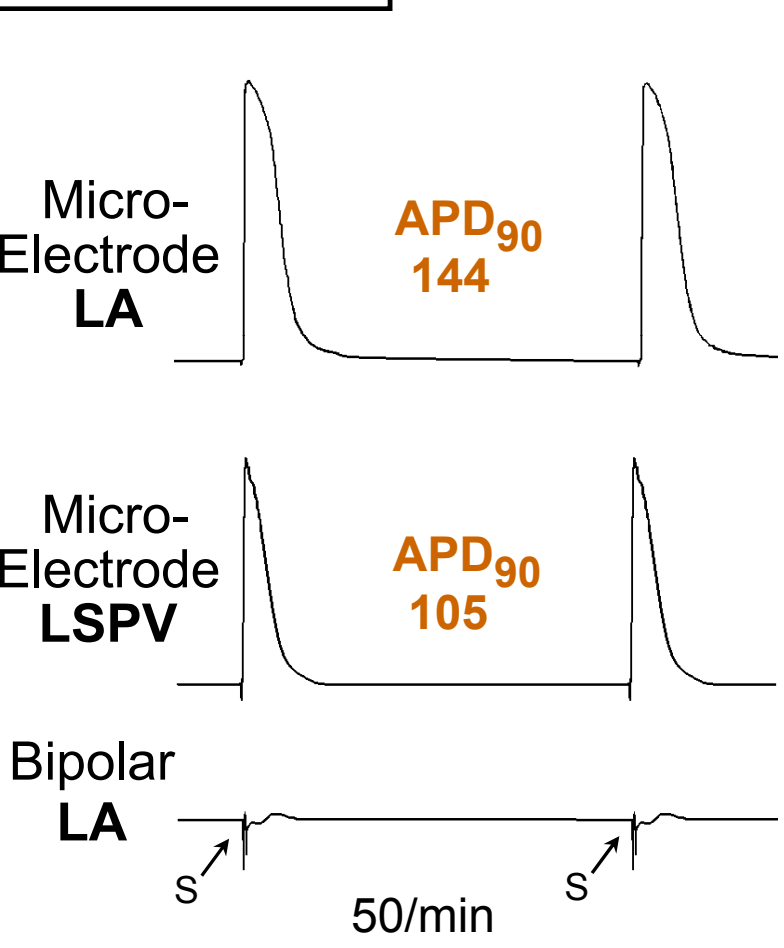
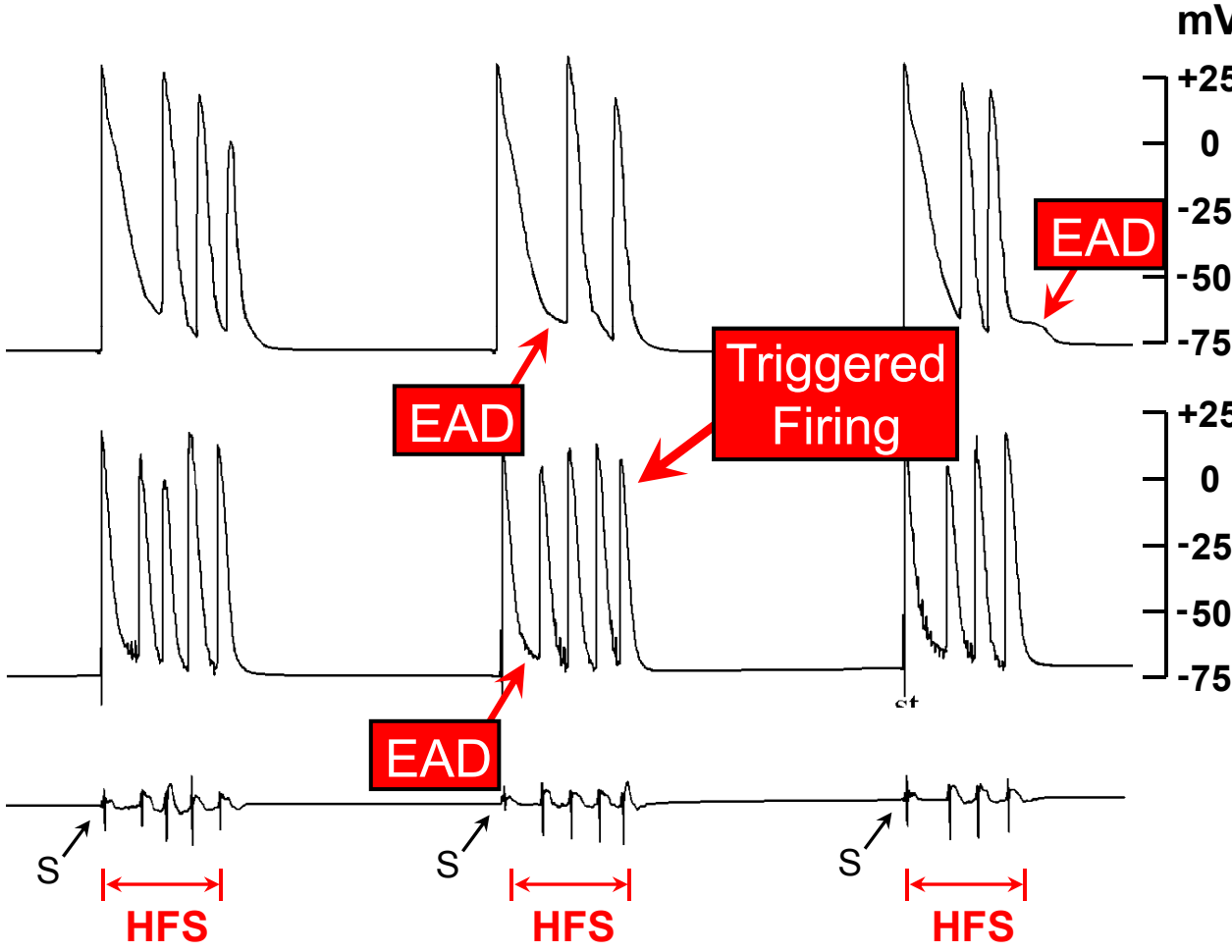




Early Afterdepolarizations (EADs) and Triggered Firing

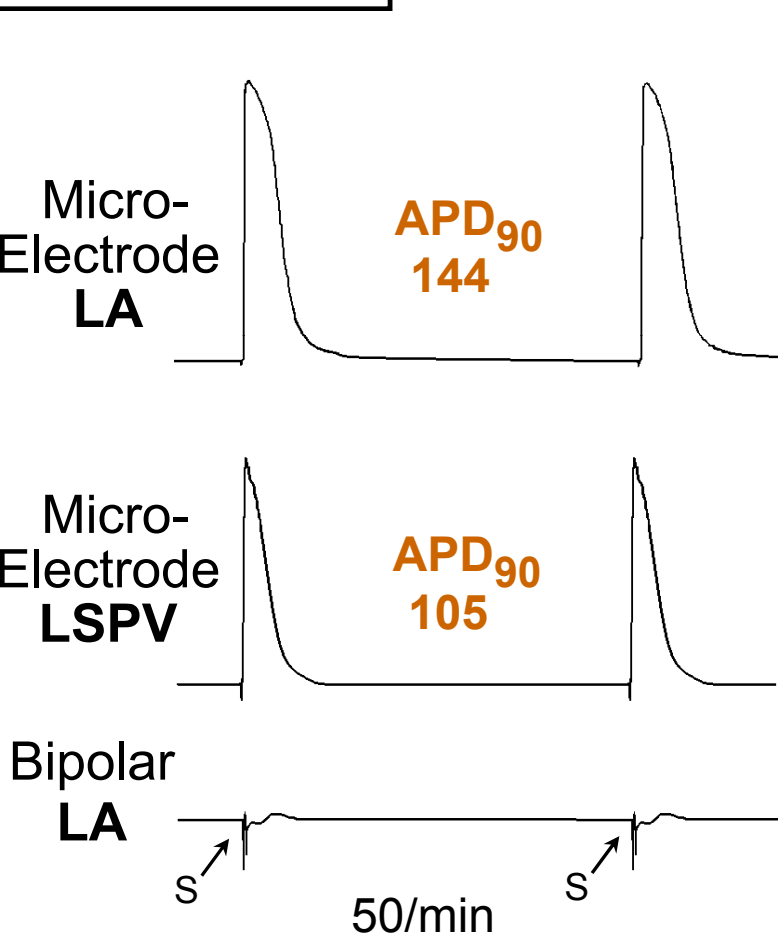
Patterson et al, Heart Rhythm 2005;2:624

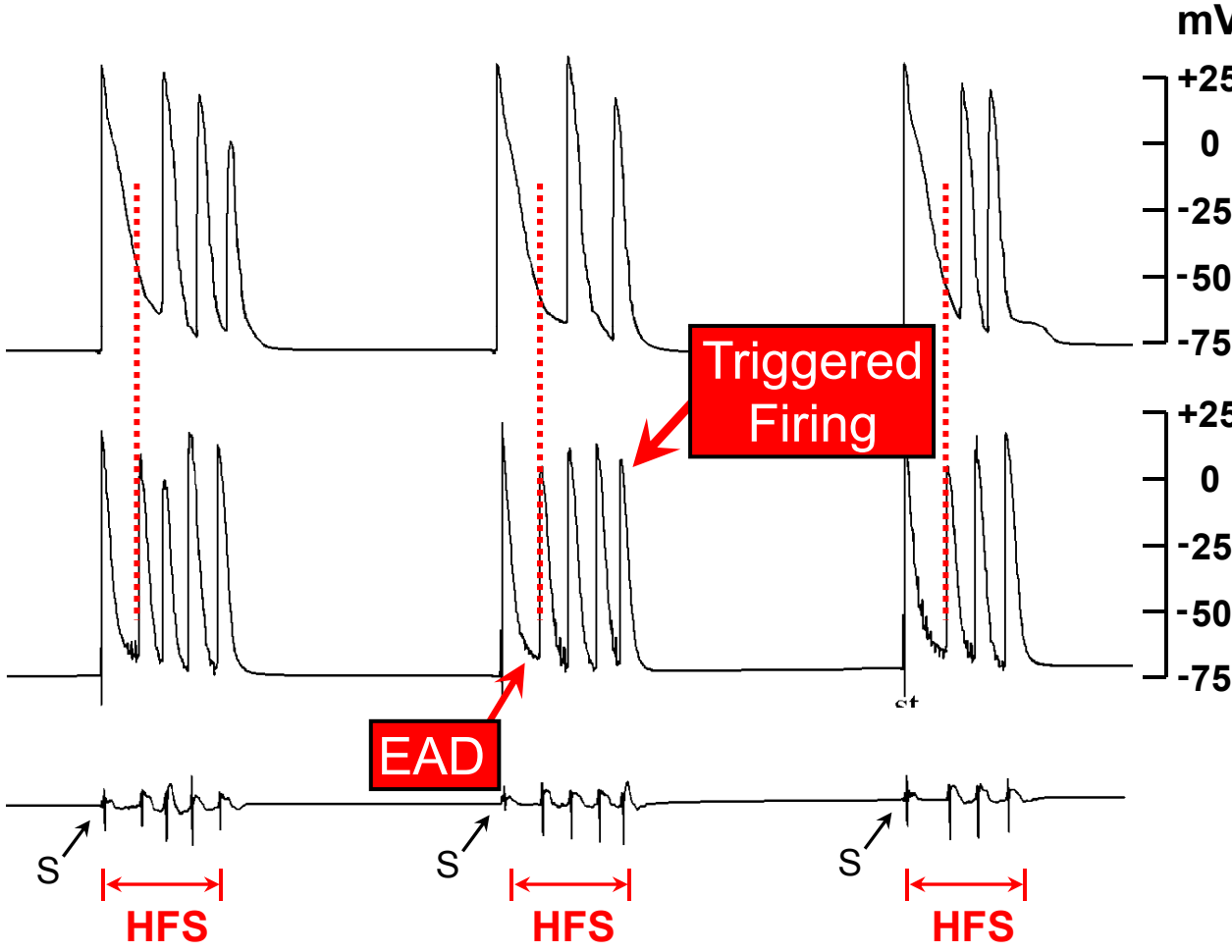
Different Response to High Frequency Stimulation (HFS)

Canine LSPV Preparation

Baseline

HFS: 100 Hz, 0.1 ms Pulses, Train 300 ms, 100 V

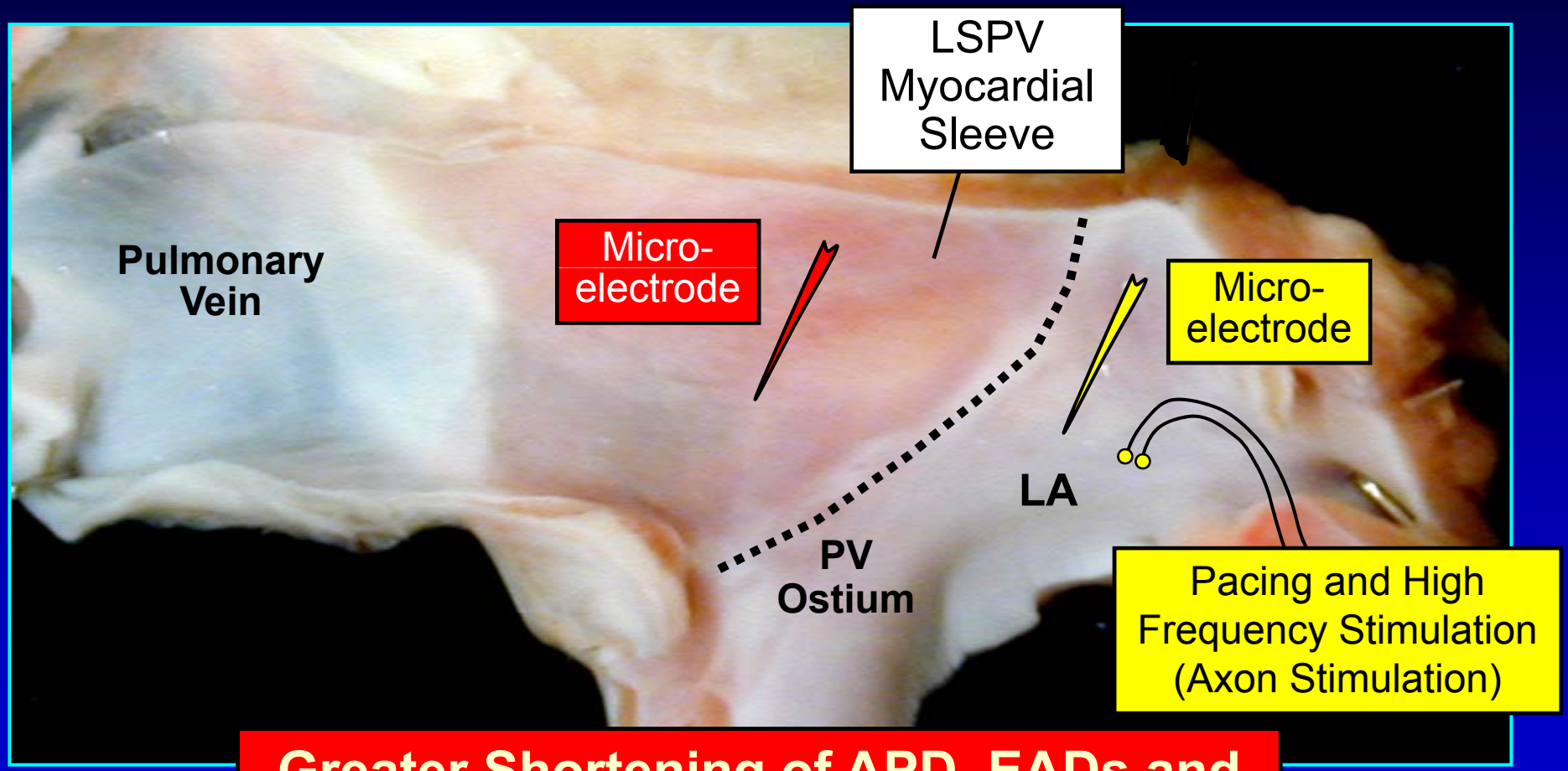




EADs and Triggered Firing in LSPV (Not in LA)

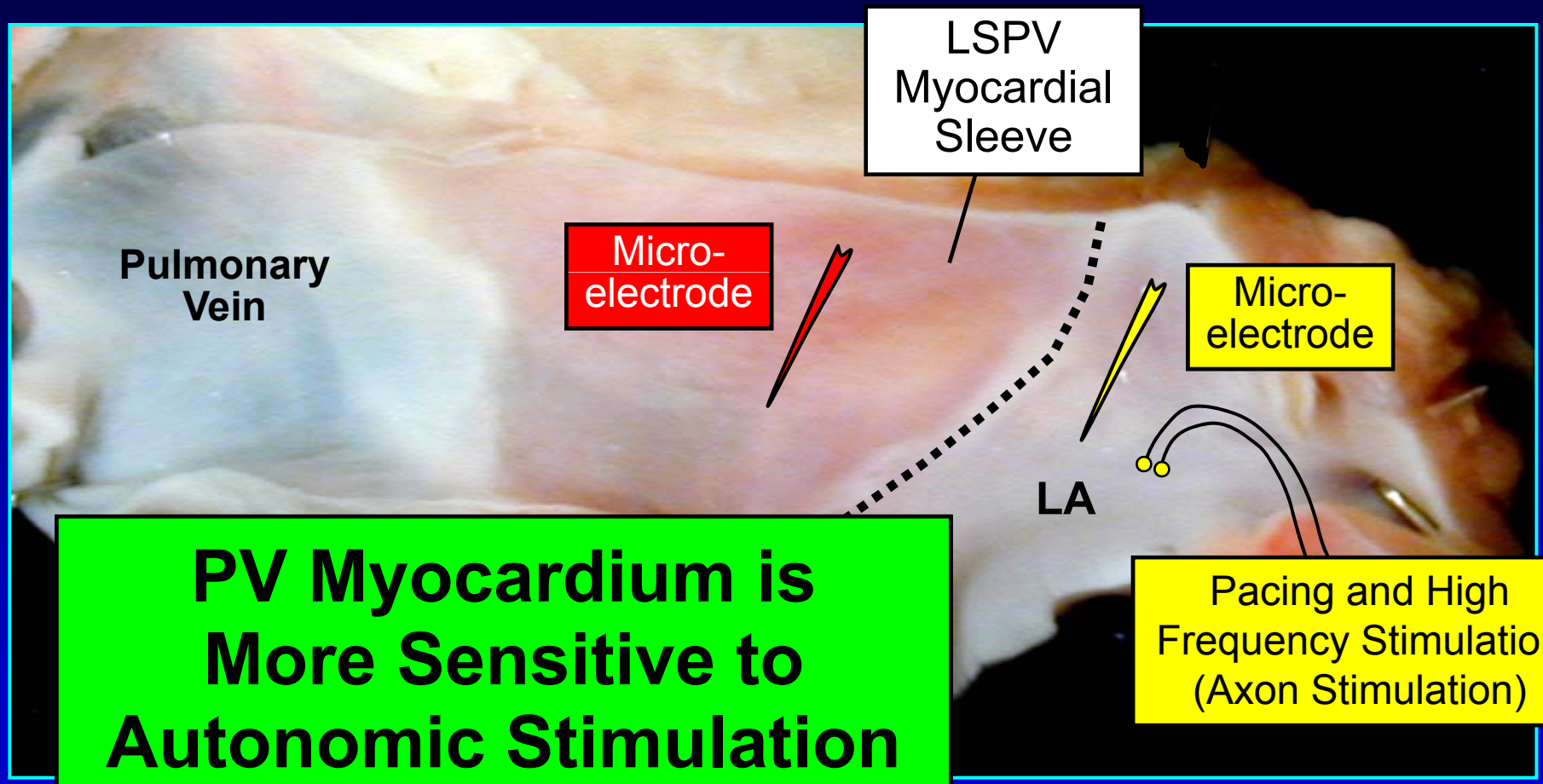
Patterson et al, Heart Rhythm 2005;2:624

Difference in Response to GP Stimulation Between LA and PV Myocardium

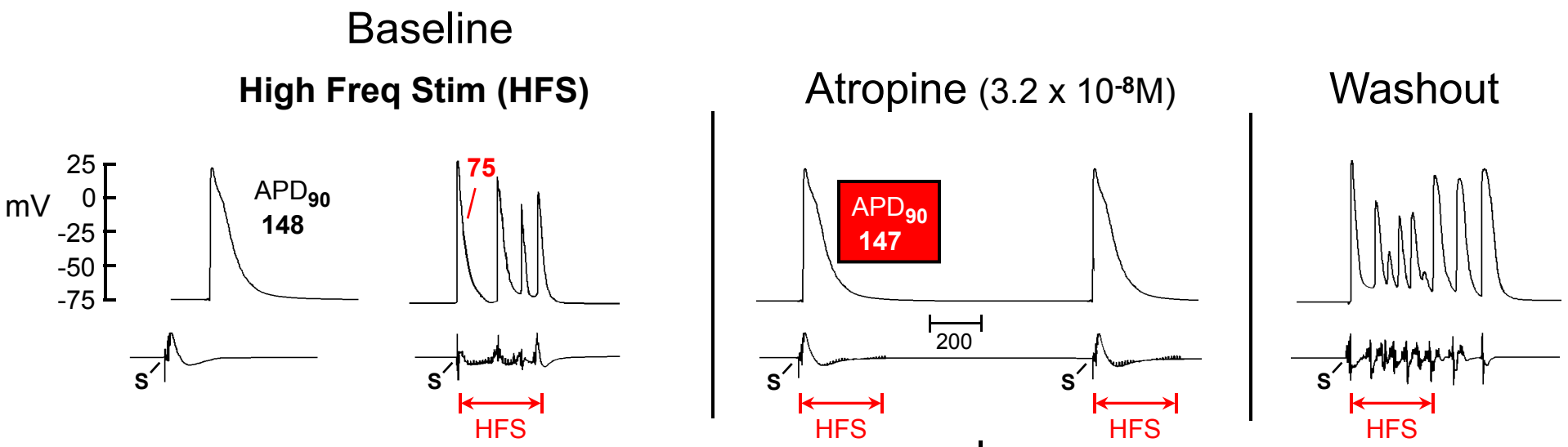


Greater Shortening of APD, EADs and Triggered Firing in LSPV - Not in LA Closer to Stimulation Site

