PJRT (Pediatric EP Journal Review by Trainees)

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Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

Background: ICDs have been shown to significantly reduce risk of sudden cardiac death (SCD) and all-cause mortality in adults with ischaemic heart disease and LV systolic dysfunction. The benefit of ICDs in chronic non-ischaemic heart disease is limited.

Objectives: To determine the benefit of ICD implantation in adults with non-ischaemic heart disease

Methods:

- Randomized control trial including symptomatic patients (NYHA class II or III, or IV if CRT planned) with non-ischaemic systolic heart failure (LVEF <35%) and elevated NT-pro-BNP (>200 ng/mL). Nonischaemic systolic heart failure was defined as normal coronary angiography, chest CTA, or nuclear myocardial perfusion imaging. Patients with permanent atrial fibrillation, resting HR >100 bpm, or renal failure were excluded.
- Patients were randomly assigned in1:1 ratio to either ICD group (556) or the control group (560, standard medical care).
- Primary outcome was all-cause mortality. Secondary outcomes were SCD and cardiovascular death.

Results:

- After a median follow-up of 67.6 months, the rate of all-cause mortality was 21.6% in the ICD group and 23.4% in the control group (HR 0.87, 95% CI 0.68-1.12; p=0.28).
- SCD occurred in 4.3% in the ICD group and 8.2% in the control group (HR 0.50, 95% CI 0.31-0.82; p=0.005).
- Device infection occurred in 4.9% in ICD group and 3.6% in control group (p=0.29)
- Inappropriate shocks occurred in 33 patients (5.9%), 28 due to Afib, 4 due to oversensing, and 1 due to SVT not AFib

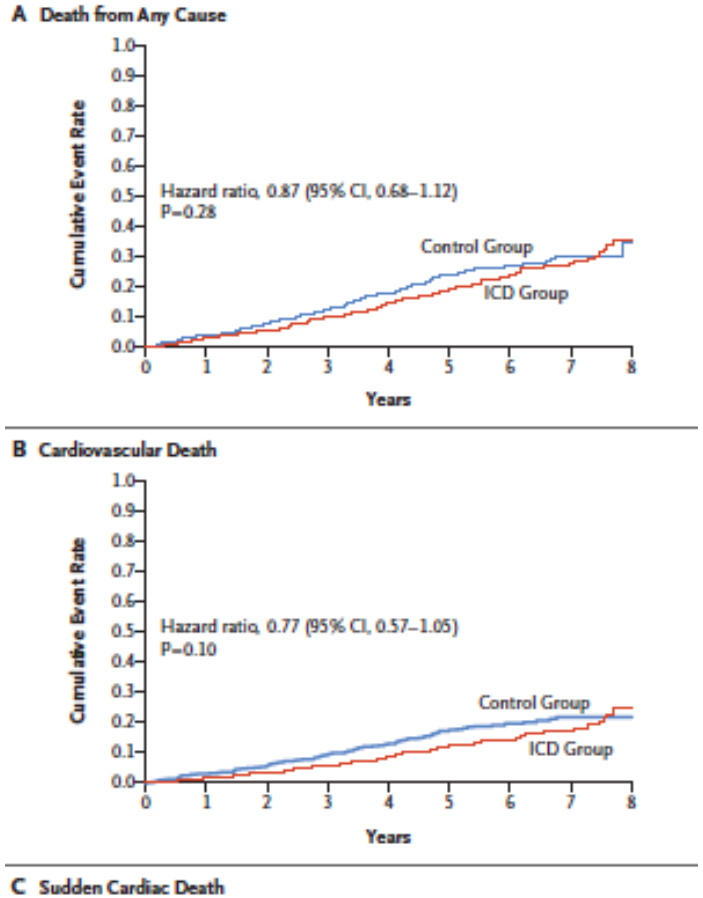


Figure 3. Rate of Death from Any Cause (Primary Outcome) in Prespecified Subgroups.

Subgroup	ICD Group	Control Group	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no.				
Age					0.009
<59 yr	17/167	34/181	0.51 (0.29–0.92)	0.02	
≥59 to <68 yr	36/173	50/202	0.75 (0.48–1.16)	0.19	
≥68 yr	67/216	47/177	1.19 (0.81–1.73)	0.38	
Sex					0.66
Female	22/151	23/156	1.03 (0.57–1.87)	0.92	
Male	98/405	108/404	0.85 (0.64–1.12)	0.24	
NT-proBNP					0.06
<1177 pg/ml	32/266	74/268	0.59 (0.38–0.91)	0.02	
≥1177 pg/ml	57/292	88/290	0.99 (0.73–1.36)	0.96	
LV ejection fraction					0.69
<25%	70/264	65/242	0.87 (0.62–1.22)	0.42	
≥25%	50/292	66/318	0.79 (0.54–1.14)	0.21	
Estimated GFR					0.86
<73 ml/min/1.73 m²	75/272	80/278	0.88 (0.64–1.21)	0.42	
≥73 ml/min/1.73 m²	45/283	50/280	0.82 (0.55–1.23)	0.33	
NYHA functional class					0.71
II	52/297	54/300	0.92 (0.63–1.35)	0.68	
III–IV	68/259	77/260	0.81 (0.58–1.13)	0.21	
Heart failure duration					0.73
<18 mo	31/254	36/277	0.88 (0.54–1.43)	0.61	
≥18 mo	89/301	95/283	0.81 (0.61–1.09)	0.17	

Conclusions:

- ICD implantation as primary prevention did not decrease the risk of all-cause mortality in adults with non-ischaemic heart failure; *in subgroup analysis, those < 59 y/o in the ICD group had a lower risk of all-cause mortality compared to controls*.
- ICD implantation did not decrease risk of cardiovascular death, but did decrease risk of SCD in ICD group.

Implications for Pediatric EP:

- The subgroup analysis suggests that ICD as primary prevention may be of benefit in reducing risk of all-cause mortality and SCD in a younger patient population Further study is required to determine if this applies to PACES' patient populations (eg. adolescents or adult ACHD patients).

Catheter Ablation of Atypical Atrioventricular Nodal Reentrant Tachycardia

Circulation. 2016;134:1655–1663. DOI: 10.1161/CIRCULATIONAHA.116.024471 November 22, 2016

Background: Data on the optimal ablation strategy for atypical AVNRT is scare, owing to its low prevalence. This is important as atypical AVNRT is associated with lower successful ablation rates. Conventional slow pathway ablation has been reported as safe and effective for atypical AVNRT; in most studies, ablation was guided by identifying the slow pathway through consideration of retrograde atrial activation or other techniques. These approaches, however, may results in risk of complete heart block.

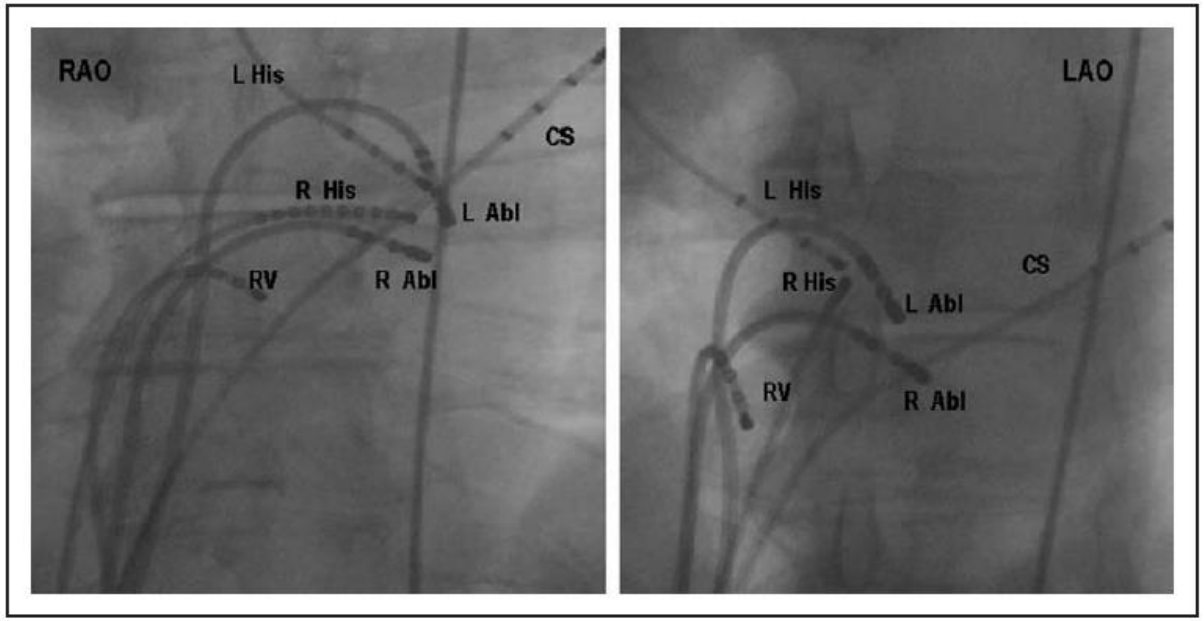
Objectives: To assess the efficacy and safety of conventional slow pathway ablation (as applied for typical AVNRT) in atypical AVNRT (*in what is reported as the largest published series of atypical AVNRT)*