Difference in Response to GP Stimulation Between LA and PV Myocardium

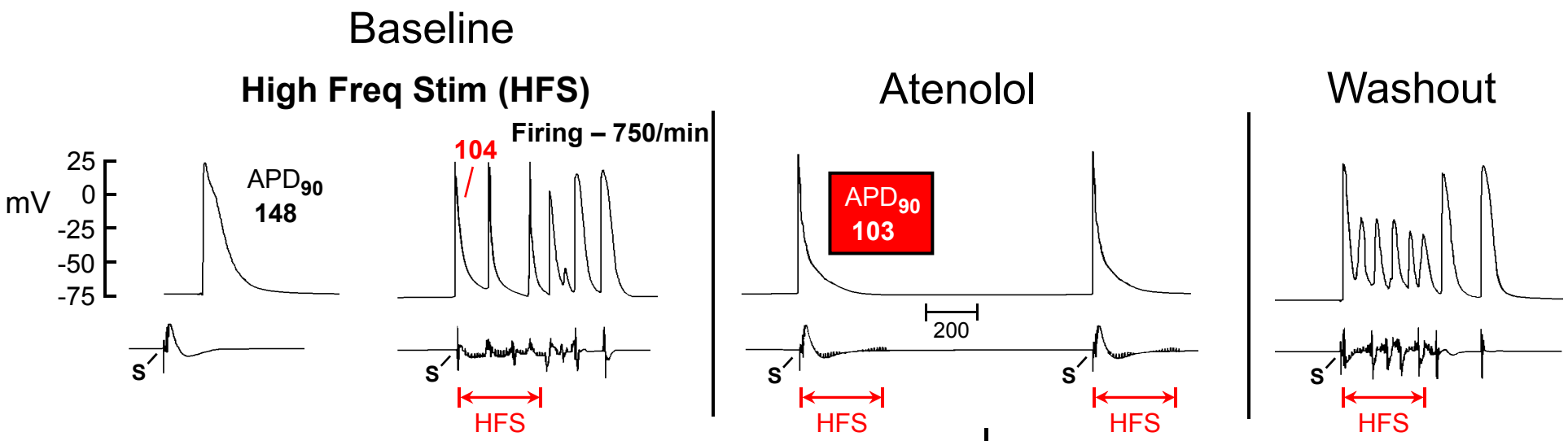


PV Myocardium is More Sensitive to Autonomic Stimulation than LA Myocardium



Atropine

- Prevents Shortening of APD
- Prevents Triggered Firing

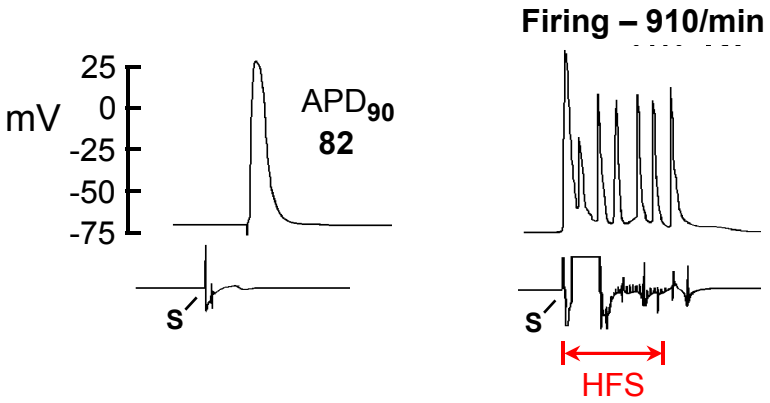


Atenolol

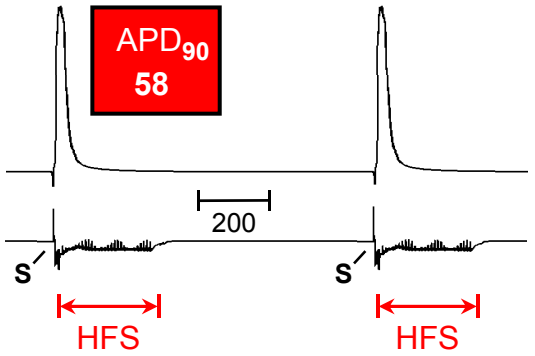
- Allows APD Shortening
- Prevents Triggered Firing

Baseline

High Freq Stim (HFS)

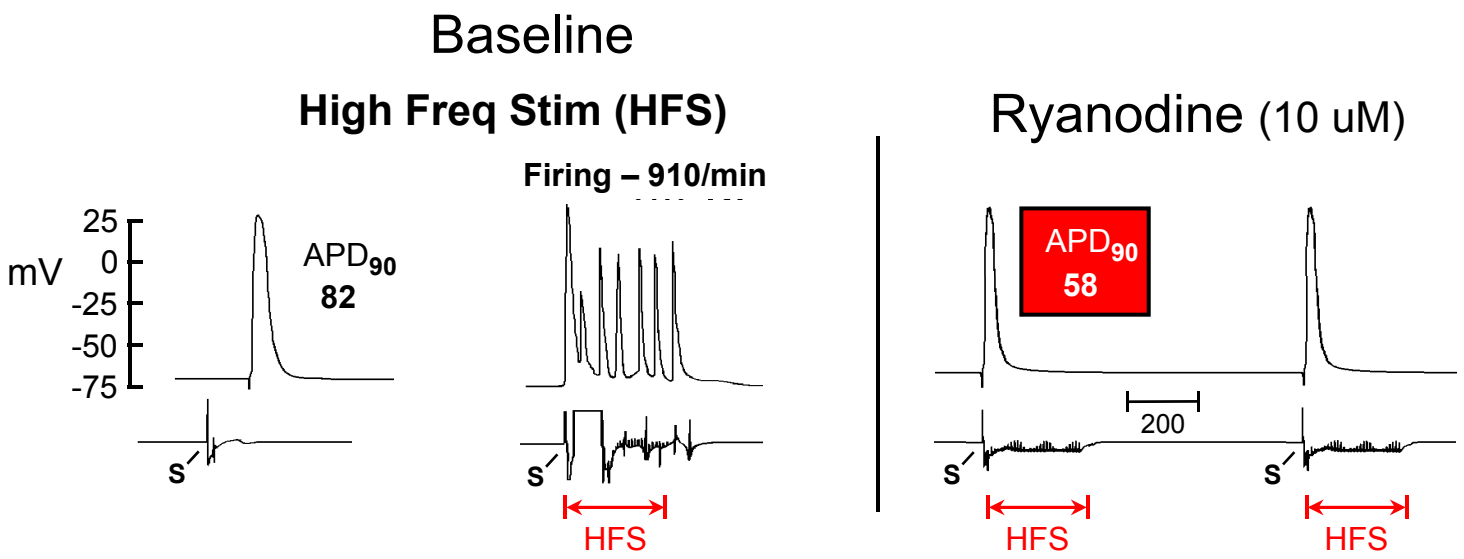


Ryanodine (10 uM)



Ryanodine

- Allows Some APD Shortening
- Prevents EADs and Triggered Firing



EADs and Triggered Firing are Dependent on Calcium Release from Sarcoplasmic Reticulum (SR)

Ryanodine

- Allows Some APD Shortening
- Prevents EADs and Triggered Firing

Hypothesis for Pulmonary Vein Firing (and AF) Induced by Autonomic Stimulation

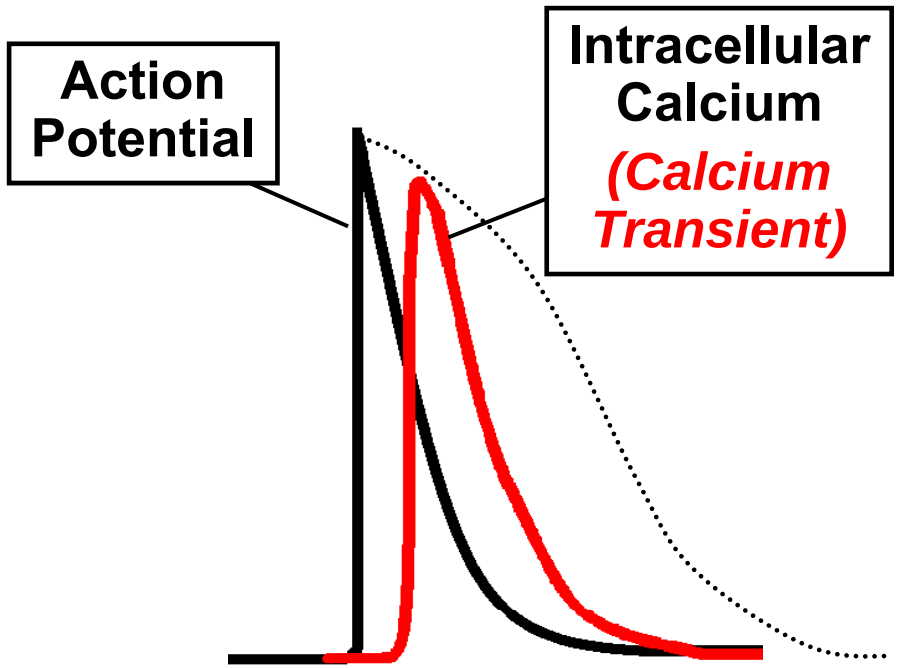
"Calcium-Transient Triggering"

University of Oklahoma

Patterson et al, Heart Rhythm 2005; 2:624

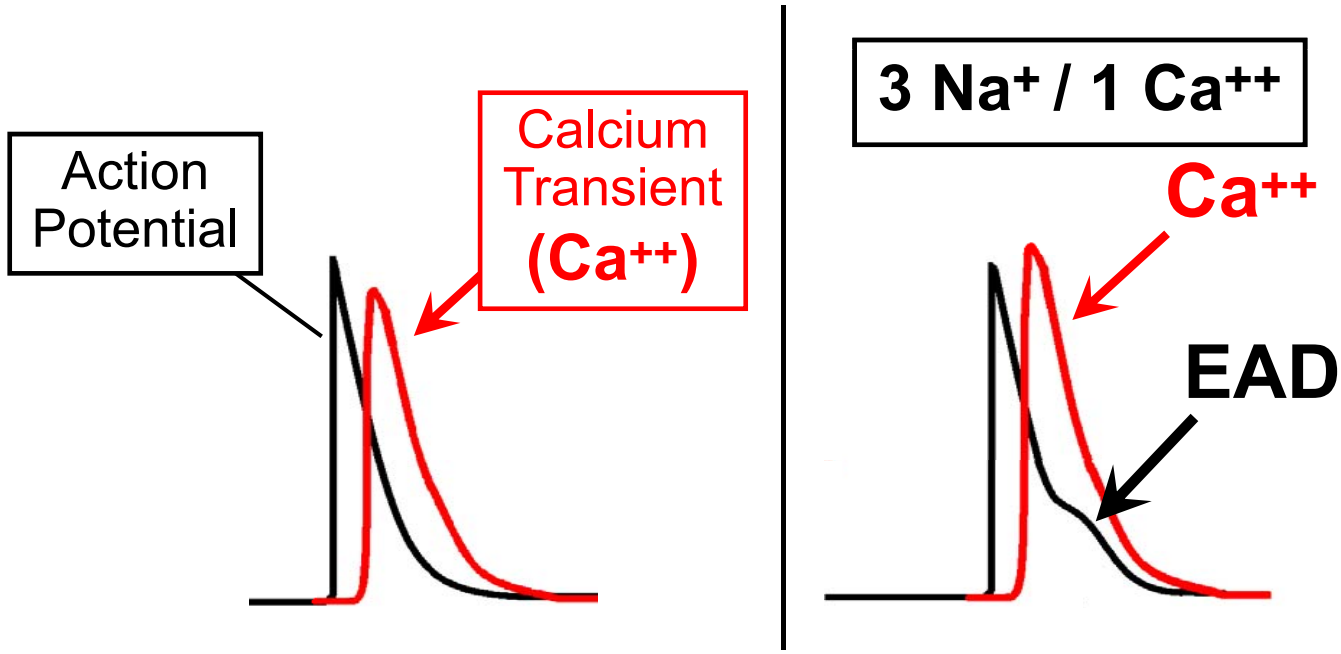
Based on 2 Properties of <u>Pulmonary Vein Myocardial Cells</u>

- **Short action potential duration**
- **Intracellular calcium concentration (calcium transient) remains high after repolarization**



"Calcium-Transient Triggering" Hypothesis

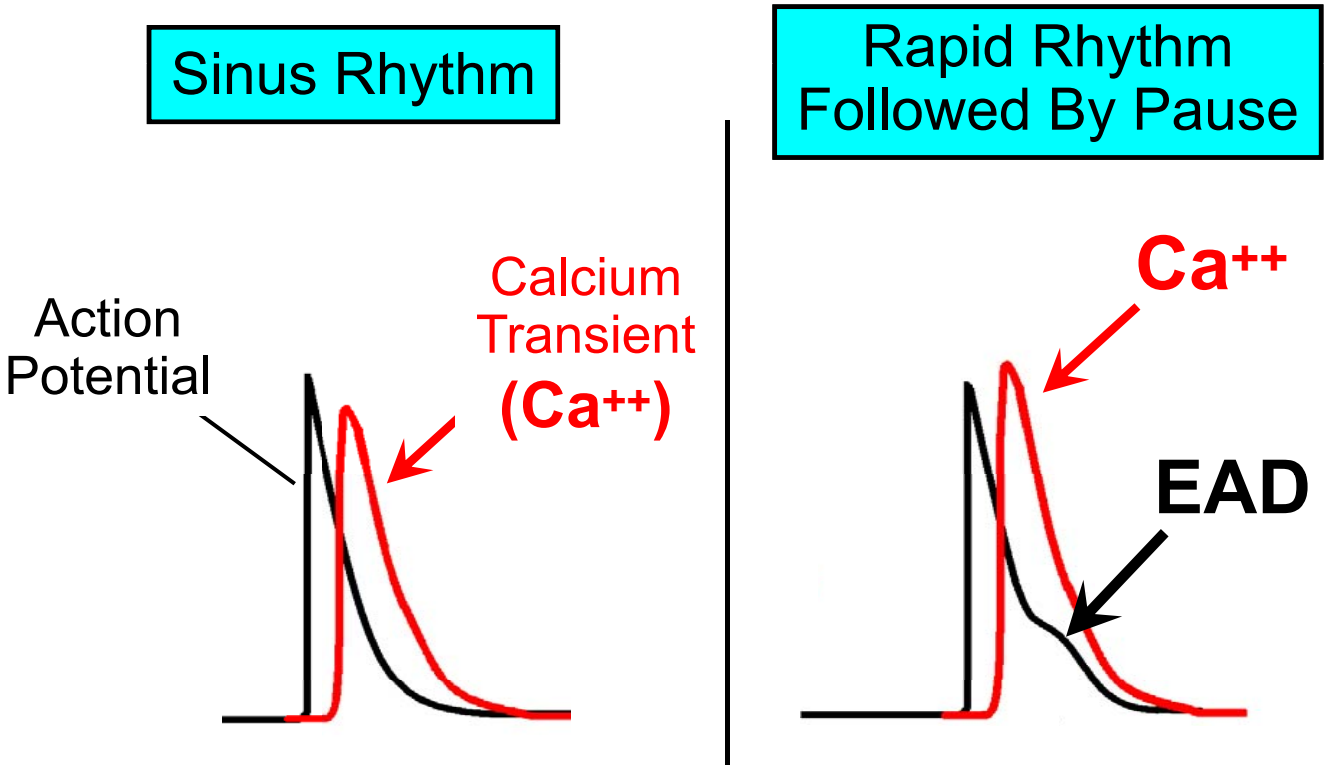
Mechanism of Early Afterdepolarizations (EADs) in PVs



High Ca^{++} → **Na^+/ Ca^{++} Exchanger** (1 Ca^{++} (Out) → 3 Na^+ (In)) → **Net Inward Current (+)** → **EAD**

"Calcium-Transient Triggering" Hypothesis

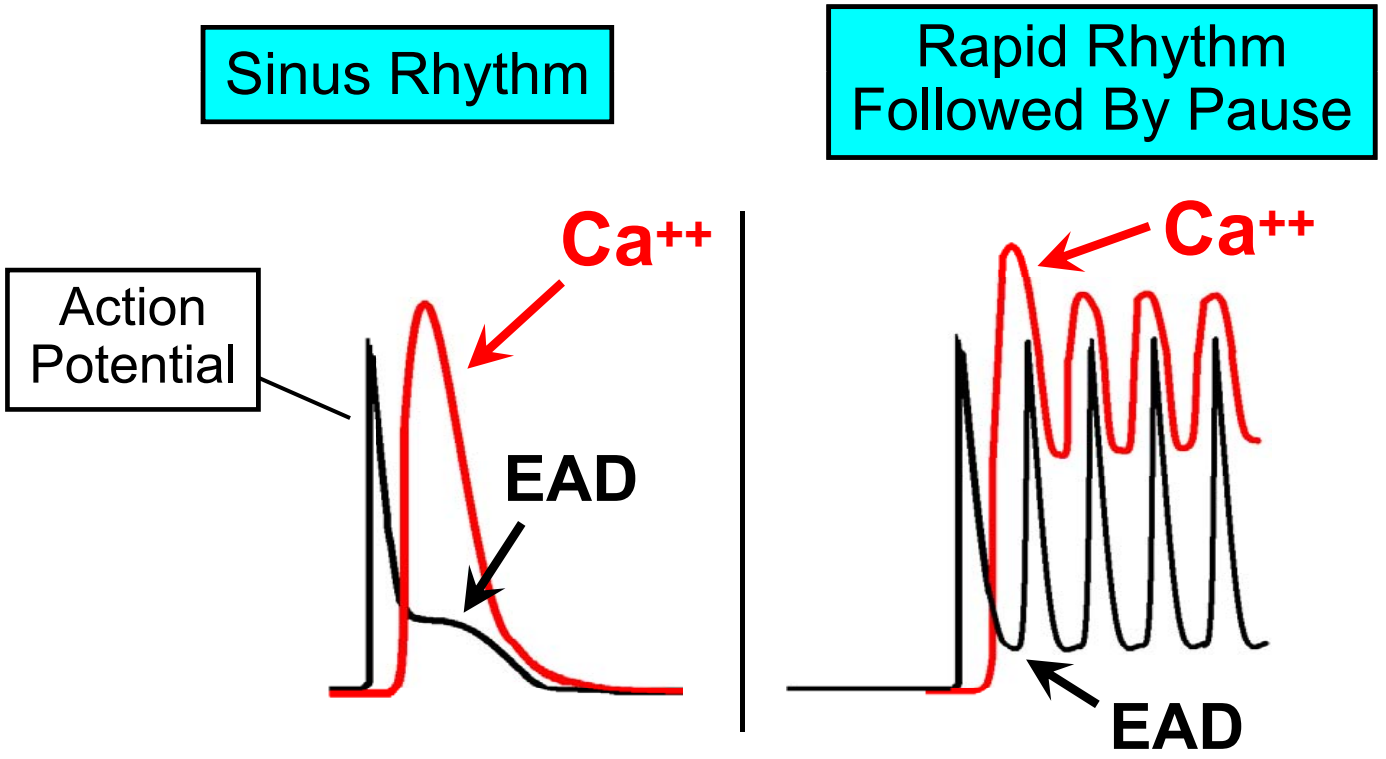
EAD Increased by Pause After Rapid Rate



Rapid Rhythm → Calcium Loading → Pause → **Large Calcium Release From SR**

"Calcium-Transient Triggering" Hypothesis

Increased Autonomic (GP) Activity or Sensitivity



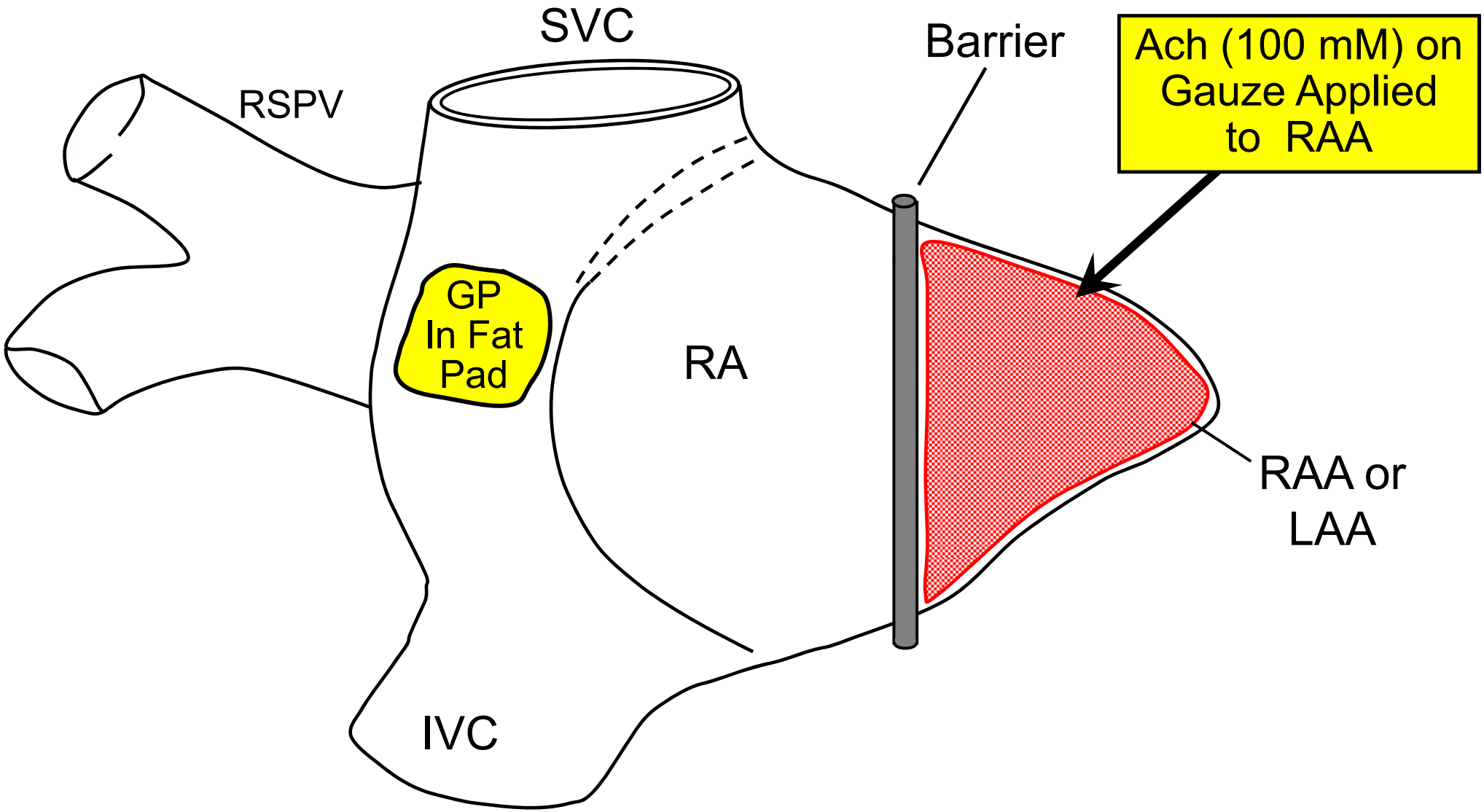
Increased GP Activity

↑ Acetylcholine
Shortens Action Potential

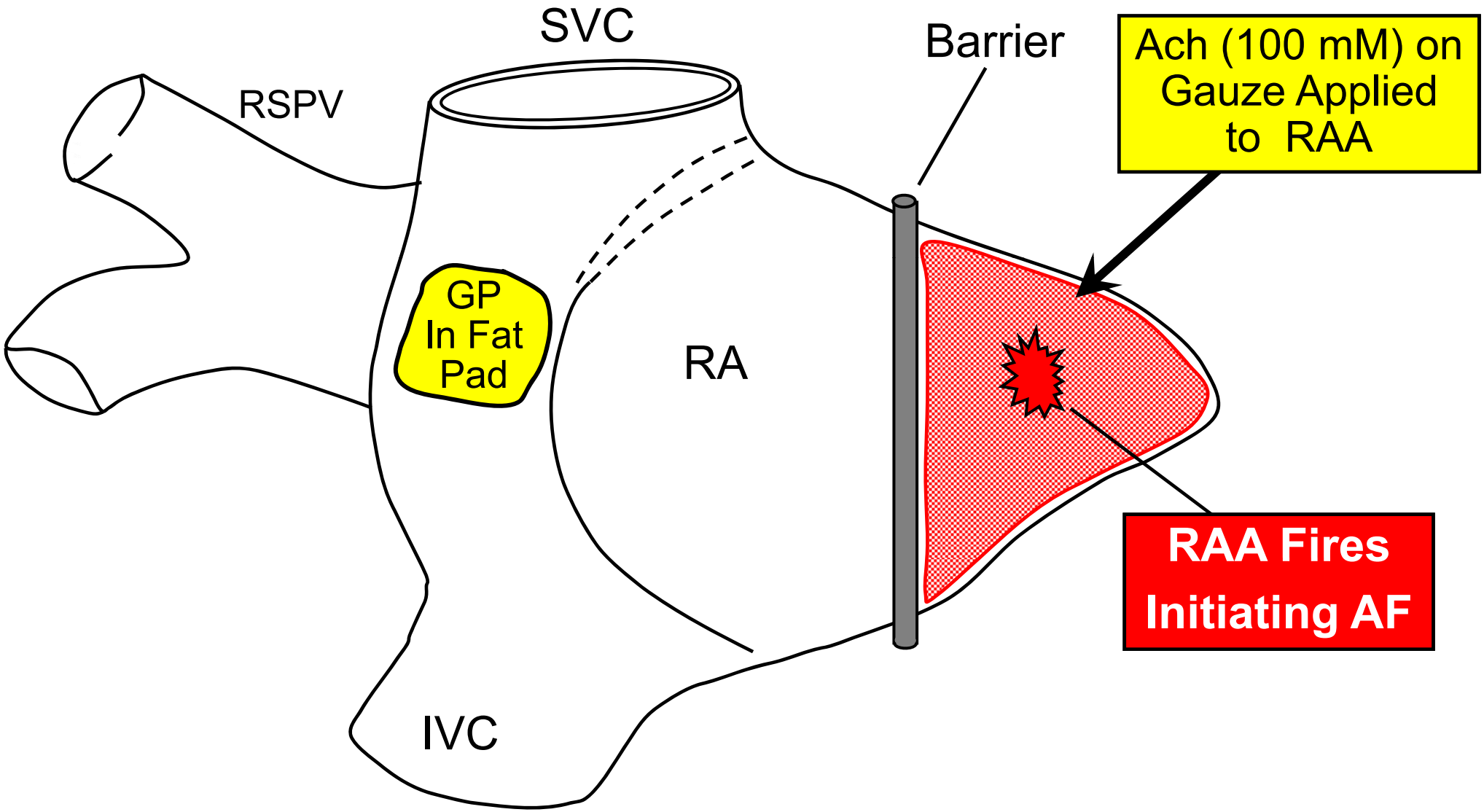
↑ Norepinephrine
Increases Calcium Loading

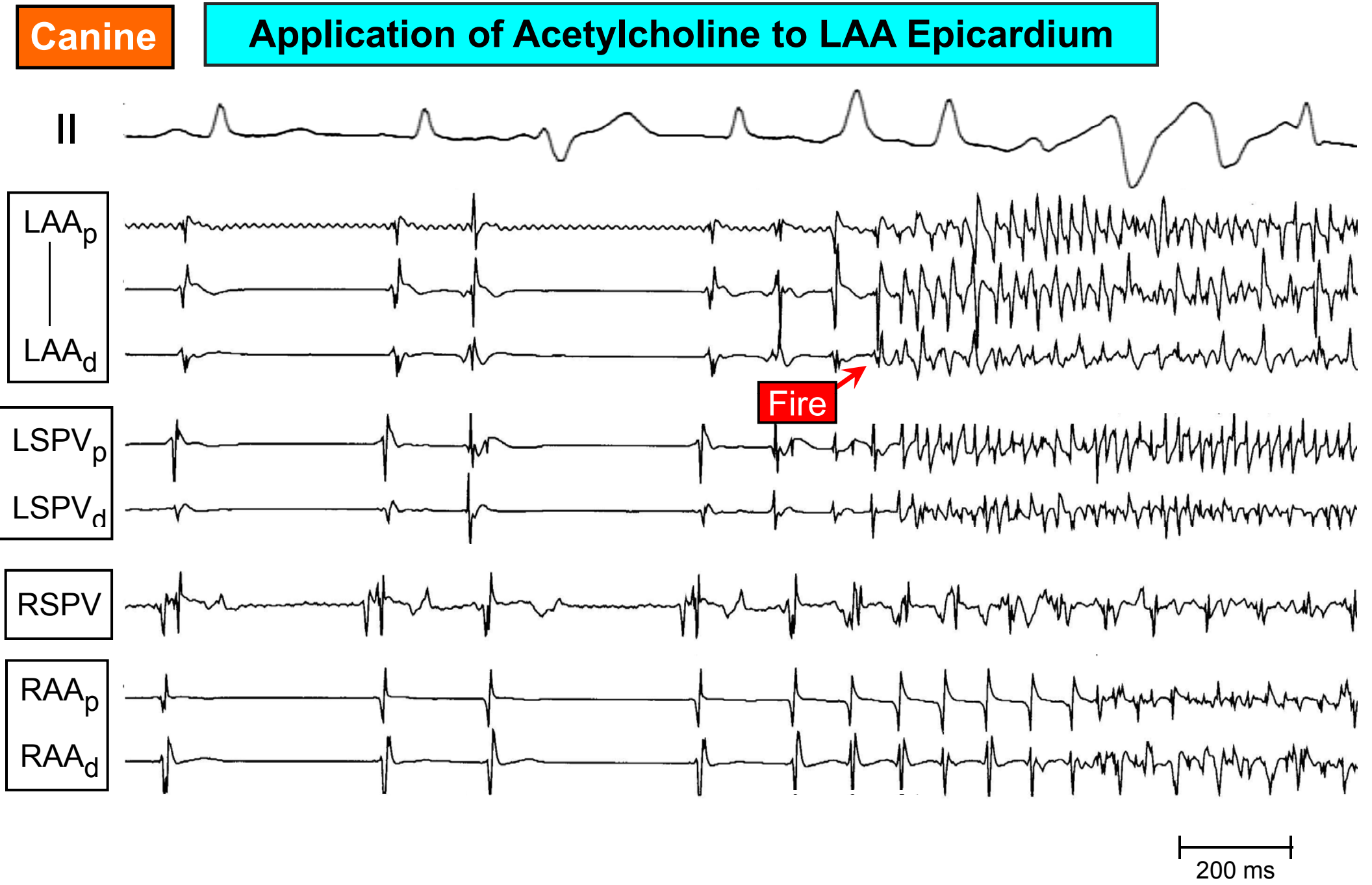
↑ **EADs** → **Triggered Firing**

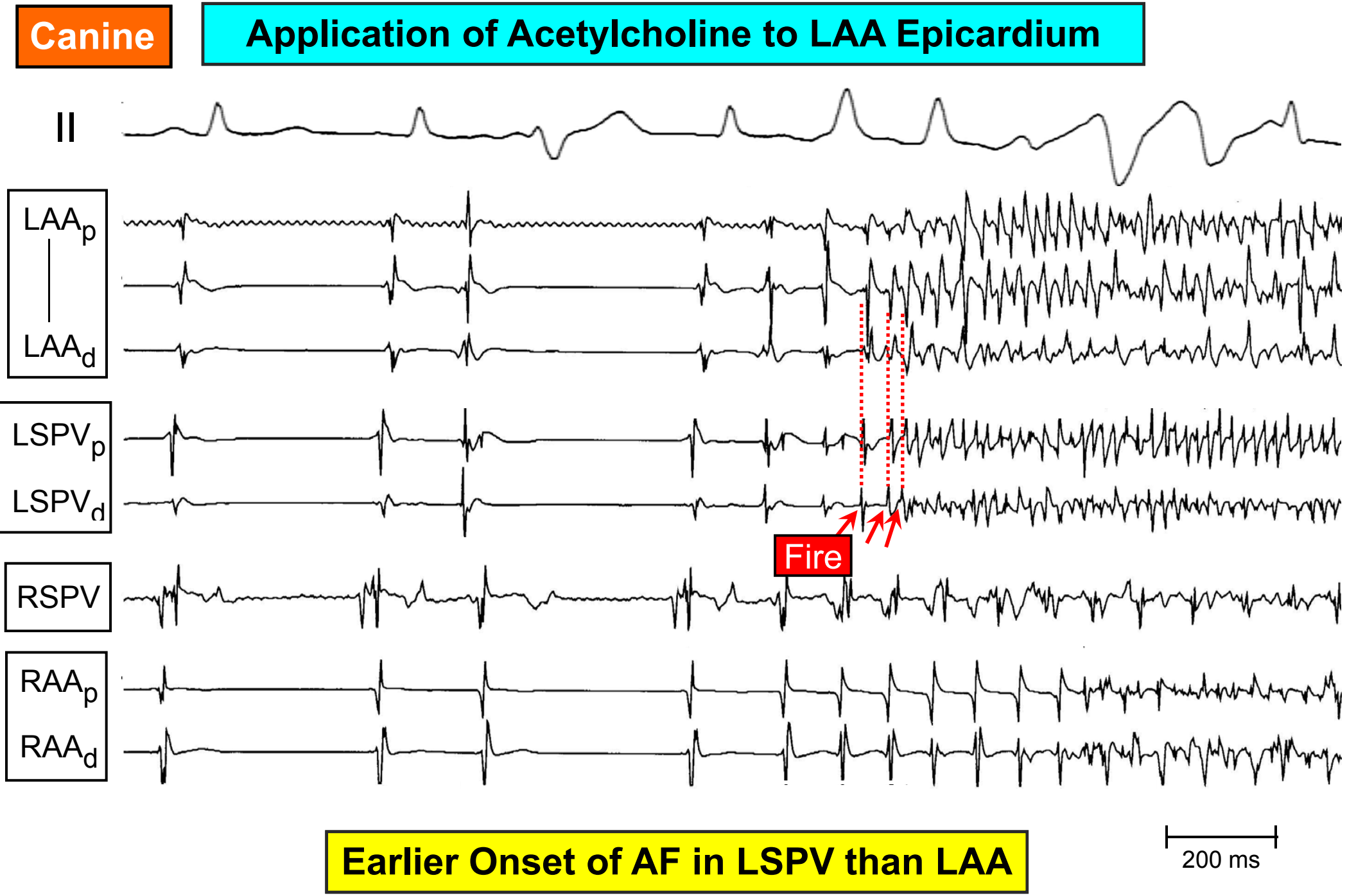
Acetylcholine (Ach) to RAA Epicardium



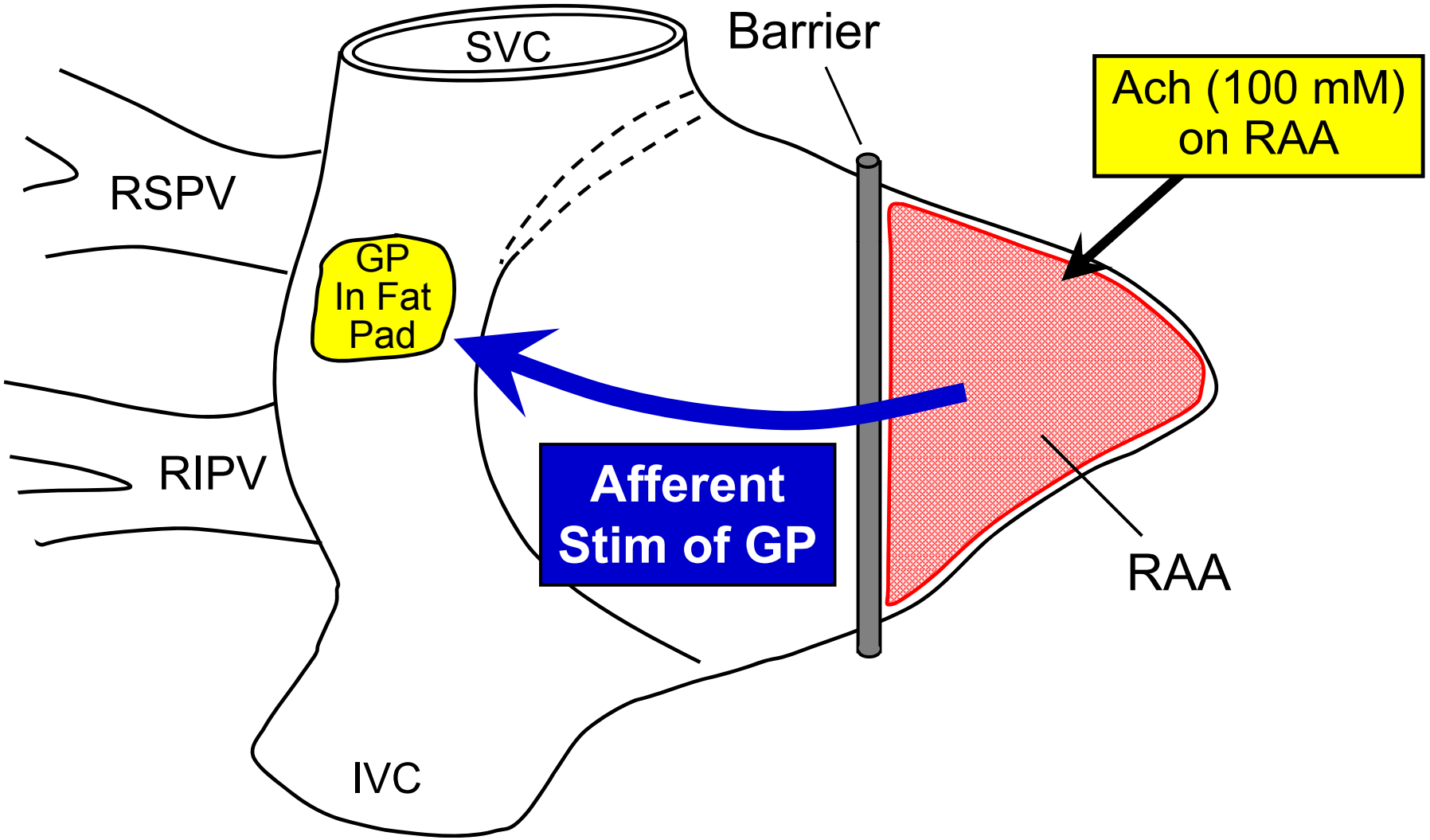
Acetylcholine (Ach) to RAA Epicardium



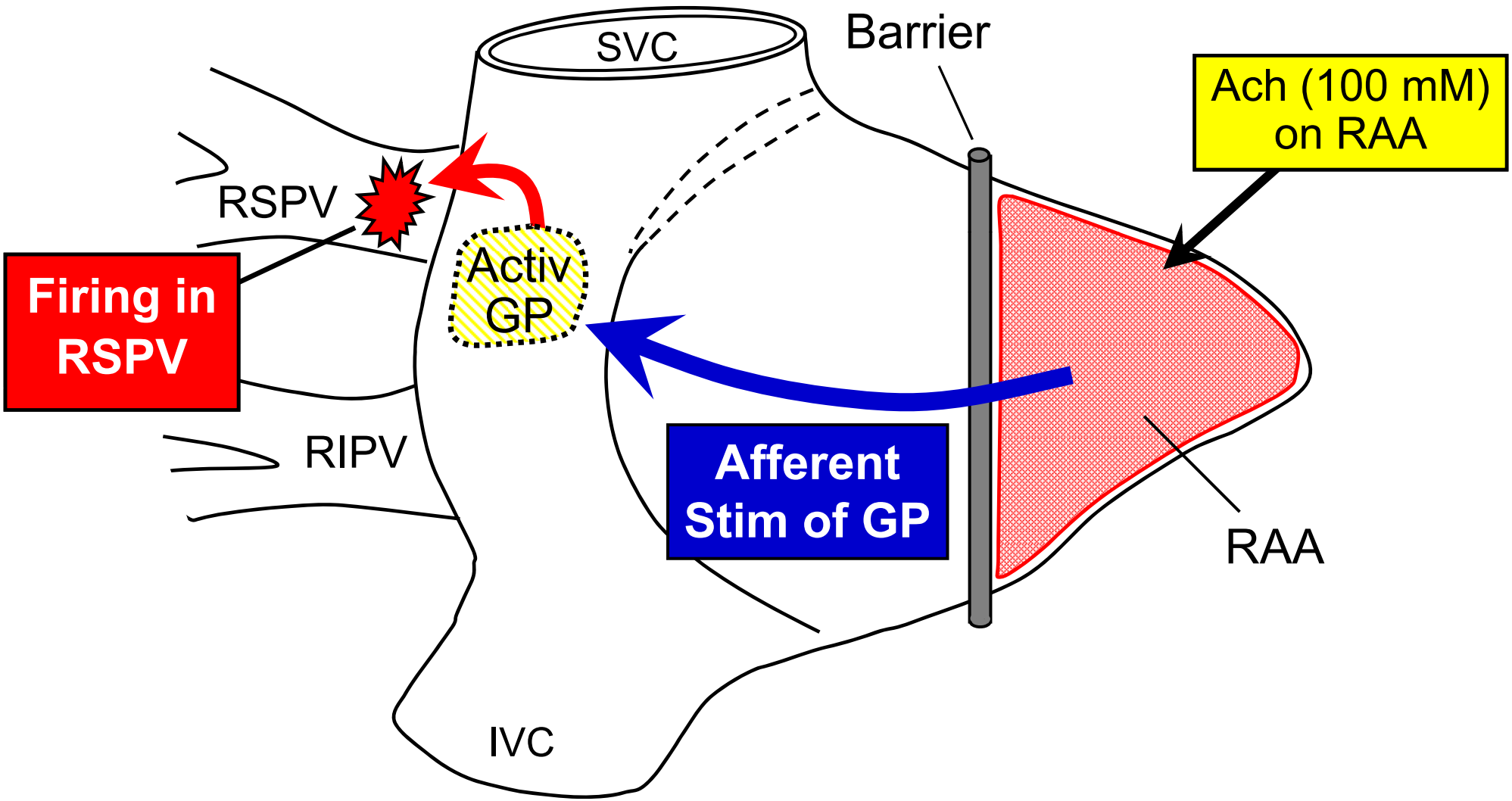

Canine
Application of Acetylcholine to LAA Epicardium
II
LAAp
LAAd
Fire
LSPVp
LSPVd
RSPV
RAAp
RAAd
200 ms


Canine
Application of Acetylcholine to LAA Epicardium
II
LAAp
LAAd
LSPVp
LSPVd
Fire
RSPV
RAAp
RAAd
Earlier Onset of AF in LSPV than LAA
200 ms

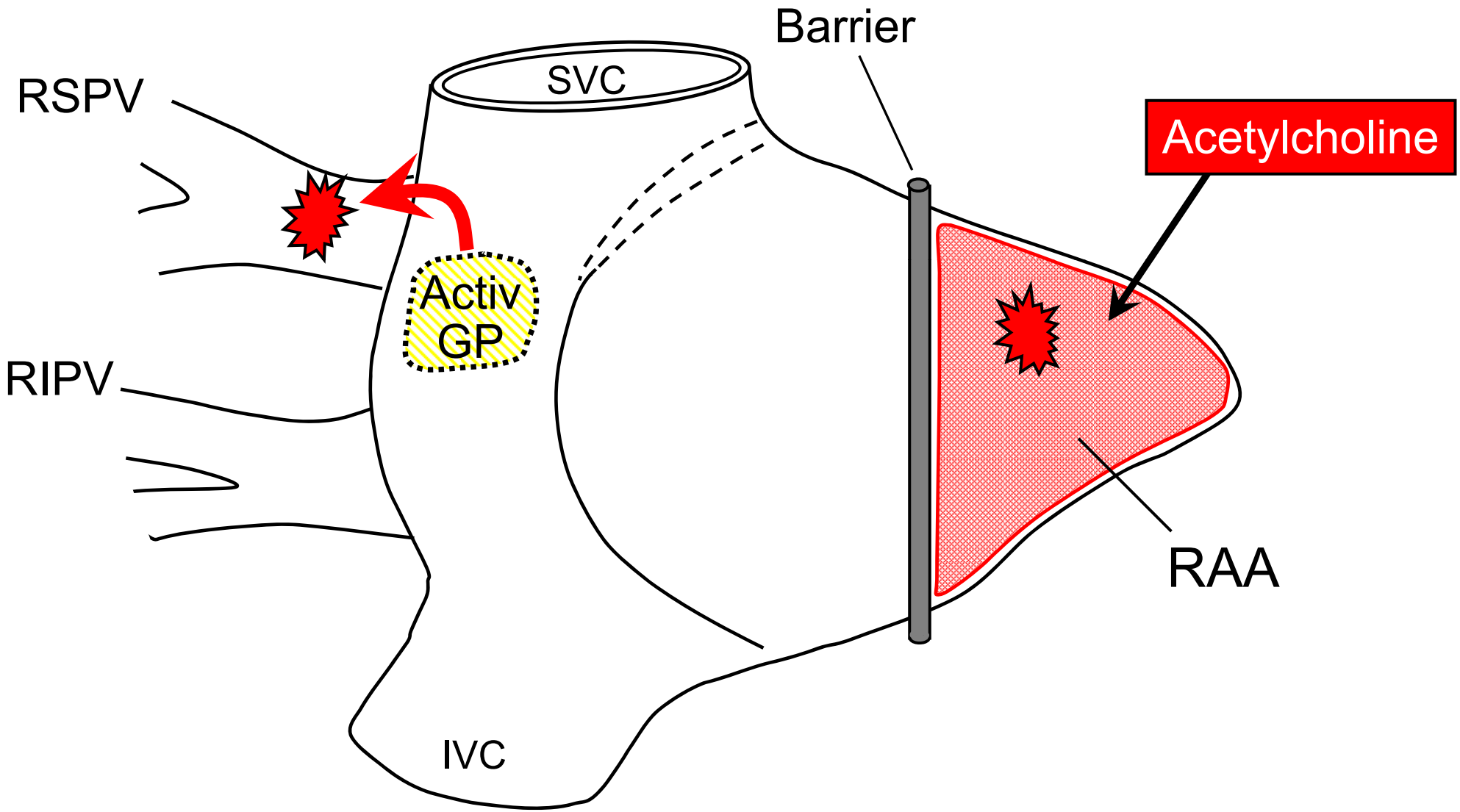
Acetylcholine (Ach) on RAA → Afferent Stimulation of GP