Methods:

- Multicenter international study involving adults with symptomatic AVNRT with at least 1 episode every 2 months
- All patients with a diagnosis of atypical AVNRT subjected to catheter ablation were compared to an age- and sex-matched control group of typical AVNRT patients
- Of 2079 patients with AVNRT subjected to slow pathway ablation, 113 patients had atypical AVNRT or coexistent typical/atypical AVNRT (mean age 48.5 +/- 18.1 yrs, 68 female).

Results:

- Fluoroscopy and RFA times did not differ between atypical and typical groups (20.3 +/- 12.2 vs 20.8 +/- 12.9 min, p=0.72 and 5.9 +/- 5.0 vs 5.5 +/- 4.5 min, p=0.65, respectively).
- Slow pathway ablation was accomplished from the right septum in 110 patients, left septum in 3 patients.
- There was no need for additional ablation lesions at other anatomic sites, nor was there any complete heart block reported
- Recurrence rates were 5.6% in atypical group and 1.8% in typical group in the 3 months following ablation (p=0.167).



Slow pathway mapping. Right and left-sided mapping of the slow pathway in the RAO and LAO projections. The left-sided ablation catheter delivered via transseptal approach to map the inferoposterior septum.

Table 2. Ablation Characteristics

	Atypical AVNRT n=113	Typical AVNRT n=113	*P* Value
Fluoroscopy time, min	20.112.2	20.8±12.9	0.730
Radiofrequency delivery time, min	5.9±5.0	5.5±4.5	0.650
Junctional rhythm during radiofrequency, patients	110	111	1.000
Atrioventricular block, patients	0	3 (transient)	0.247

Conclusions: Conventional ablation at the anatomic area of the slow pathway is the therapy of choice for symptomatic AVNRT, regardless of whether it is typical or atypical AVNRT, with similar fluroscopy and RFA times and no significant difference in the risk of recurrence.

Limitations and Implications for Pediatric EP:

- Comparison unbalanced as matched atypical AVNRT undergoing slow pathway ablation to typical AVNRT undergoing slow pathway ablation
- Follow-up period short and differences in recurrence may be statistically higher in atypical AVNRT in longer term
- Did not assess newer ablation techniques involving electroanatomic mapping, which is frequently used in pediatrics

Genotypic and Phenotypic Predictors of Complete Heart Block and Recovery of Conduction after Surgical Repair of Congenital Heart Disease

Heart Rhythm, Article in press

Laura Murray, Andrew H.Smith, C.Flack, Kim Crum, Jill Owen, Prince J.Kannankeril

Background: Genetic mutation in GJA5 have been linked to a familial form of progressive AV block. GJA5 encodes for Connexin-40 protein that is primarily expressed in the distal part of the AV conduction axis and contributes to the rapid conduction of the His bundle[1,2].
Complete heart block (CHB) is also a major complication of congenital heart surgery. While postoperative CHB has been perceived to be related to the anatomical substrate and surgical technique, there is little data on the role of genetics in CHB incidence and recovery.