Activated GP → Triggered Firing in RSPV



Acetylcholine on RAA → Firing in Both RAA and PV



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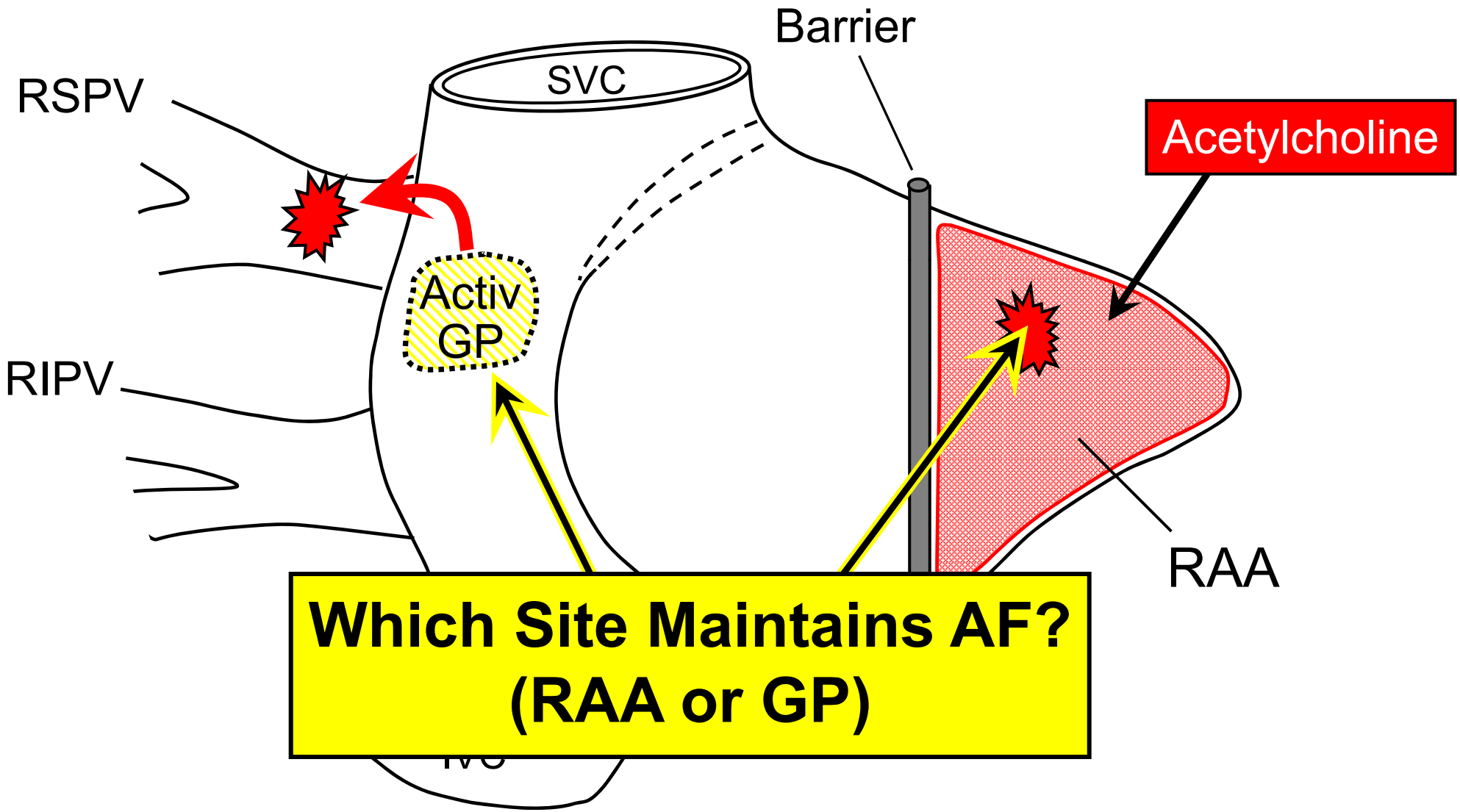
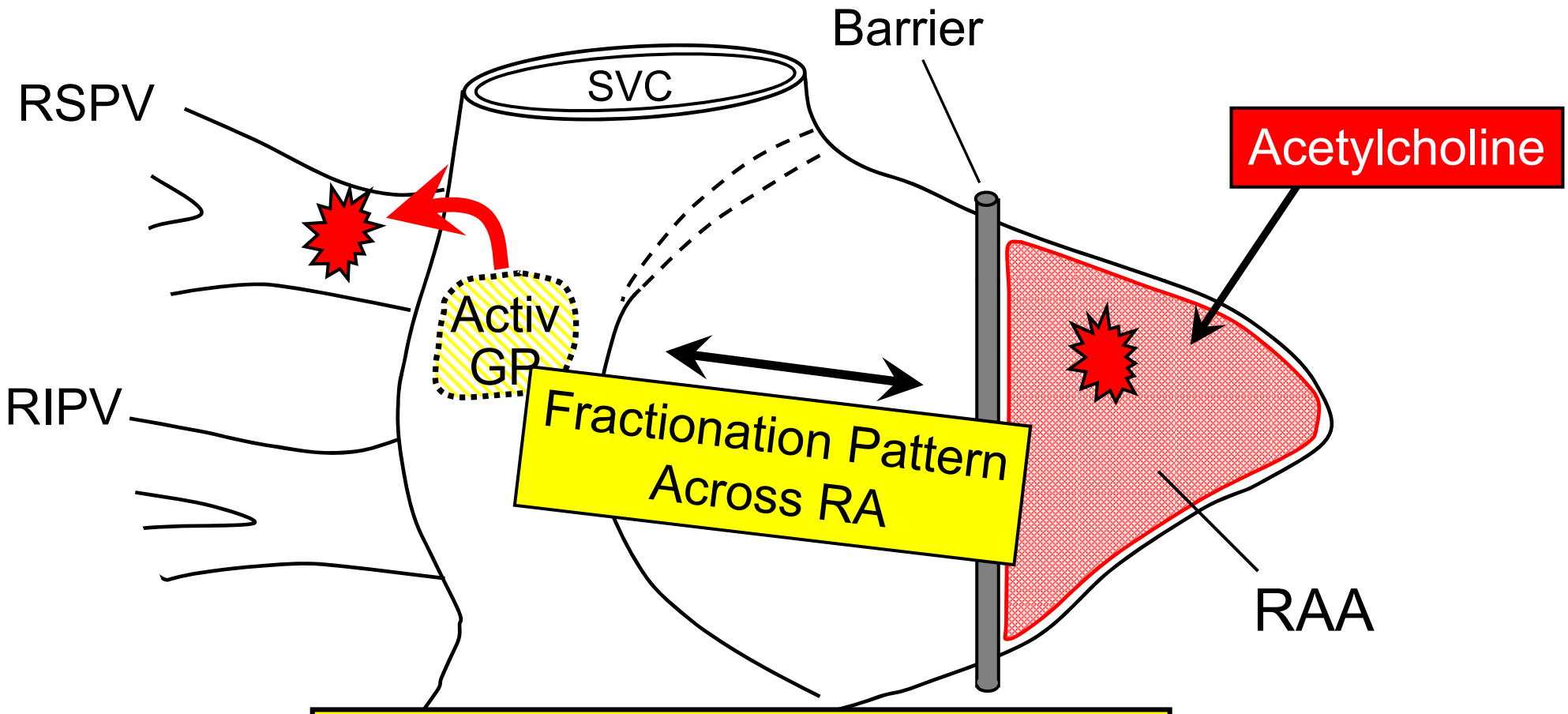


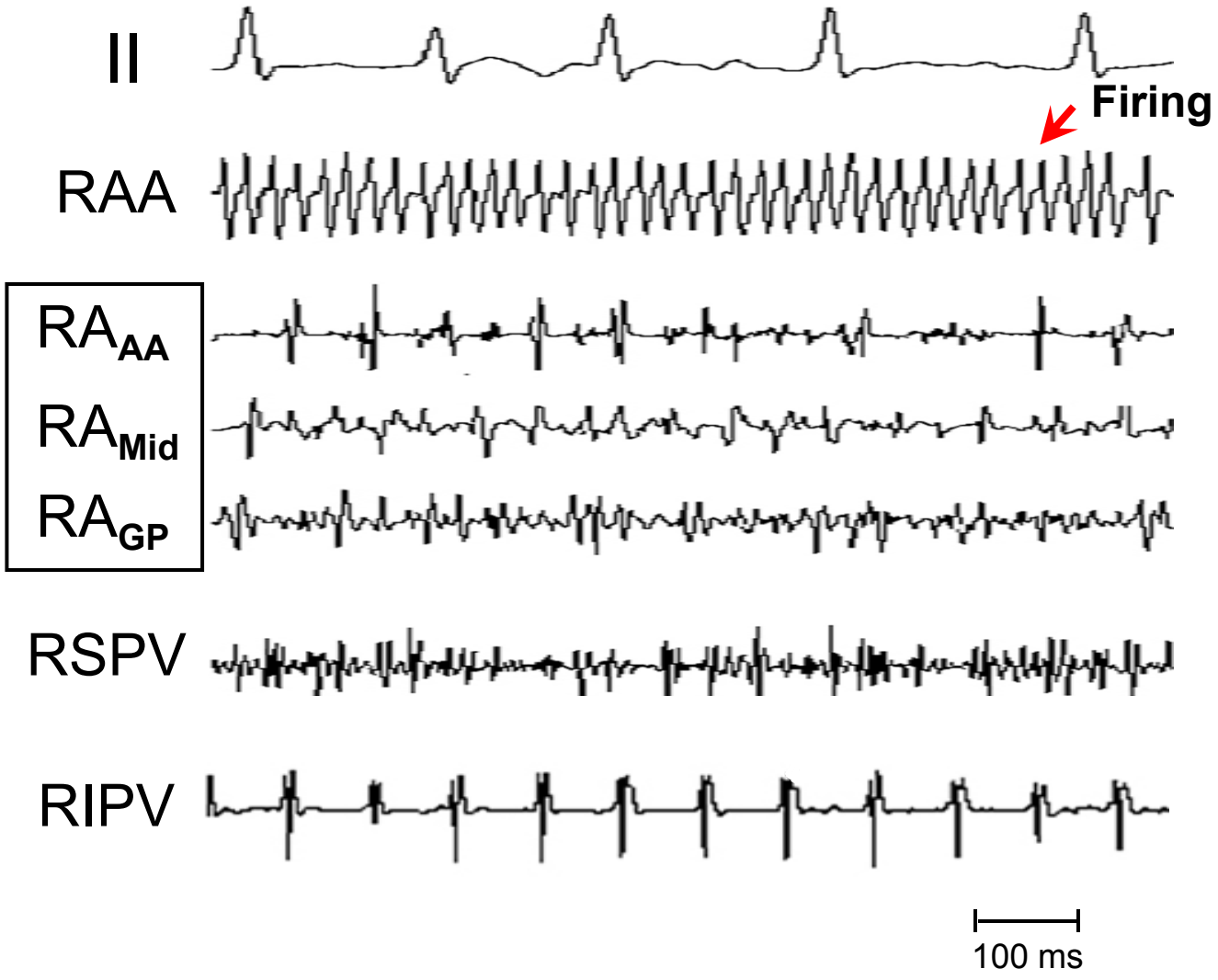
Acetylcholine on RAA → Firing in Both RAA and PV



Which Site Maintains AF?
(RAA or GP)

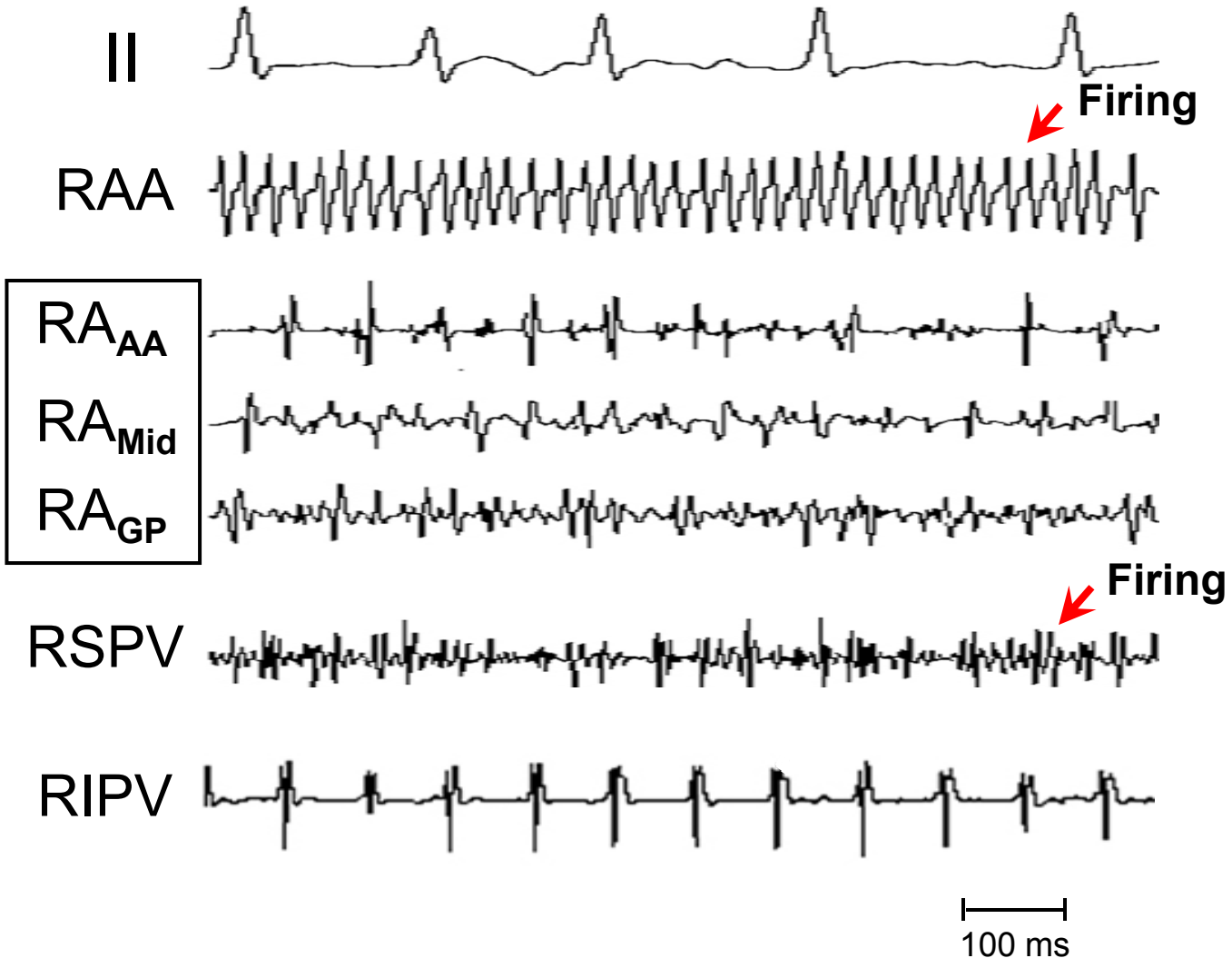
Differences in Fractionation Across RA

Acetylcholine Applied to Right Atrial Appendage



Differences in Fractionation Across RA

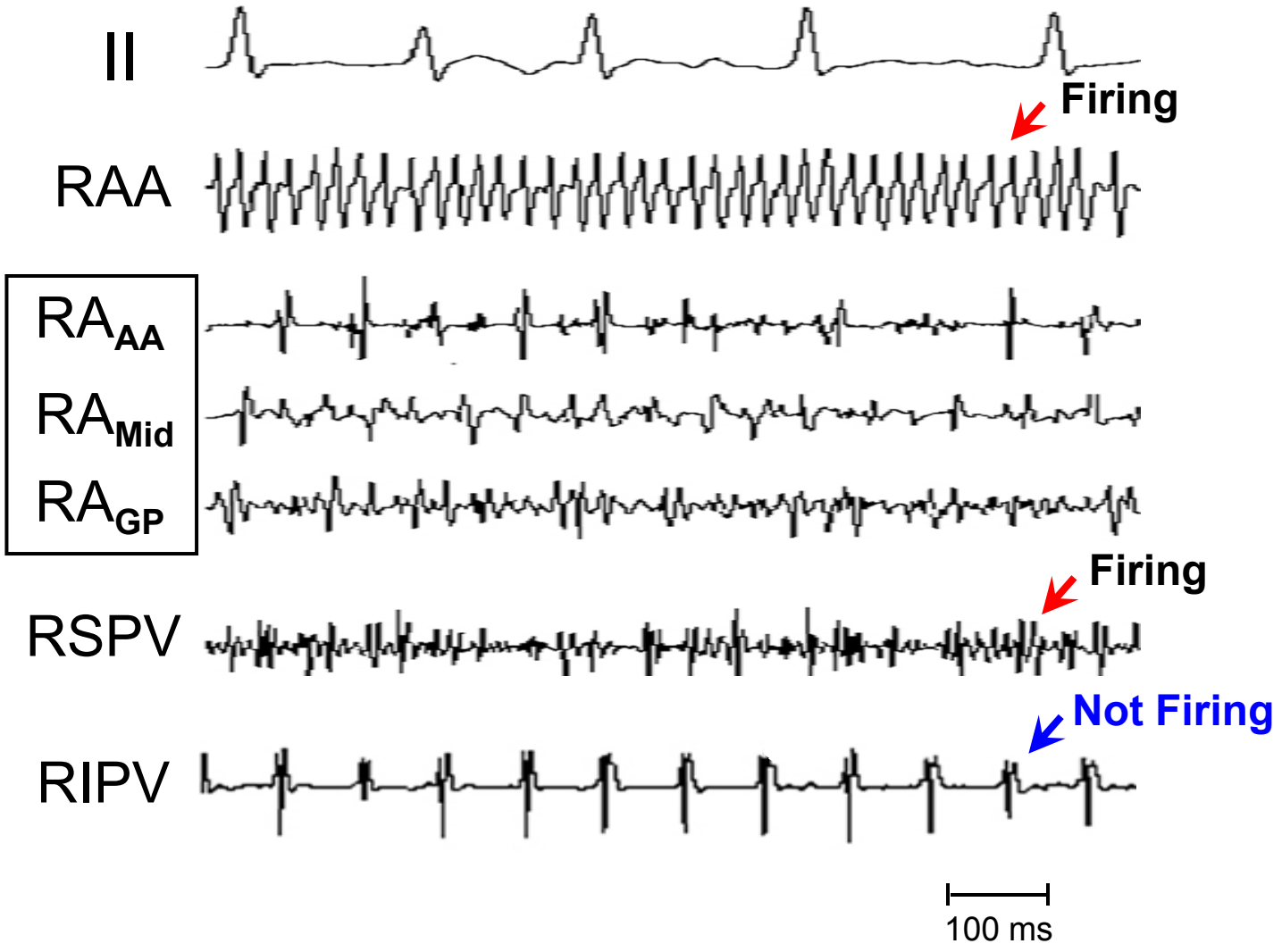
Acetylcholine Applied to Right Atrial Appendage



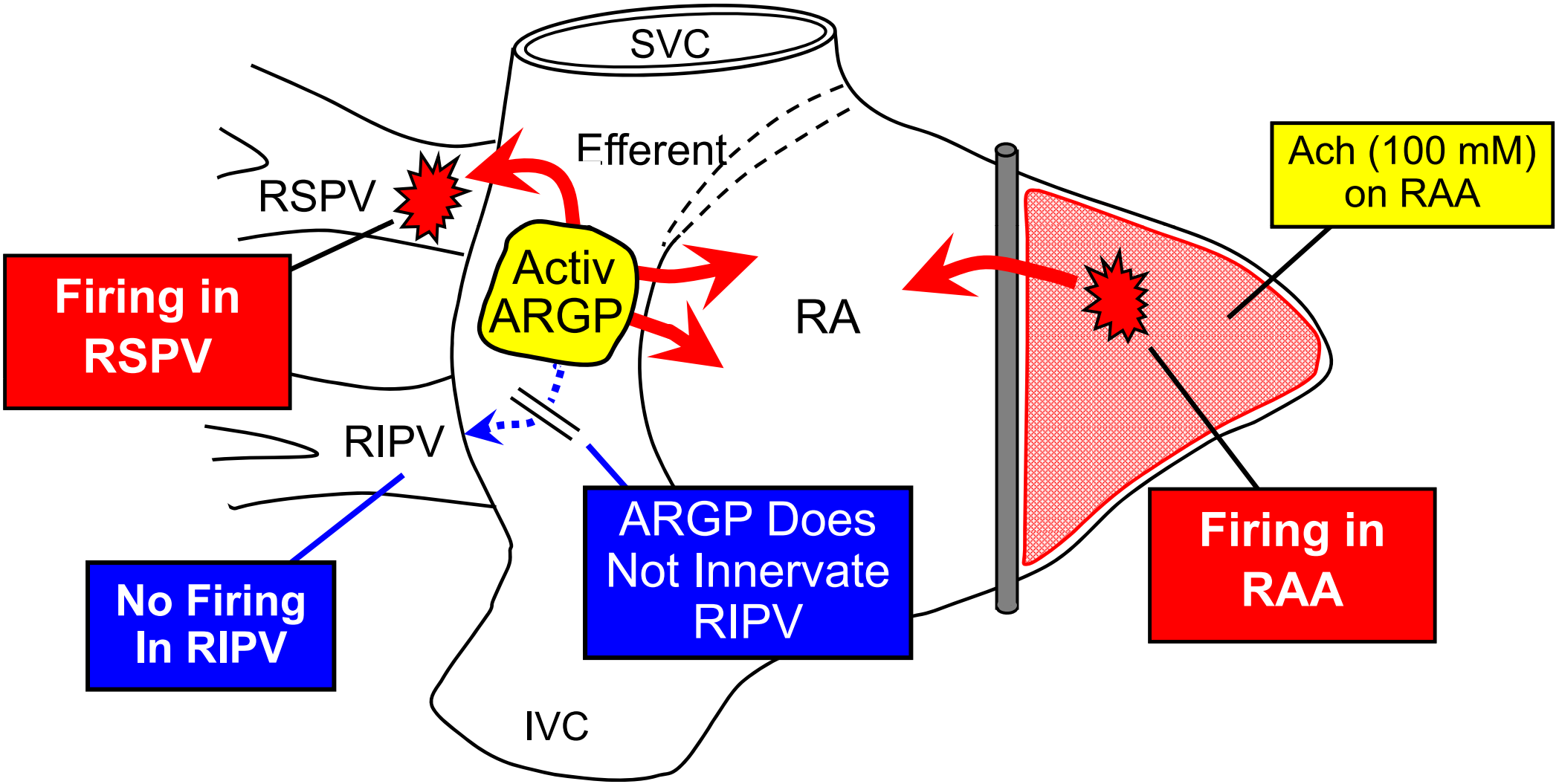
Complex Fractionated Atrial Electrograms *(CFAE)*

Differences in Fractionation Across RA

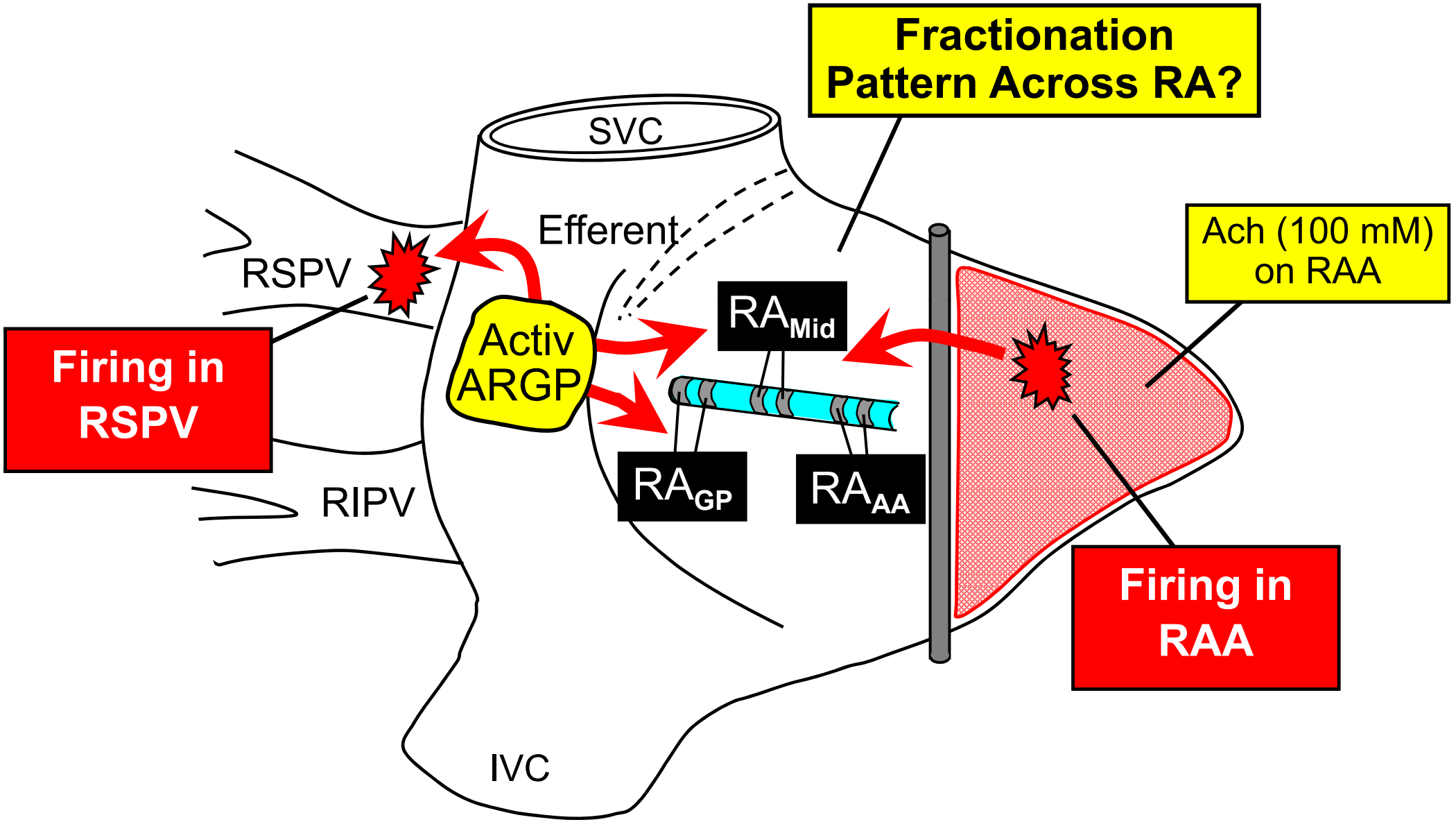
Acetylcholine Applied to Right Atrial Appendage



Anterior Right GP (ARGP)
Primary Target is RSPV, Not RIPV

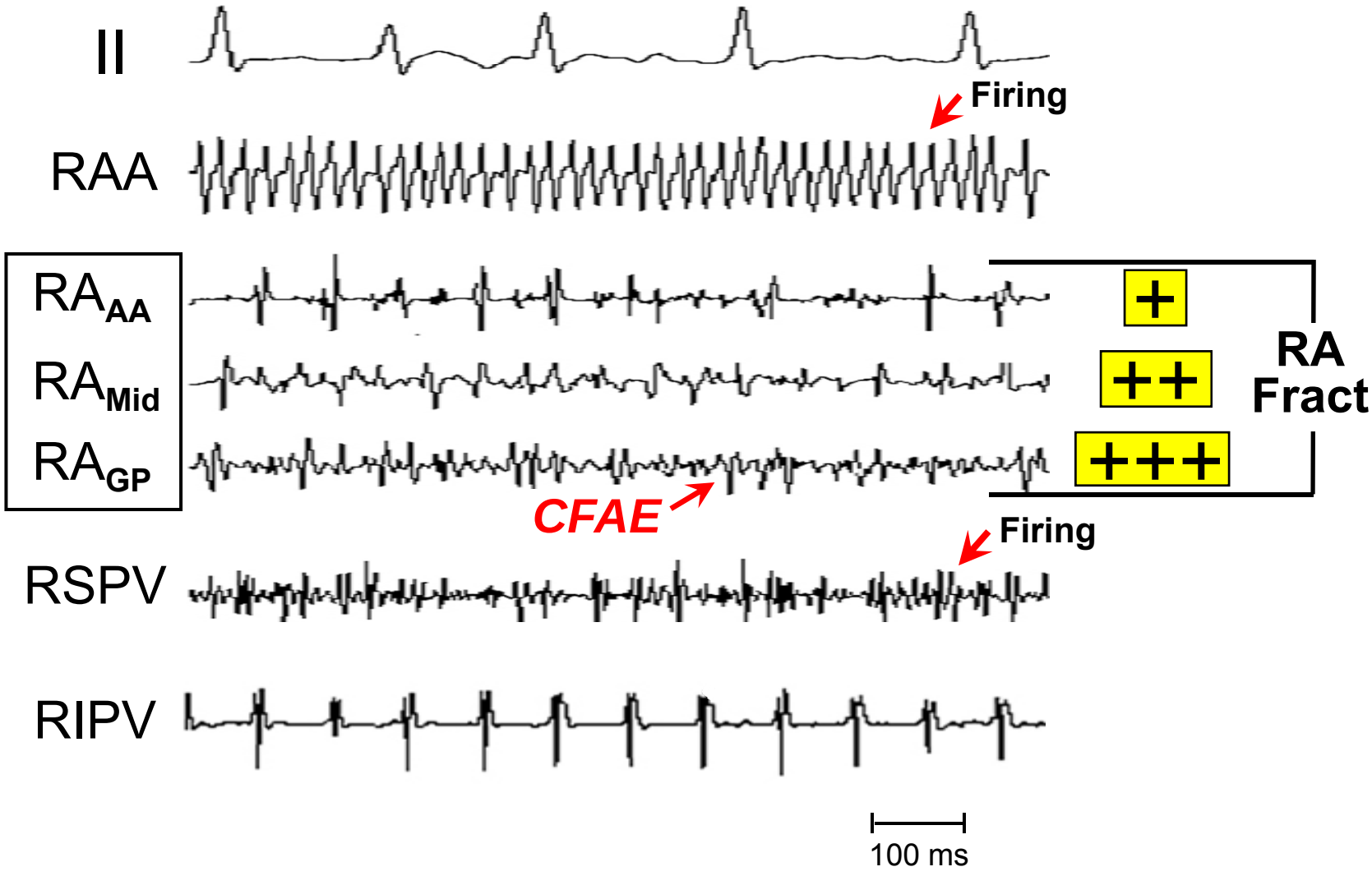


Differences in Fractionation Across RA



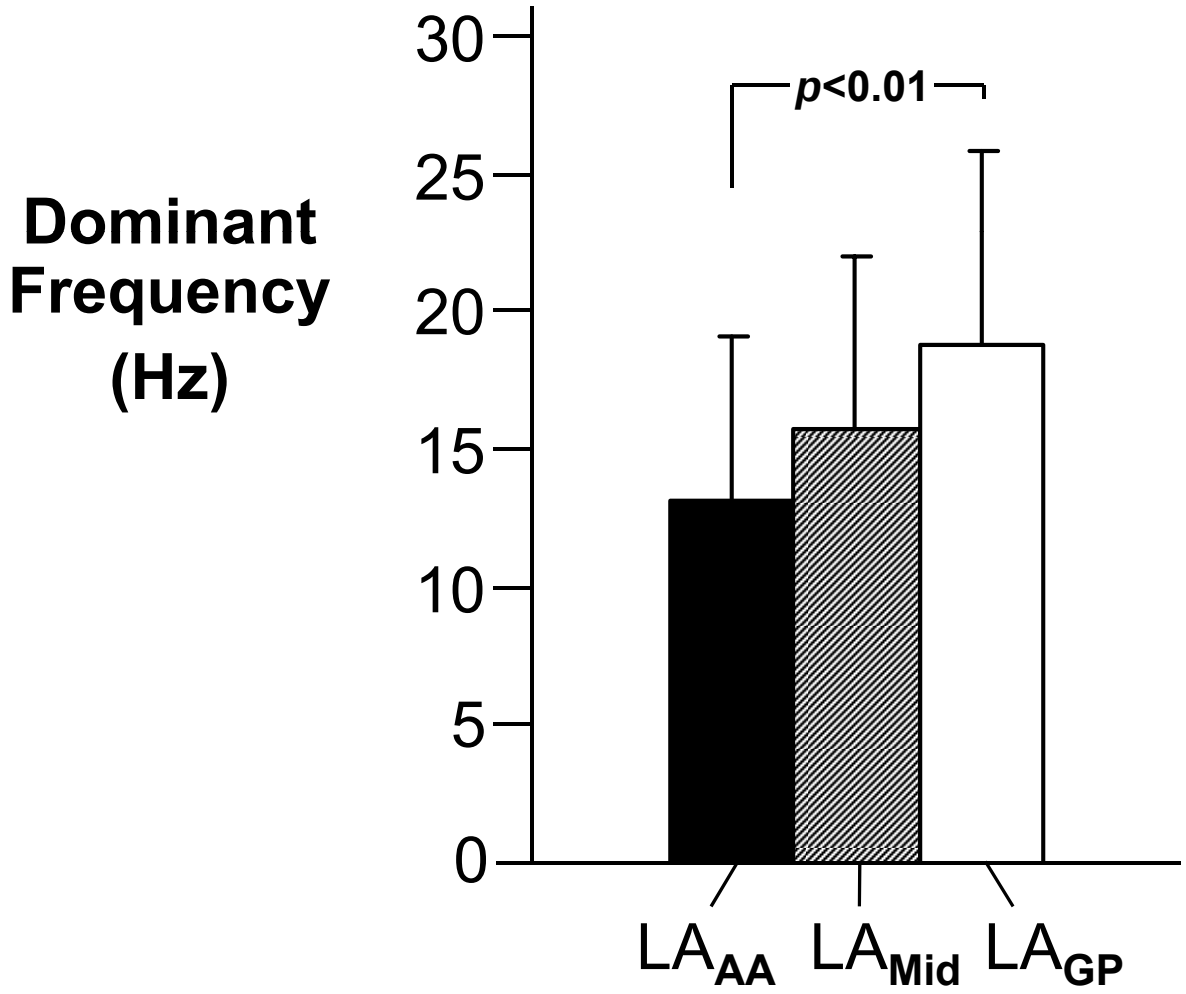
Differences in Fractionation Across RA

Acetylcholine Applied to Right Atrial Appendage

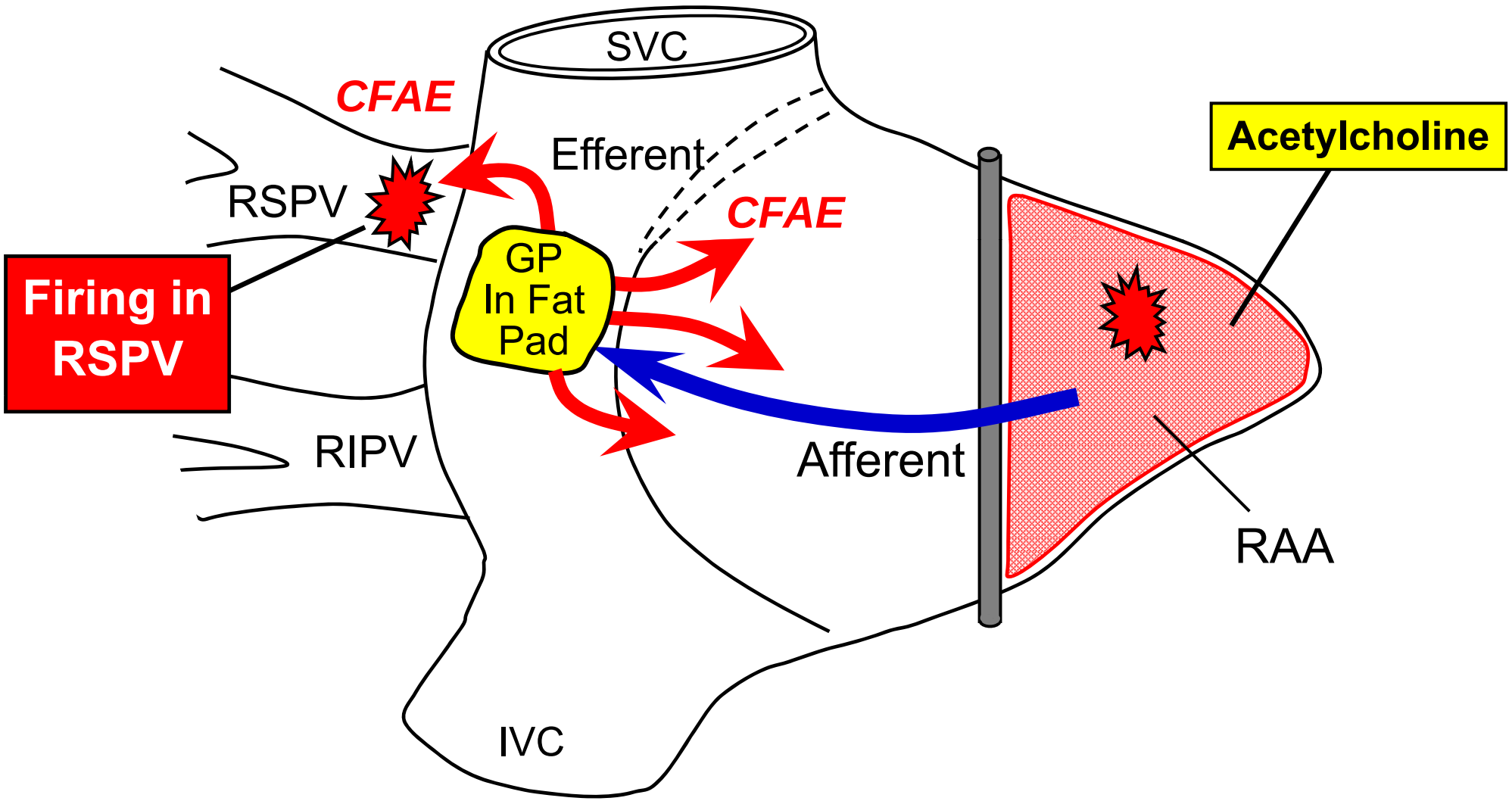


Fractionation Differences Across LA

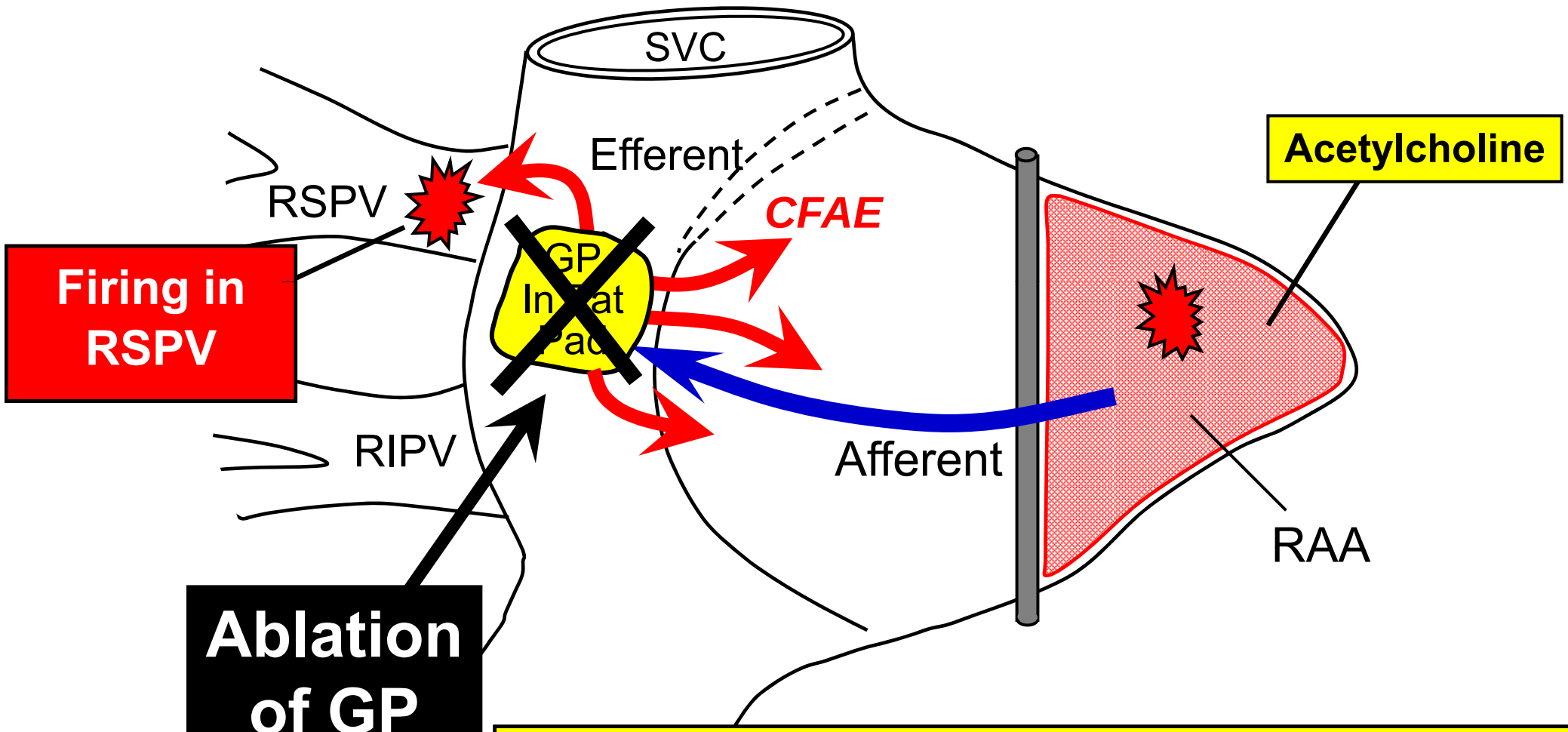
Acetylcholine (100mM) Applied to Left Atrial Appendage



Activation of GP → Induces Firing in PV and Atrium Surrounding the GP → *CFAE*



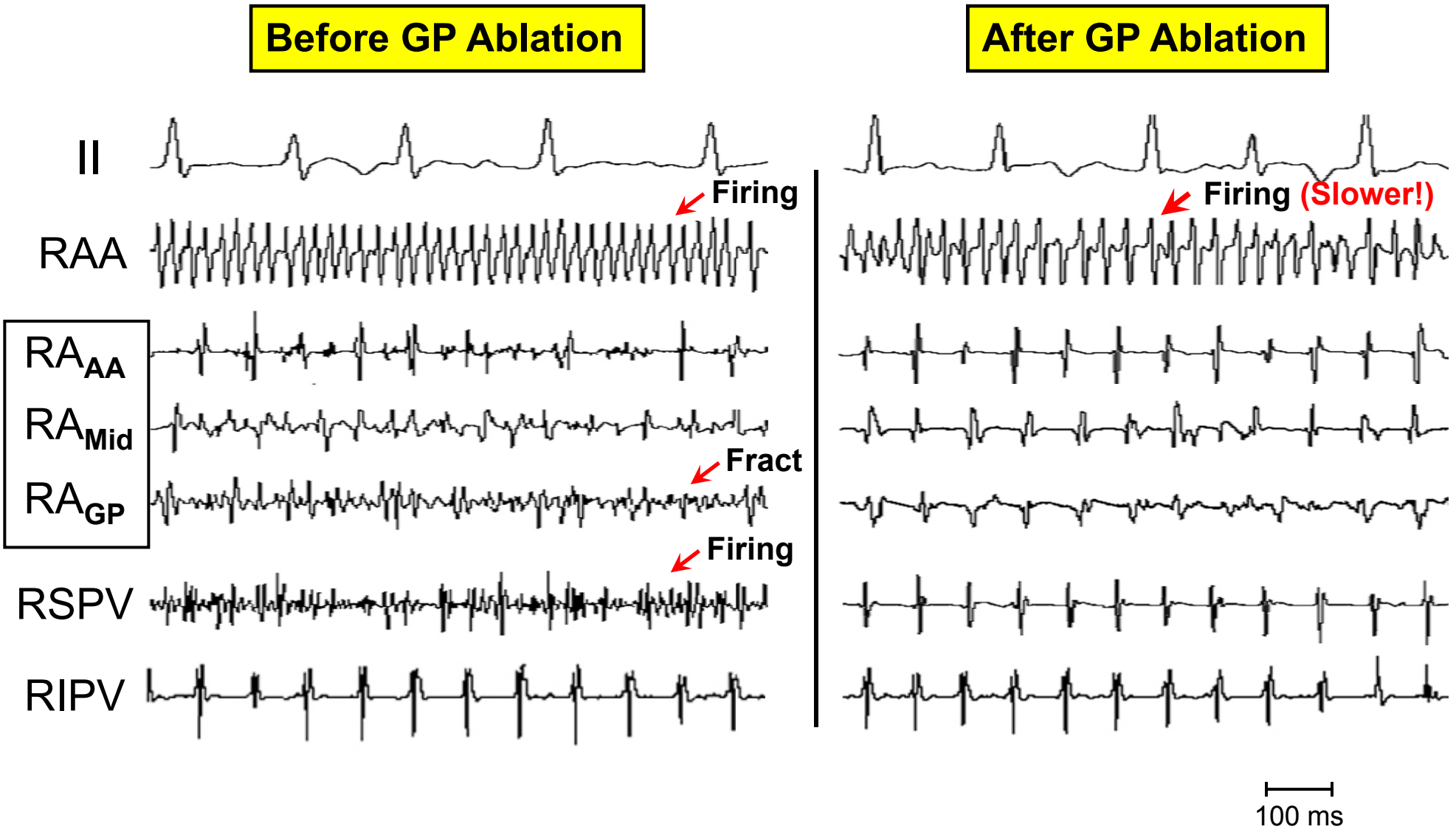
Differences in Fractionation Across RA



How Would the Pattern of Fractionation Change With GP Ablation?