Objective: To identify the predictors of CHB development and recovery after congenital heart surgery.

Methods: Single center retrospective observational study. Pre-operative and perioperative data were collected on all patients undergoing surgical repair over the past 9 years. All patients underwent genotyping of the common missense GJA5 mutation (rs10465885).

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[1] Jansen J.A., van Veen T.A., de Bakker J.M., van Rijen H.V. Cardiac connexins and impulse propagation. J Mol Cell Cardiol. 2010;48:76–82
[2] Boyett M.R., Inada S., Yoo S. Connexins in the sinoatrial and atrioventricular nodes. Adv Cardiol. 2006;42:175–197

Results:

- Among 1199 patients who underwent surgical repair, 56 patients (4.7%) developed CHB postoperatively.
- Preoperative factors associated with development of postoperative CHB were age and weight at surgery, preoperative use of digoxin, surgical era, and missense mutation in GJA5.
- Homozygous mutation (rs10465885 TT) genotype is an independent predictor of developing CHB (odds ratio 2.1).
- Of the 56 patients with CHB, 35 patients (63%) showed recovery of 1:1 AV nodal conduction.
- Junctional acceleration in the first 48 hours and intermittent AV block were predictors of AV nodal recovery. GJA5 mutation was not linked to recovery from CHB.

Limitations:

This is an observational study from a single center. For this genetic association to be proven a causation, it needs to replicated in an independent cohort. The question remains as to whether improved understanding of these factors would impact clinical decision-making.

Conclusion:

Homozygous GJA5 mutation is an independent predictor for developing postoperative CHB but is not linked to AV nodal recovery. Patients who had junctional acceleration or intermittent AV nodal conduction are more likely to recover.

Reviewer's Comments:

AV heart block remains a postoperative complication with an incidence that hasn't changes over the last decade. This article presents an interesting view of the interactions between clinical factors and genetic disposition in creating the risk for postoperative heart block.

Clinical Aspects of Type 3 Long-QT Syndrome

An International Multicenter Study

Circulation. 2016 Sep 20;134(12):872-82.

Wilde A, Moss A, Kaufman E, Shimizu W, Peterson D, Benhorin J, Lopes C, Towbin J, Spazzolini C, Crotti L, Zareba W, Goldenberg I, Kanters J, Robinson J, Qi M, Hofman N, Tester D, Bezzina C, Alders M, Aiba T, Kamakura S, Miyamoto Y, Andrews M, McNitt S, Polonsky B, Schwartz P, Ackerman M

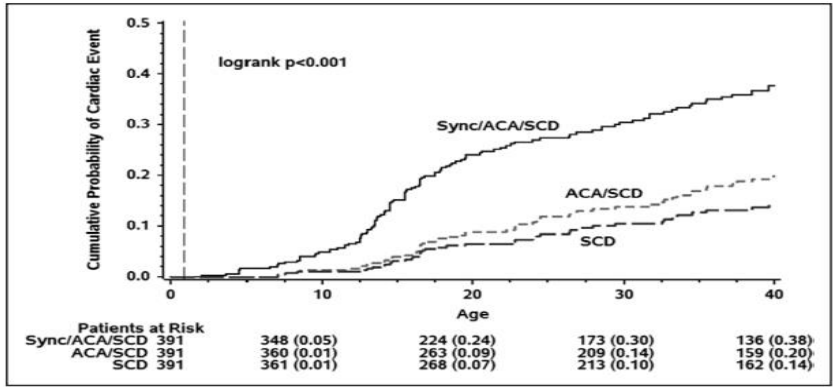
Background: Type 3 Long-QT syndrome (LQT3) is caused by a gain-of-function mutation in the SCN5A-encoded sodium channel. Risk stratification of LQT3 is not well defined. The effectiveness of b-blocker therapy has not been studied in a large cohort.