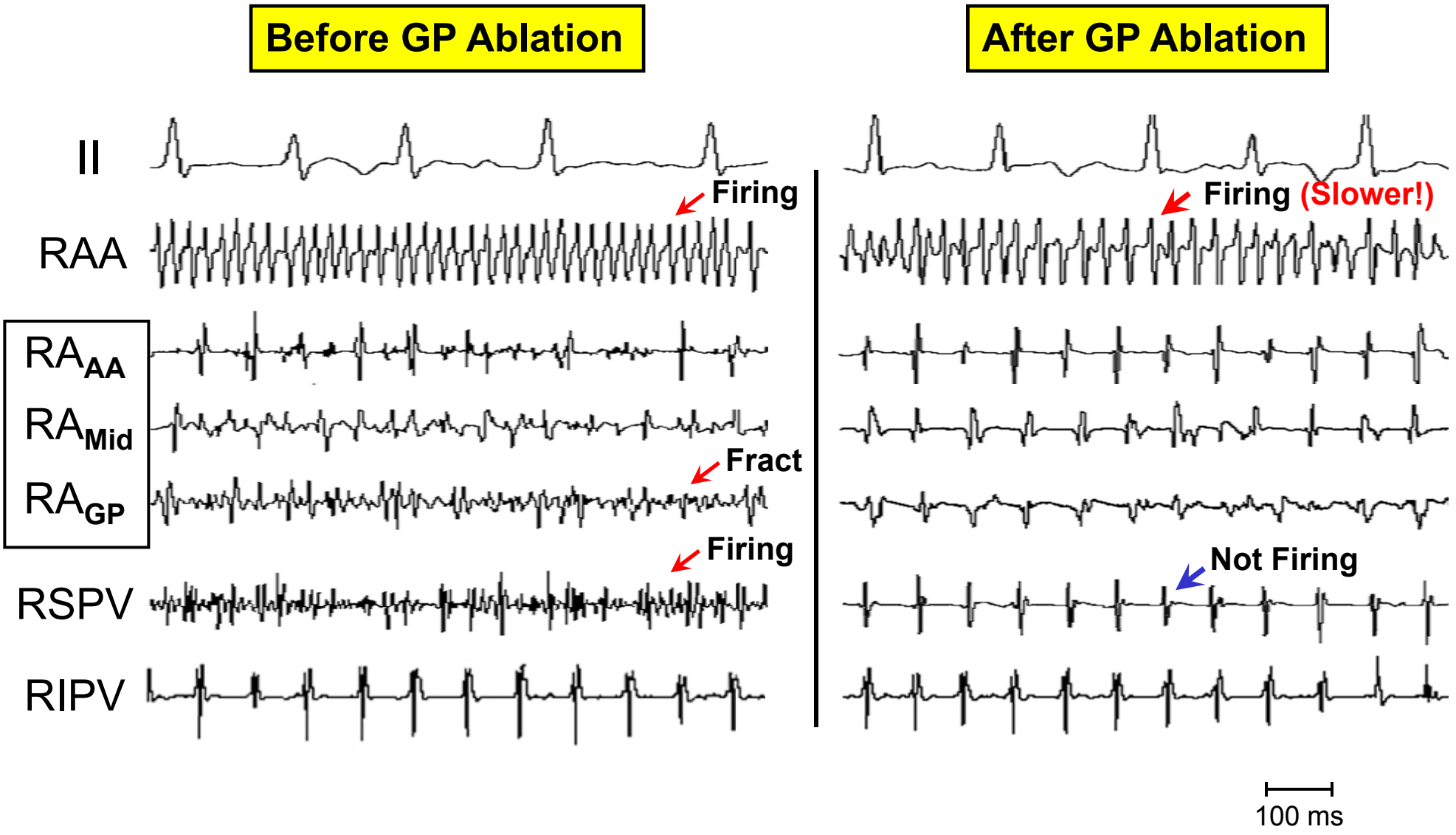
Differences in Fractionation Across RA

Acetylcholine Applied to Right Atrial Appendage



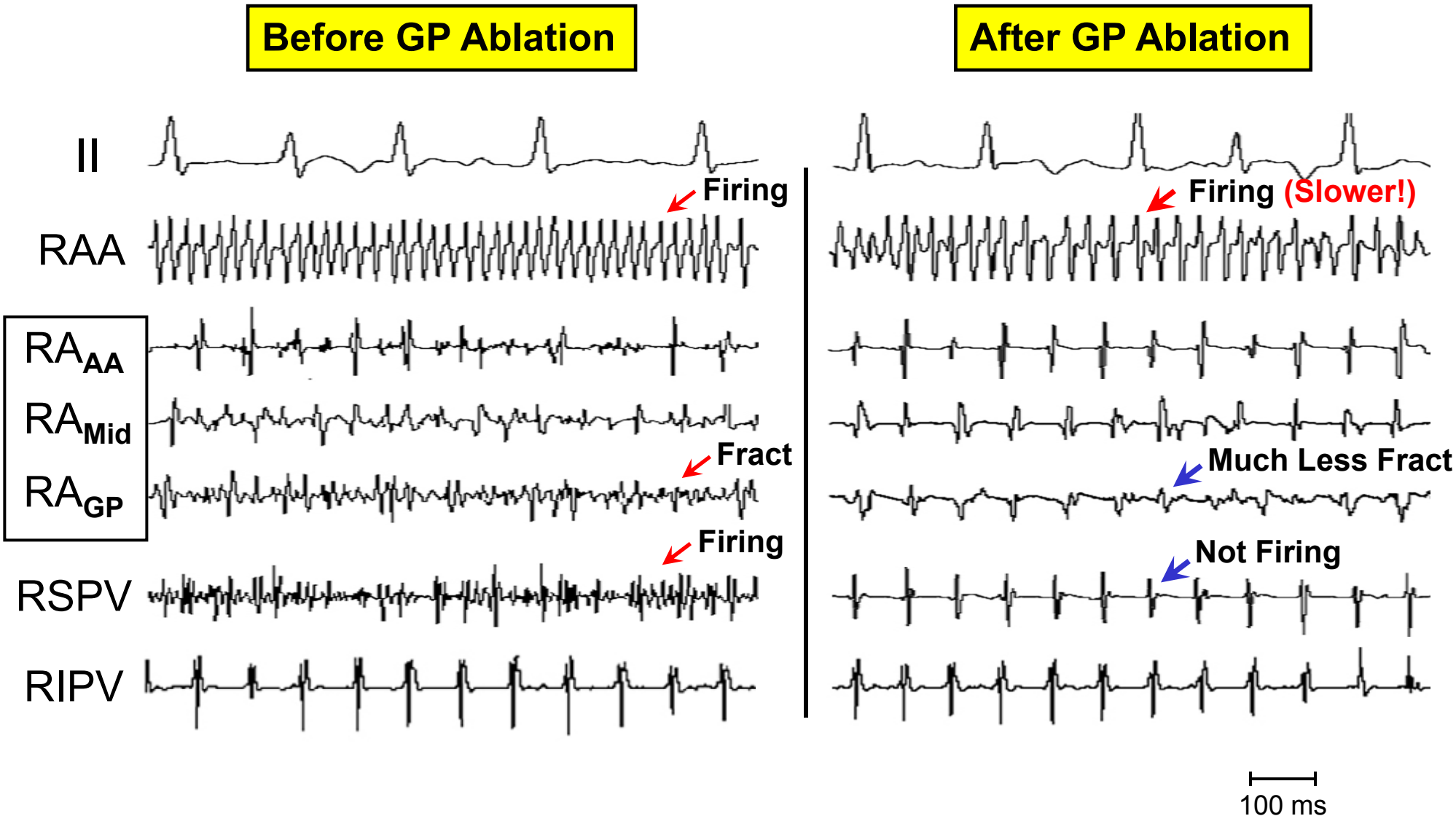
Differences in Fractionation Across RA

Acetylcholine Applied to Right Atrial Appendage



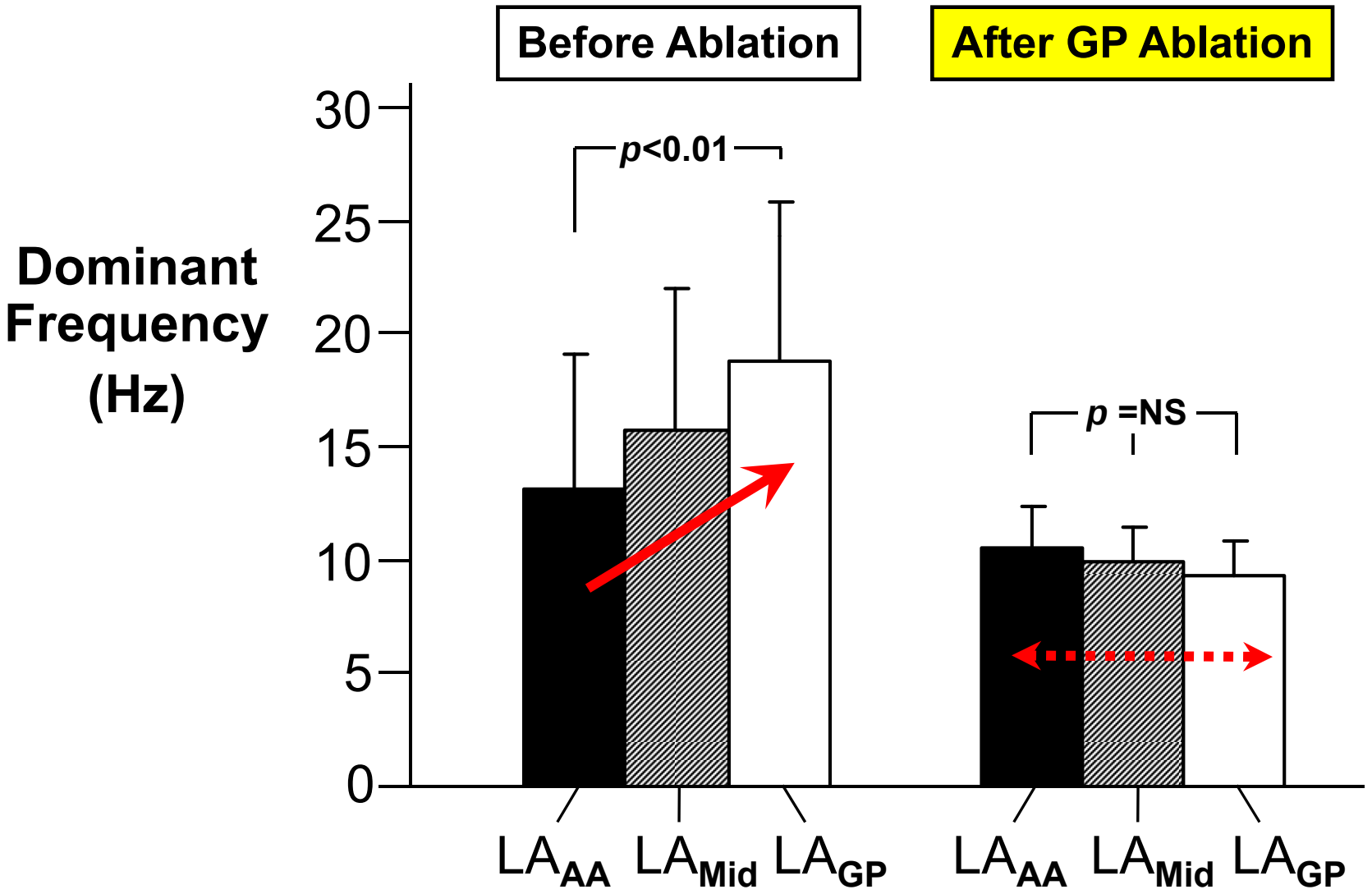
Differences in Fractionation Across RA

Acetylcholine Applied to Right Atrial Appendage

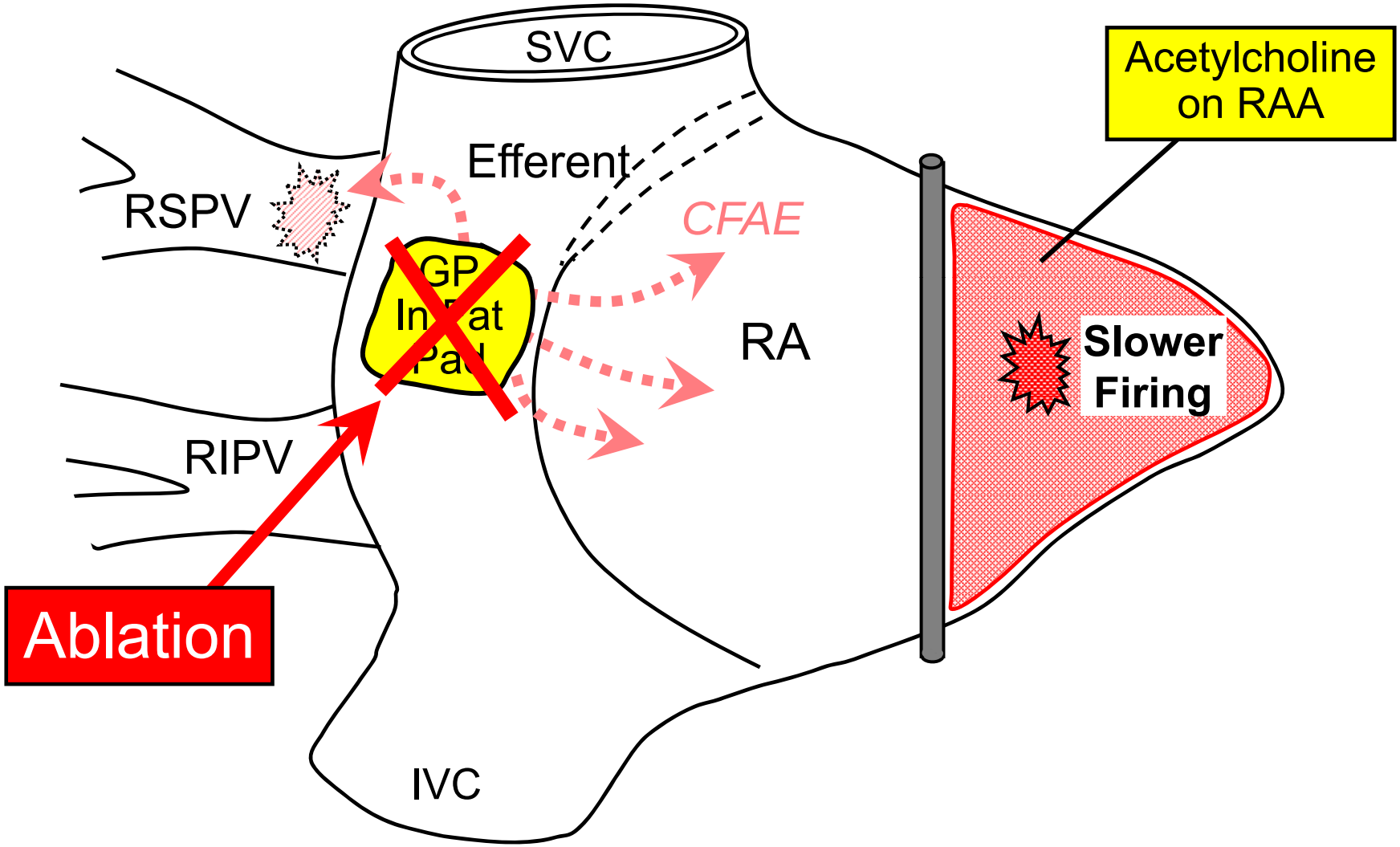


Fractionation Gradient Across LA was Eliminated by GP Ablation

Acetylcholine (100mM) Applied to Left Atrial Appendage

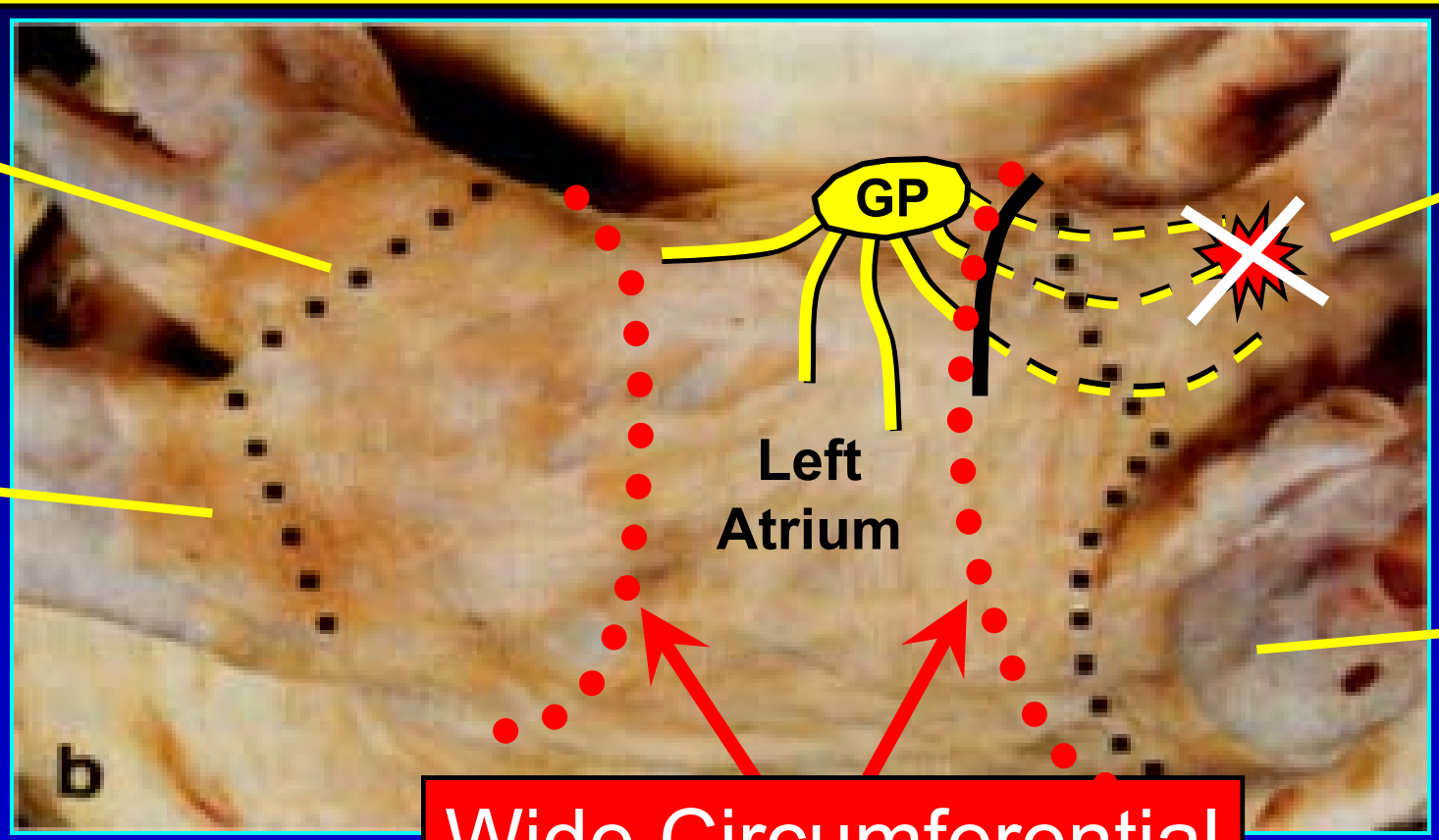


GP Ablation Eliminates Firing in RSPV and RA Fractionation



Hypothesis

PV Isolation Stops Firing in PV by Blocking Autonomic Nerves from Ganglionated Plexi (GP) to PV



Left Superior PV

Right Superior PV

Left Inferior PV

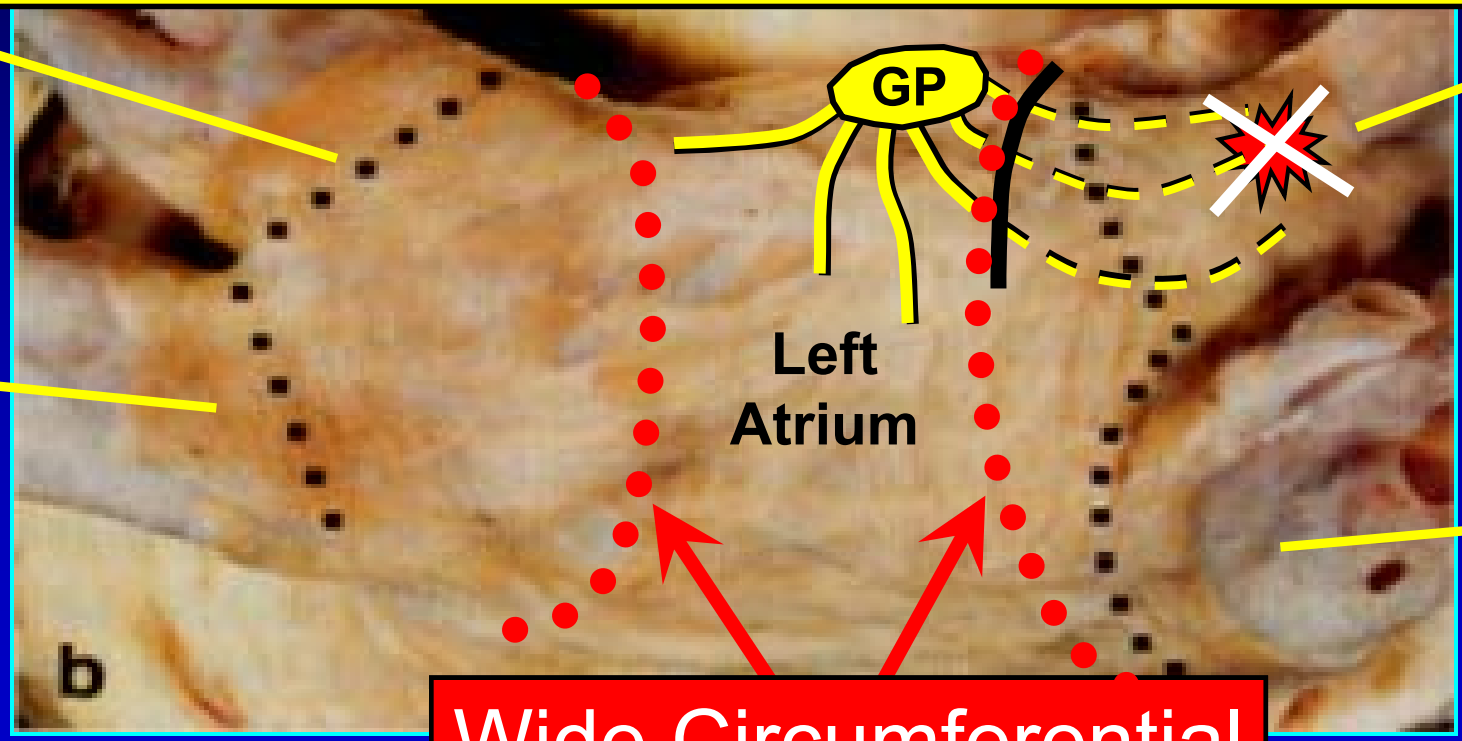
Right Inferior PV

Wide Circumferential PV Isolation

Hypothesis

PV Isolation Stops Firing in PV by Blocking Autonomic Nerves from Ganglionated Plexi (GP) to PV

- PV Isolation Has Same Target as GP Ablation



Superior PV

Superior PV

Left Inferior PV

Right Inferior PV

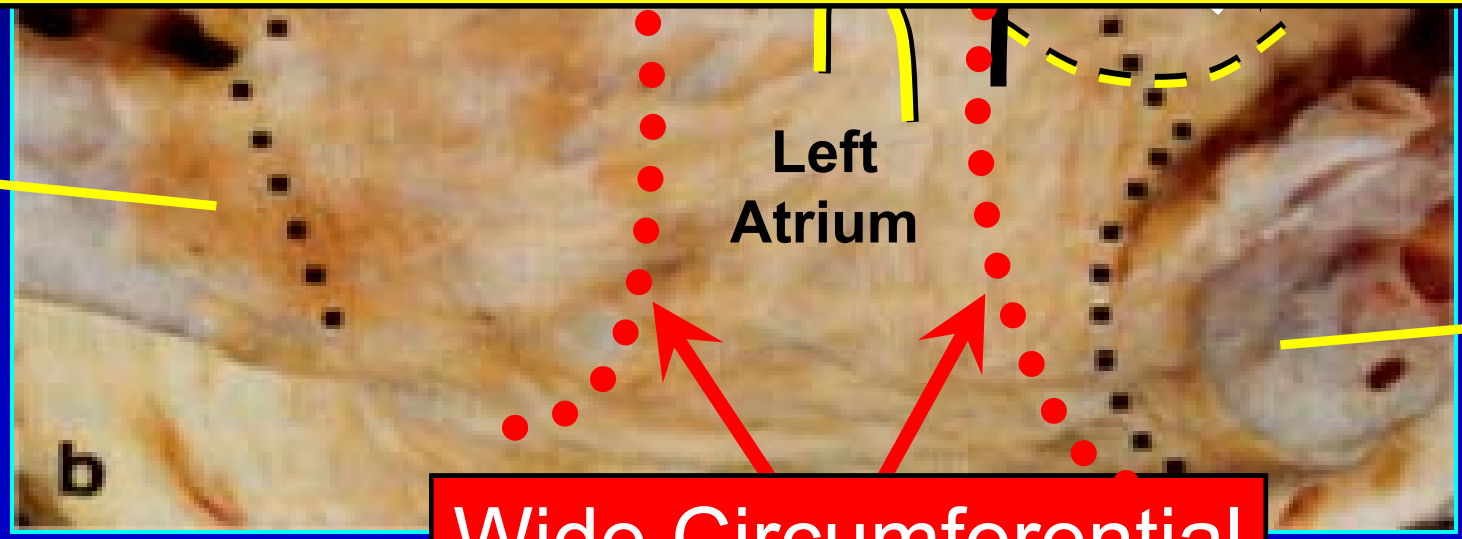
Wide Circumferential PV Isolation

Hypothesis

PV Isolation Stops Firing in PV by Blocking Autonomic Nerves from Ganglionated Plexi (GP) to PV

- PV Isolation Has Same Target as GP Ablation

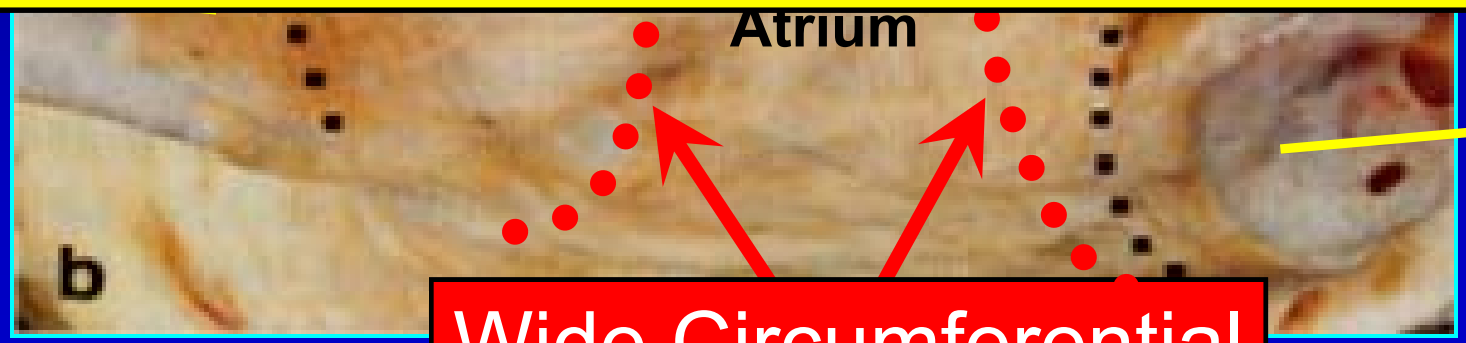
- PV Reconnection Common After PVI and Axons (From GP) May Regenerate (Producing Late AF Recurrence)



Hypothesis

PV Isolation Stops Firing in PV by Blocking Autonomic Nerves from Ganglionated Plexi (GP) to PV

- **PV Isolation Has Same Target as GP Ablation**
- **PV Reconnection Common After PVI and Axons (From GP) May Regenerate (Producing Late AF Recurrence)**
- **GP Ablation is Permanent (Destroys Cell Bodies), but Can't Locate all of GP (GP Ablation is Incomplete)**