Objective: To determine the factors associated with cardiac events (CE) in patients with SCN5A-mediated LQT3 as well as the efficacy of β-blocker therapy in this group.

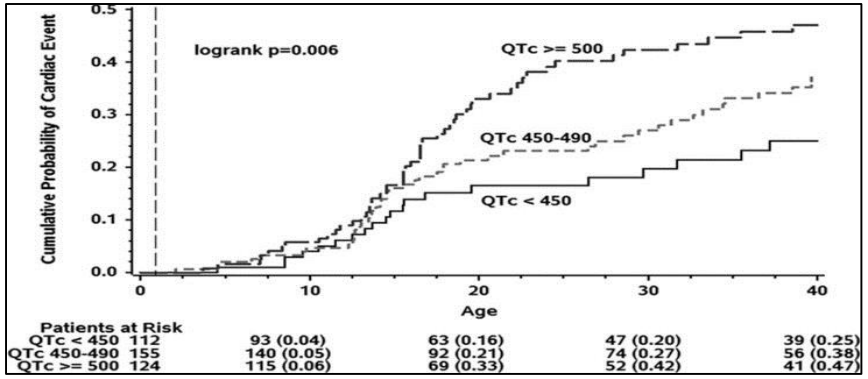
Methods: The study population were patients (LQT3 with positive SCN5A testing) enrolled in 7 LQTS registries internationally. Phenotype and genotype parameters were acquired at enrollment, and follow-up was censored at 41 years of age.

Results:

- The LQT3 cohort included 391 patients (after excluding patients developing CE in the first year of life). 118 patients (30%) developed CE by 40 years of age.
- The risk for a first event increased rapidly during adolescence and continued to increase in both sexes, although higher in females, during the adult years.
- β-blockers reduced the risk of CE by 80% among females (*P*=0.03) and by 49% among males (not significant, given their lower event-rate).



Kaplan-Meier cumulative probability of first LQT3-triggered cardiac event for combinations of syncope, ACA, and SCD



Kaplan-Meier cumulative probability of cardiac events (syncope/aborted cardiac arrest/LQT3-related sudden cardiac death, whichever comes first) for 3 QTc ranges, conditional on event-free survival to age 1 year.

• When the end point was restricted to aborted cardiac arrest (ACA) or sudden cardiac death (SCD), time-dependent syncope doubled the risk for the more malignant cardiac events (*P*=0.02)
• Mutation type and mutation location did not have a significant effect on outcome, although patients with particular mutations (E1784K and D1790G) had a rather benign clinical course.

Limitations:

The main limitation is the relatively small number of cardiac events particularly in males as well as the small number of treated patients (only 30% were on β-blockers). CE after 41 years of age was also not evaluated.

Conclusion:

A high-risk subpopulation of LQT3 patients with QTc ≥500 ms and a history of syncope can be identified. β-blocker therapy significantly reduces the risk for cardiac events. High-risk patients may require adjunctive therapy.