Wide Circumferential PV Isolation

Hypothesis

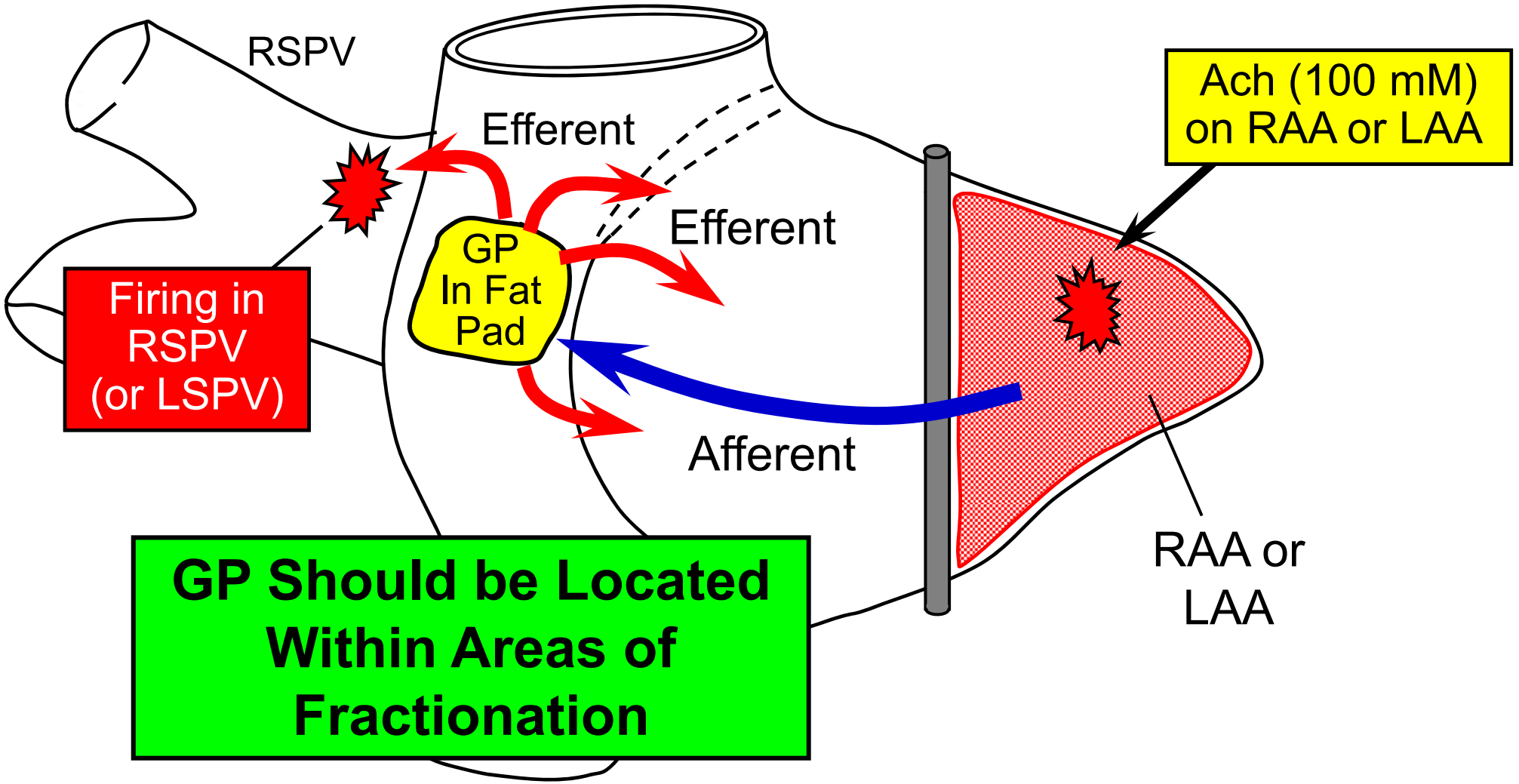
PV Isolation Stops Firing in PV by Blocking Autonomic Nerves from Ganglionated Plexi (GP) to PV

- **PV Isolation Has Same Target as GP Ablation**
- **PV Reconnection Common After PVI and Axons (From GP) May Regenerate (Producing Late AF Recurrence)**
- **GP Ablation is Permanent (Destroys Cell Bodies), but Can't Locate all of GP (GP Ablation is Incomplete)**

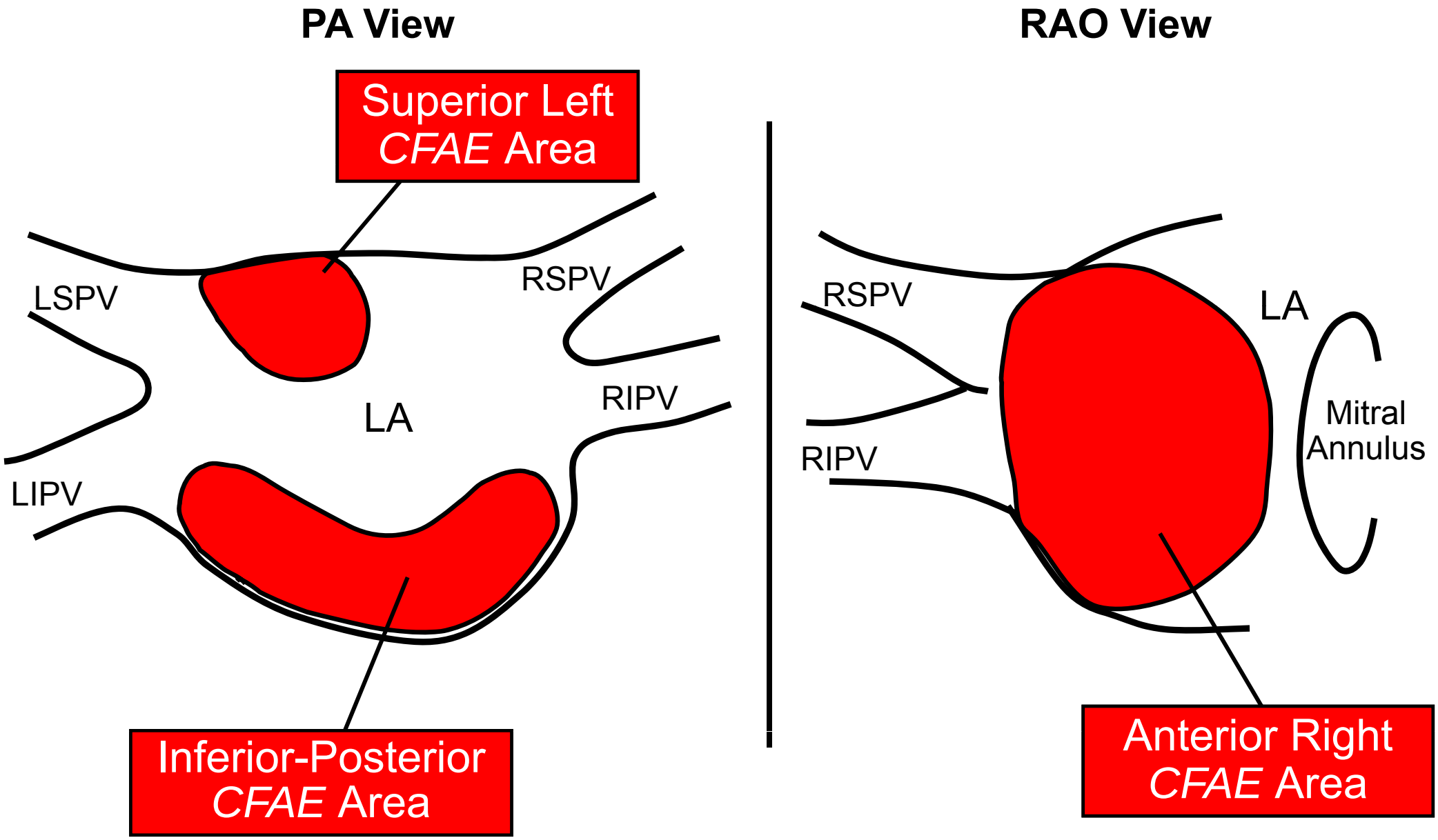
PVI and GP Ablation are Both Imperfect (Technical Limitations), but the Combination of PVI and GP Ablation May Be Synergistic

PV Isolation

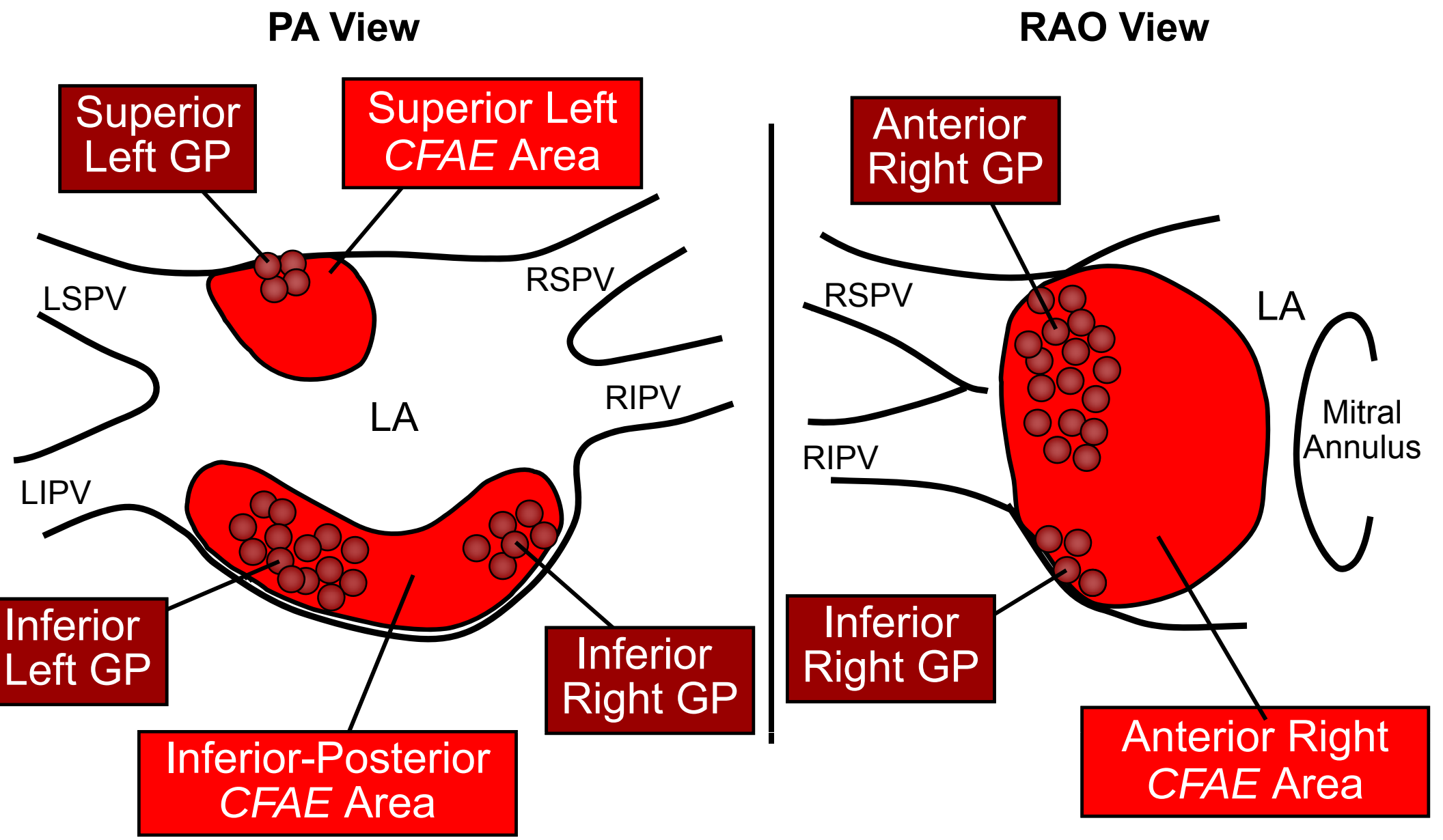
Activation of GP → Induces Firing in PV and Atrium Surrounding the GP → *CFAE*

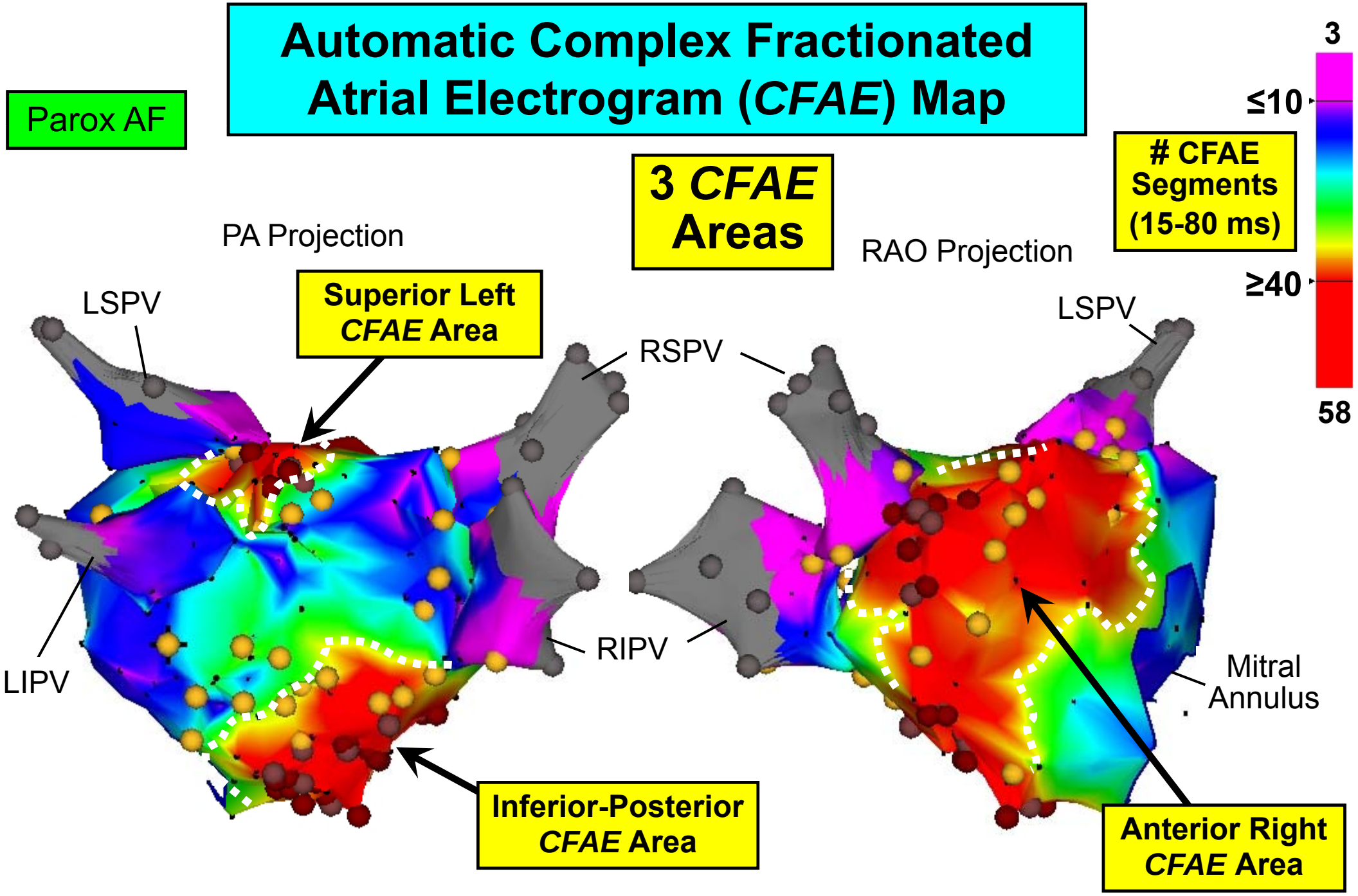


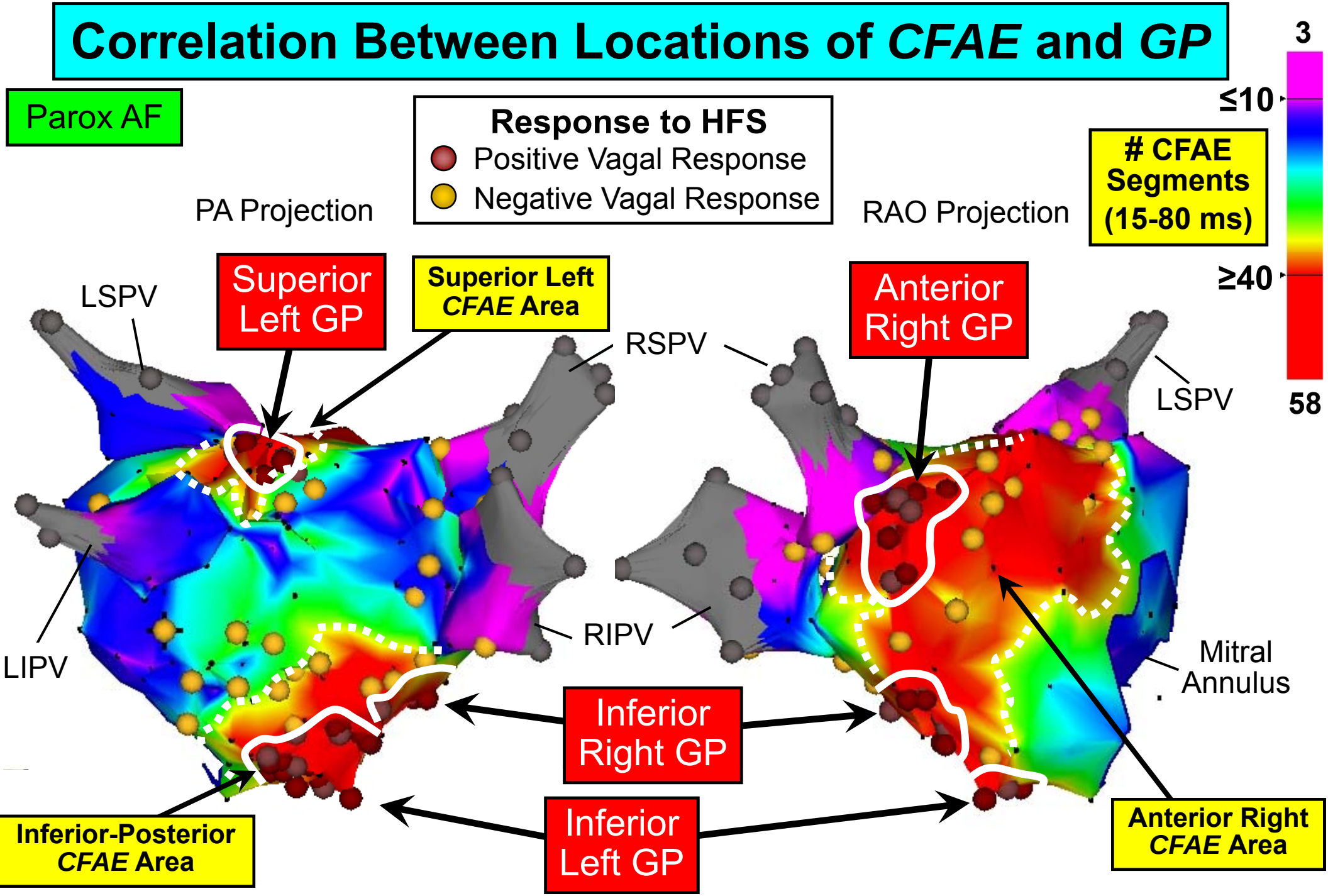
Usually 3 Areas of *CFAE* in Left Atrium

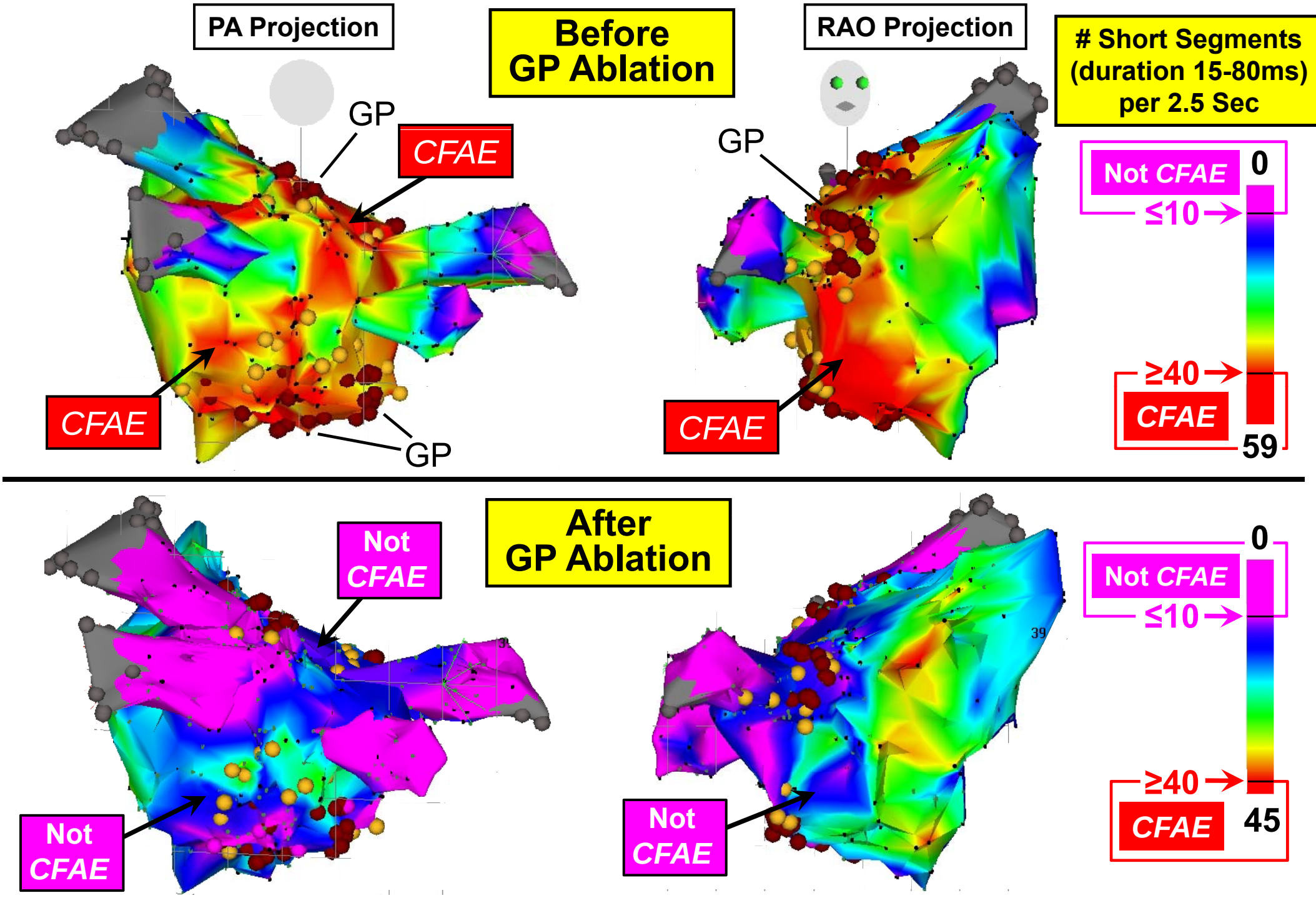


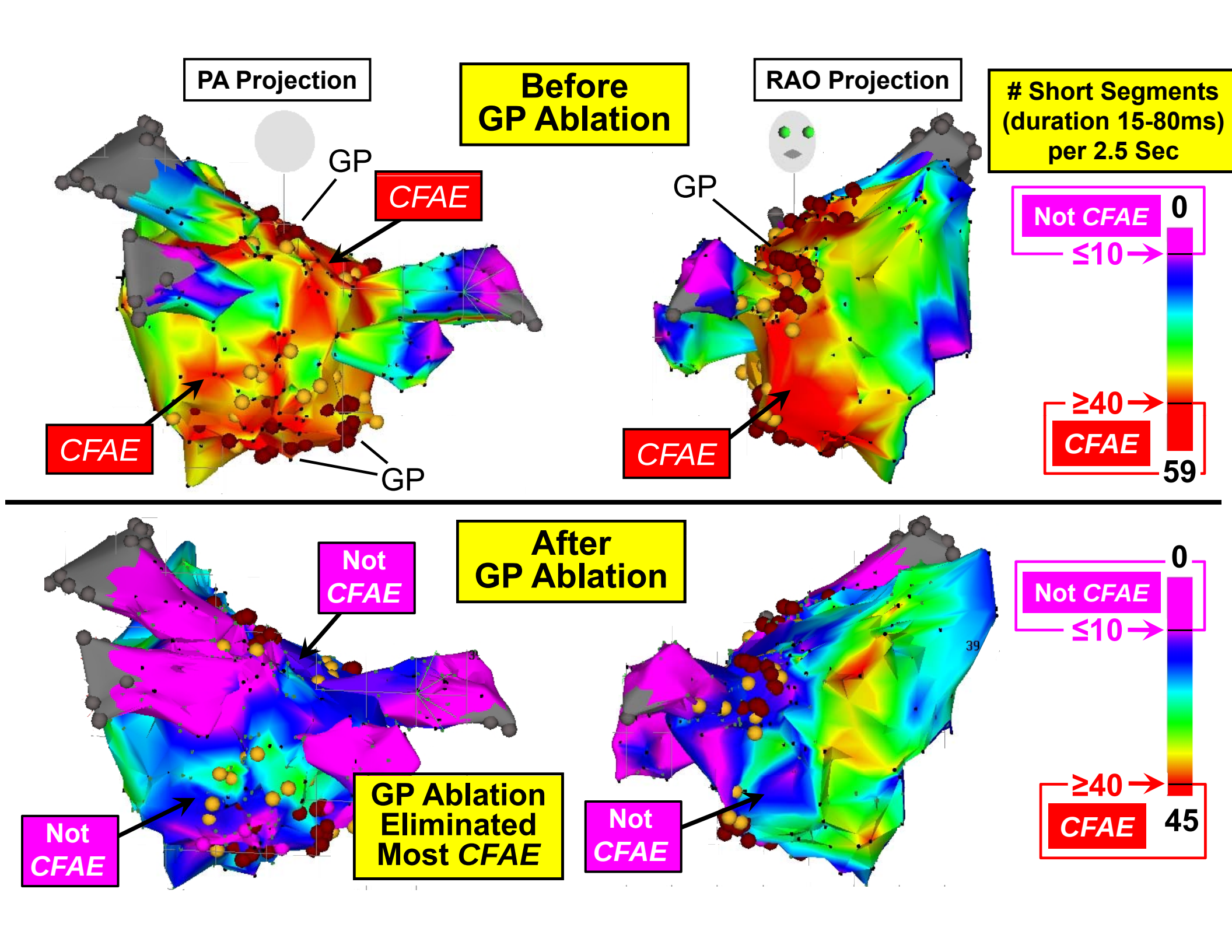
Correlation Between Locations of *CFAE* and *GP*




Automatic Complex Fractionated Atrial Electrogram (CFAE) Map
Parox AF
3 CFAE Areas
CFAE Segments (15-80 ms)
3
≤10
≥40
58
PA Projection
RAO Projection
LSPV
Superior Left CFAE Area
RSPV
LSPV
LIPV
RIPV
Mitral Annulus
Inferior-Posterior CFAE Area
Anterior Right CFAE Area


Correlation Between Locations of CFAE and GP
Parox AF
Response to HFS
Positive Vagal Response
Negative Vagal Response
PA Projection
RAO Projection
CFAE Segments (15-80 ms)
3
≤10
≥40
58
Superior Left GP
Superior Left CFAE Area
Anterior Right GP
LSPV
RSPV
LSPV
LIPV
RIPV
Mitral Annulus
Inferior Right GP
Inferior Left GP
Inferior-Posterior CFAE Area
Anterior Right CFAE Area


PA Projection
Before GP Ablation
RAO Projection
Short Segments (duration 15-80ms) per 2.5 Sec
GP
CFAE
CFAE
GP
GP
CFAE
Not CFAE
0
≤10
≥40
CFAE
59
After GP Ablation
Not CFAE
Not CFAE
Not CFAE
0
Not CFAE
≤10
≥40
CFAE
45

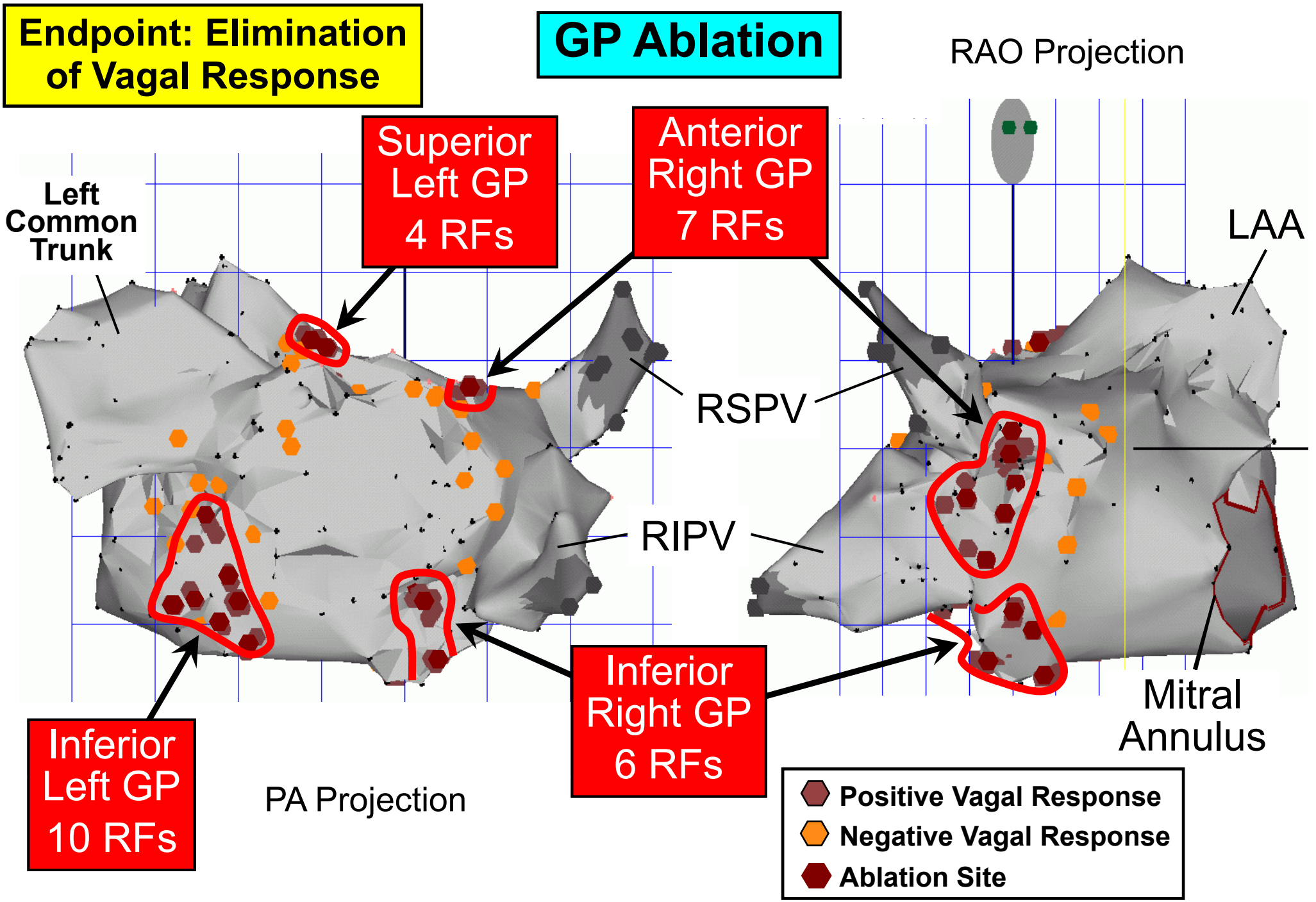

PA Projection
Before GP Ablation
RAO Projection
Short Segments (duration 15-80ms) per 2.5 Sec
GP
CFAE
CFAE
GP
GP
CFAE
Not CFAE
0
≤10
≥40
CFAE
59
After GP Ablation
Not CFAE
Not CFAE
GP Ablation Eliminated Most CFAE
Not CFAE
0
Not CFAE
≤10
≥40
CFAE
45

Area of Fractionation (*CFAE*)

≥35 segments/2.5 seconds

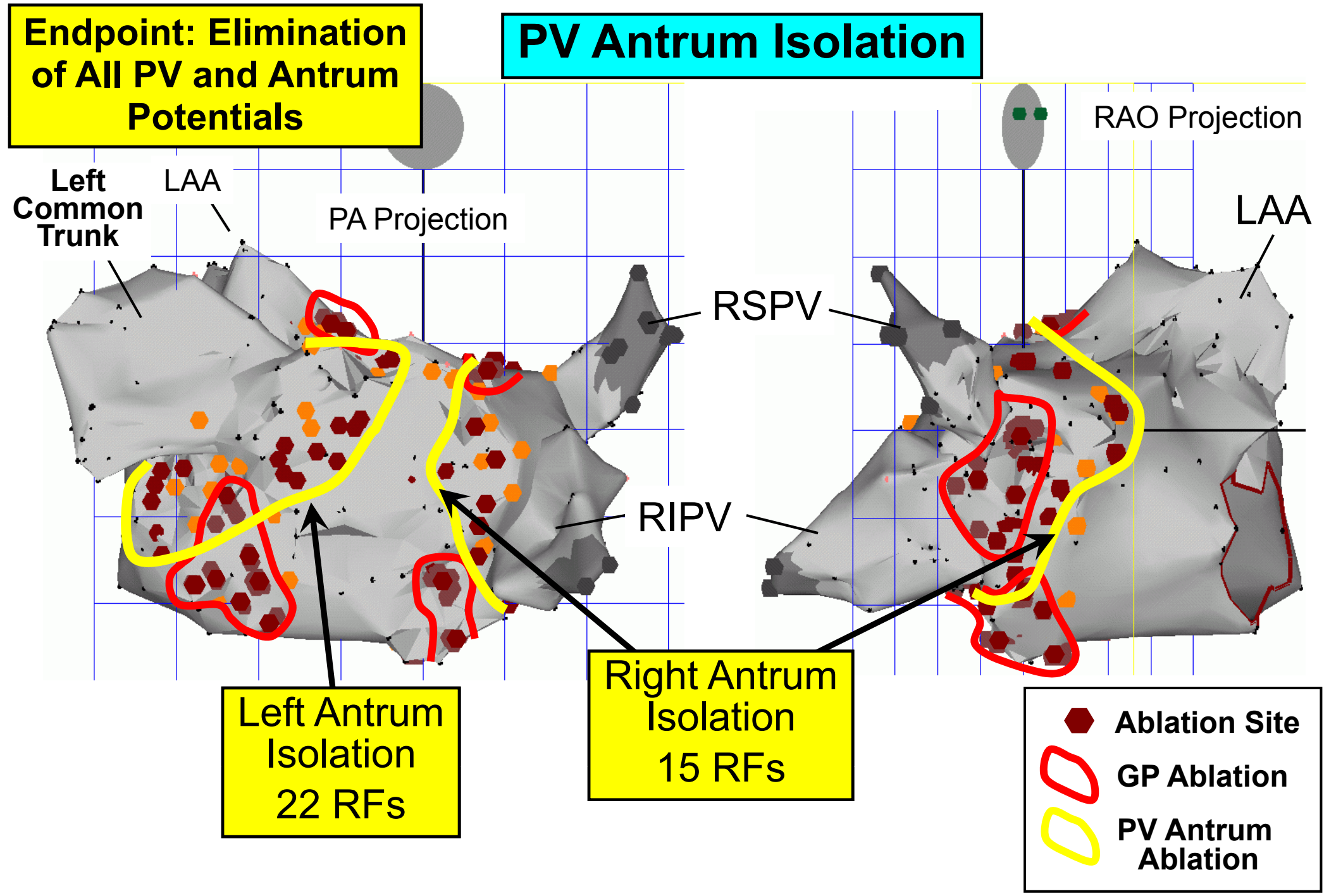
Before GP Ablation	After GP Ablation	
26.9 cm^2	2.3 cm^2	$p < 0.001$

n = 5 patients


Endpoint: Elimination of Vagal Response
GP Ablation
RAO Projection
Superior Left GP 4 RFs
Anterior Right GP 7 RFs
Left Common Trunk
LAA
RSPV
RIPV
Inferior Right GP 6 RFs
Inferior Left GP 10 RFs
Mitral Annulus
PA Projection
Positive Vagal Response
Negative Vagal Response
Ablation Site

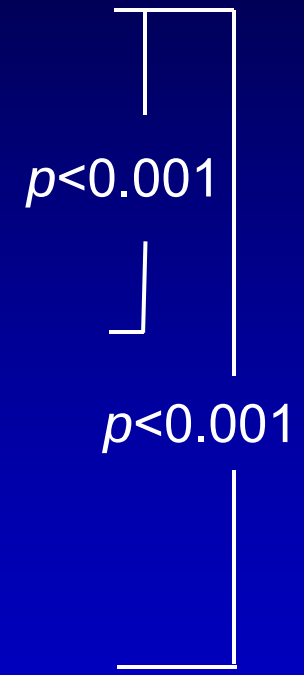
Spontaneous PV Firing (No Isoproterenol)

Before Ablation	54/83 pts (65%)	$p<0.001$
Post-GP Ablation	12/83 pts (15%)	

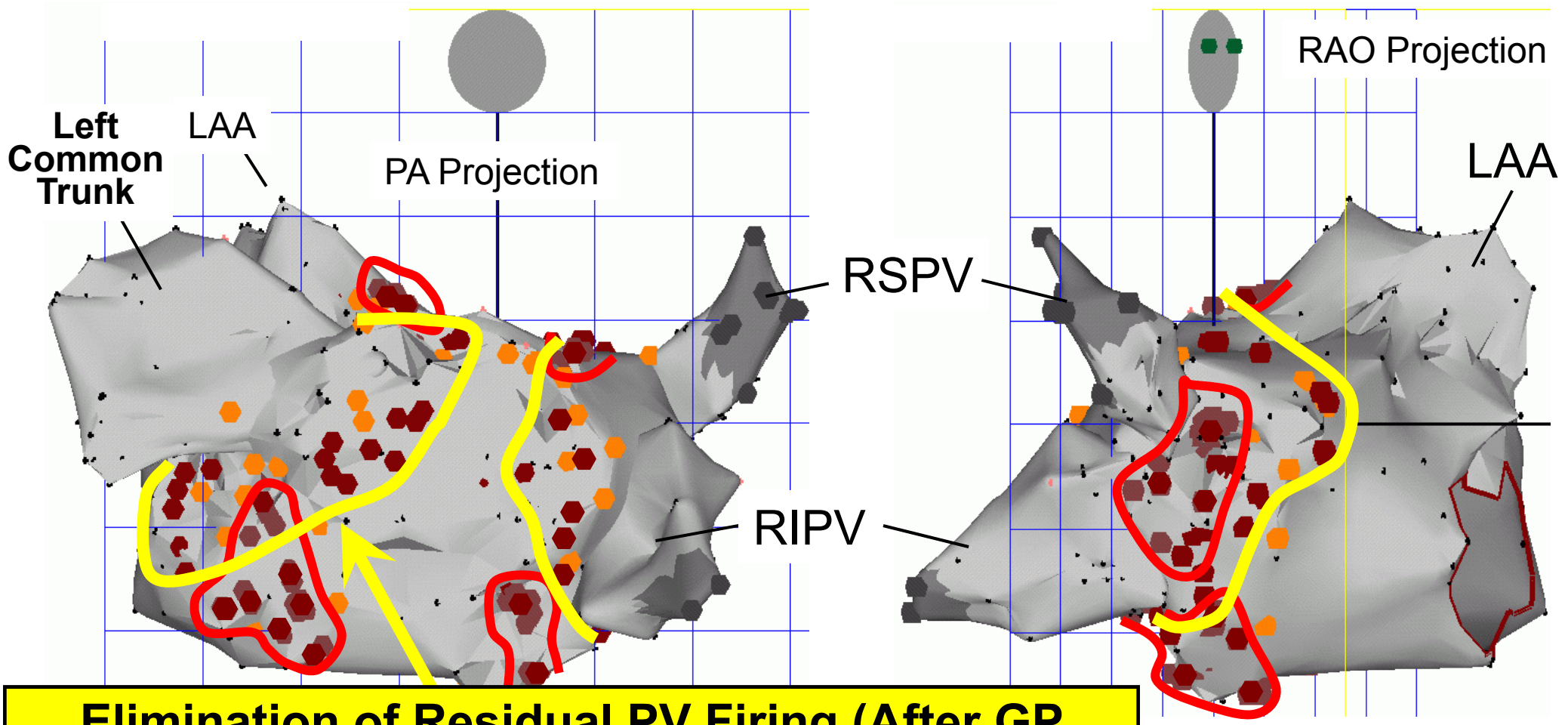

Endpoint: Elimination of All PV and Antrum Potentials
PV Antrum Isolation
Left Common Trunk
LAA
PA Projection
RSPV
RIPV
RAO Projection
LAA
Left Antrum Isolation 22 RFs
Right Antrum Isolation 15 RFs
Ablation Site
GP Ablation
PV Antrum Ablation

Spontaneous PV Firing (No Isoproterenol)

Before Ablation	54/83 pts (65%)
Post-GP Ablation	12/83 pts (15%)
Post-Antrum Isolation	0/83 pts (0%)



PV Antrum Isolation

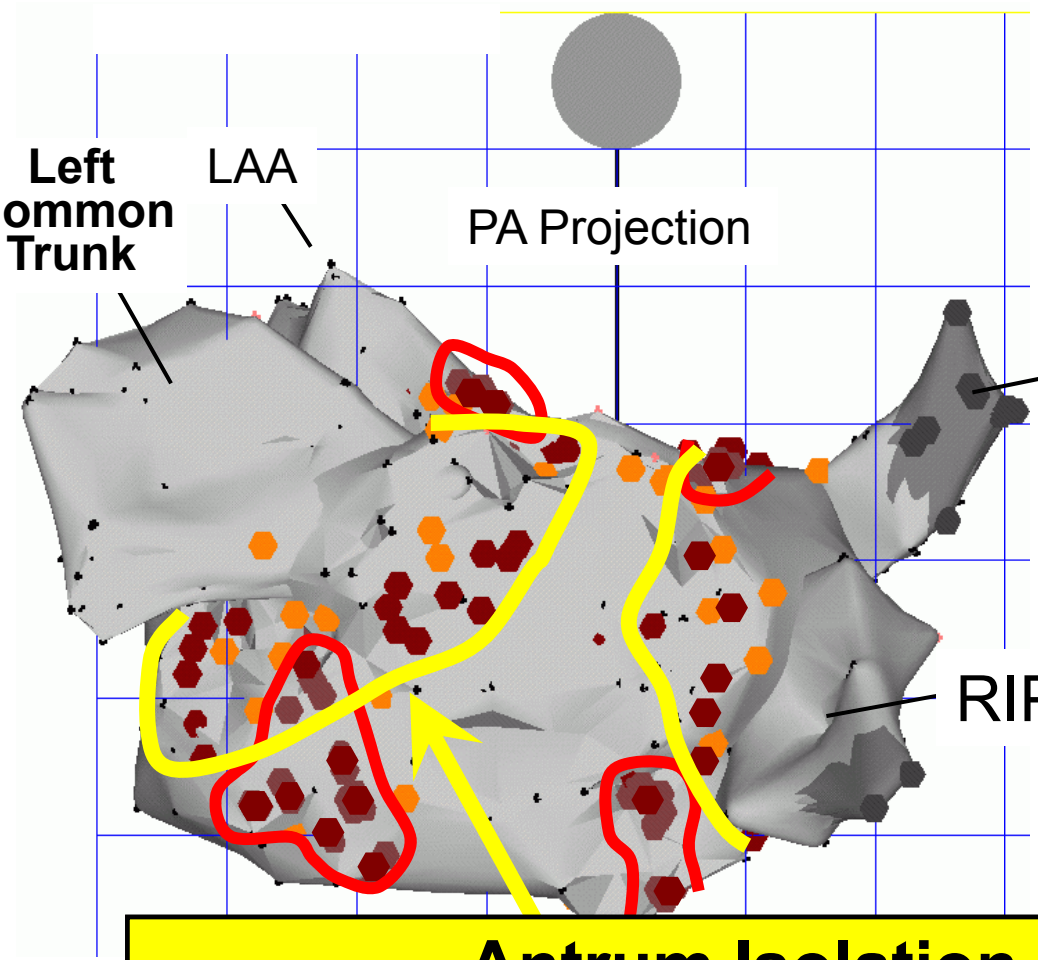


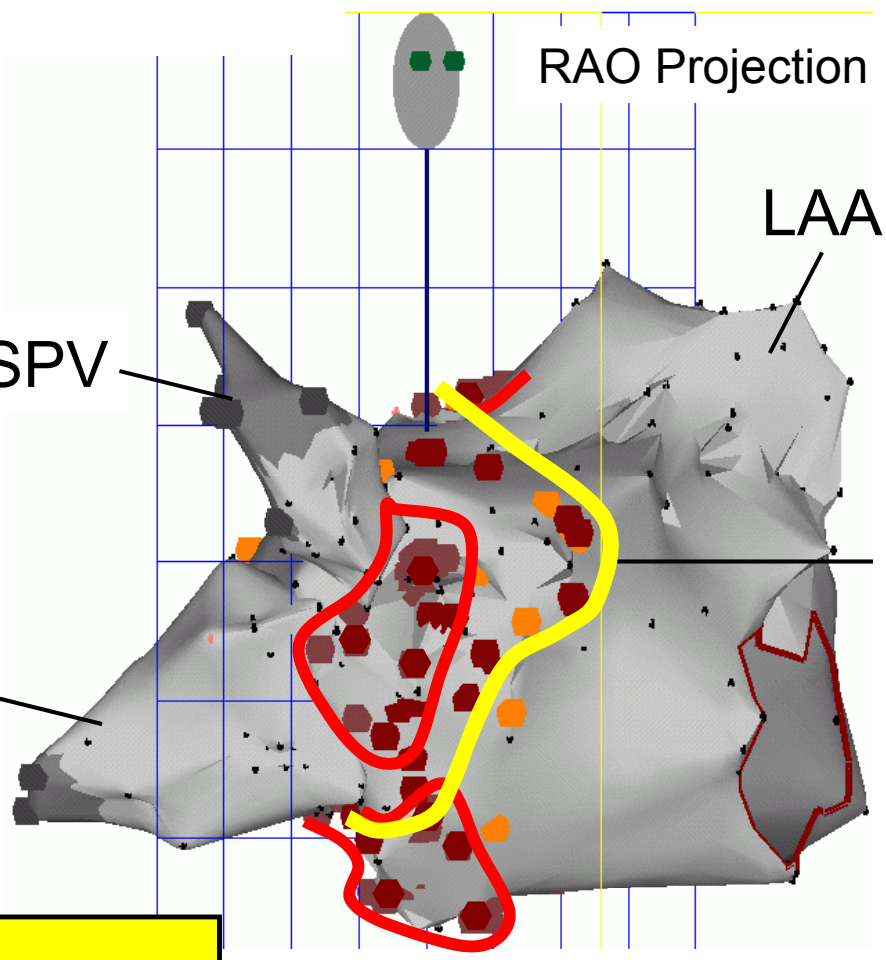
Elimination of Residual PV Firing (After GP Ablation) by Antrum Isolation Suggests Antrum Isolation Blocks Axons from Remaining GP

(Indicates GP Ablation Was Incomplete)

- Ablation Site
- GP Ablation
- PV Antrum Ablation

PV Antrum Isolation





Antrum Isolation Blocks Axons from GP

(But Axons Regenerate! - So Ablate as Much GP Tissue as Feasable!)

- Ablation Site
- GP Ablation
- PV Antrum Ablation