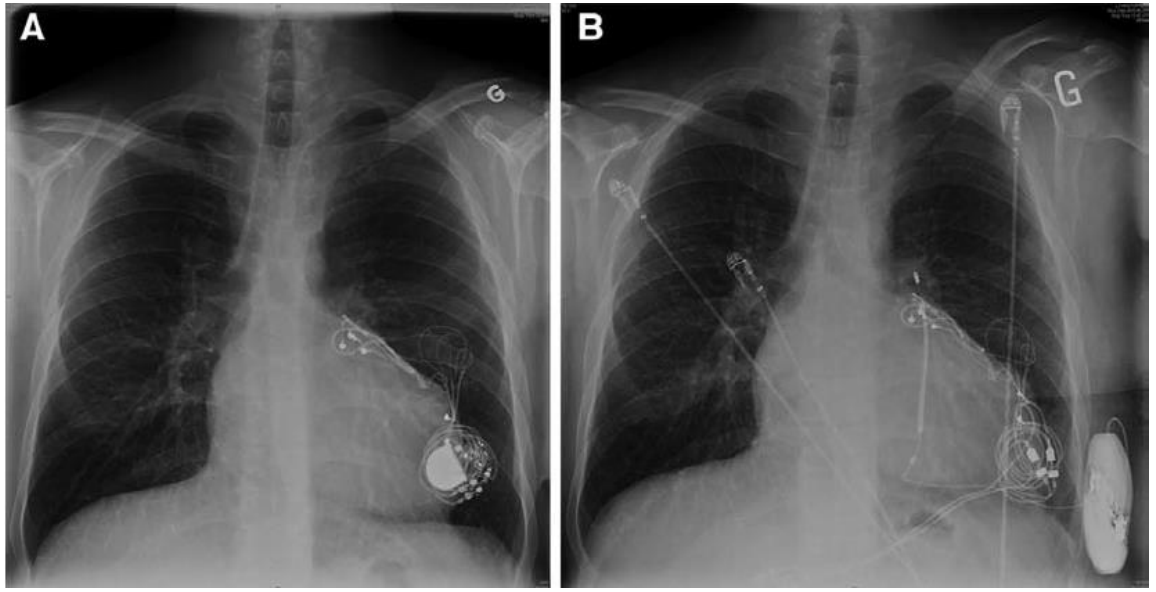
Reviewer's Comments:

This is the largest LQT3 cohort study highlighting the population with the highest risk of acute events. Most important, it provides evidence that β-blocker therapy is not pro-arrhythmic, but clearly protective.

Clinical Experience With the Subcutaneous Implantable Cardioverter–Defibrillator in Adults With Congenital Heart Disease

Jeremy P. Moore, MD, MS; Blandine Mondésert, MD; Michael S. Lloyd, MD; Stephen C. Cook, MD; Ali N. Zaidi, MD; Robert H. Pass, MD; Anitha S. John, MD, PhD; Frank A. Fish, MD; Kevin M. Shannon, MD; Jamil A. Aboulhosn, MD; Paul Khairy, MD, PhD; from the Alliance for Adult Research in Congenital Cardiology (AARCC)

Moore, J et al: Clinical experience with the subcutaneous implantable cardioverter-defibrillator in adults with congenital heart disease. Circ Arrhythm Electrophysiol 2016 Sep; 9(9).



- Subcutaneous ICDs may be an option for adult CHD patients in whom transvenous placement is not an option: anatomic constraints, intra-cardiac shunting, lack of vascular access, higher rate of lead malfunction
- Hypothesis: S-ICD are most useful in ACHD patients without transvenous access, will have reliable conversion of induced ventricular arrhythmias at implant and will have reliable rhythm discrimination during follow-up
- Inclusion criteria:
  - Age > 18 years at time of implant
  - Congenital heart disease with or without surgical repair
  - Boston Scientific S-ICD: SQ-RX 1010 (n=15) or EMBLEM model A209 (n=6)
- 7 patients had pre-existing epicardial (n=6, 4 PM, 2 ICD) or transvenous (n=1, ICD) device in place
- 6 of 7 had pacing continued post-implant

Table 1. ACHD Population Characteristics

Characteristic	N=21
Age, y	34 (24–41)
Body mass index, kg/m²	24.1 (20.8–26.7)
Congenital/surgical anatomy	
Single ventricle*	11
DTGA, atrial switch	2
TOF	2
Aortic valve disease	2
CCTGA, LV-to-PA conduit	1
Ebstein anomaly	1
Hypoplastic RV	1
Congenital PS	1
Male, n (%)	13 (62)

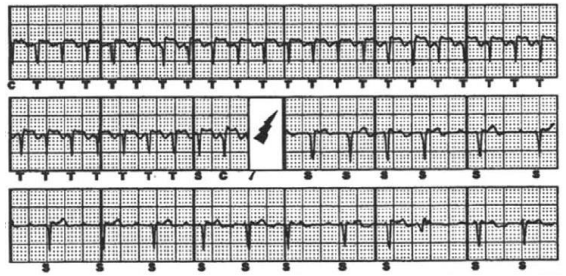
Table 2. S-ICD Characteristics

Characteristic	N=21
ICD indication	
Primary prevention	14 (67)
NSVT	7
Inducible VT	8
Syncope	9
Depressed systemic ventricular EF	8
Prolonged QRS duration	2
Other	3
Secondary prevention	7 (33)
Aborted cardiac arrest	3
Sustained VT	4
General anesthesia	12
Conscious sedation	9
VT/VF induced at implant	17 (81)
Defibrillation successful	17 (81)
Implant conditional zone, ms	200 (190 - 210)
Implant shock zone, ms	225 (220 -238)
Hospital length of stay, days	1.5 (1 - 6)

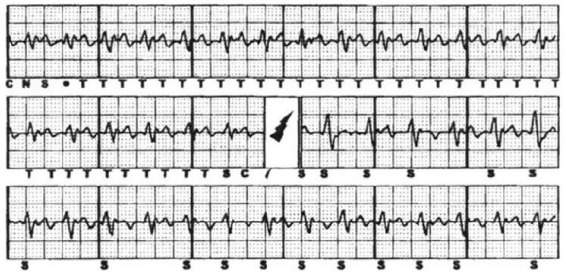
Results

- Reasons for S-ICD: limited transvenous access to sub-pulmonary ventricle (n=10), intra-cardiac shunt (n=5), lack of vascular access (n=3), patient/physician preference (n=2), pulmonary hypertension (n=1)
- 18/21 (86%) underwent defibrillation threshold testing at implant; 3 were under operator discretion, 1 VF could not be induced
- 15/17 (88%) had successful DFT at 65J with remaining 2 successful at 80J
- 1 patient received 15 total appropriate shocks and underwent catheter ablation and medical therapy
- 2 deaths and 2 transplants during follow-up period (range 3-19 months)
  - 1 from pulmonary hemorrhage
  - 1 had an asystolic arrest and had inappropriate shocks from oversensing of asystole and agonal rhythm
    - Double-inlet left ventricle s/p intra-atrial Fontan completion with syncope and inducible VT at electrophysiology study

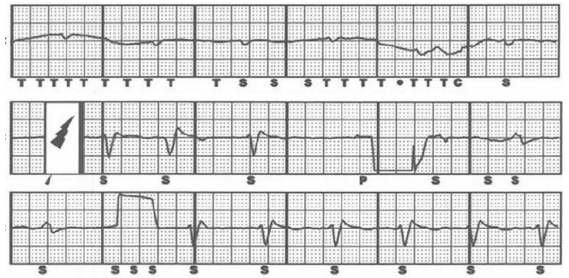
3 patients with inappropriate shocks



SVT with ventricular rate > conditional zone



T-wave oversensing



Oversensing of low-amplitude artifact due to presence of subcutaneous air

Conclusions:

- Most frequent indication is lack of venous access to sub-pulmonary ventricle
- Reliable detection and conversion of ventricular arrhythmias can be achieved despite variable ACHD anatomy
- Rhythm discrimination appears to be acceptable 1 year post implant
- Co-existing PM or ICD were not found to be a cause of sensing abnormalities
- Unipolar pacing should be avoided with S-ICD as it can interfere with detection of ventricular arrhythmias

Reviewer Comments:

- While these are small numbers, study shows that S-ICD is a reasonable consideration in the ACHD population, even in the presence of existing devices

Use of dofetilide in adult patients with atrial arrhythmias and congenital heart disease: A PACES collaborative study

Iqbal El-Assaad, MD,[1,*] Sadeer G. Al-Kindi, MD,[1,†] JoEllyn Abraham, MD,[‡] Shubhayan Sanatani, MD, FHRS,[§] David J. Bradley, MD, FHRS,[¶] Colby Halsey, MD,[‖] Ian H. Law, MD, FHRS,[#] Seshadri Balaji, MBBS, FRCP(UK), PhD,[**] Ira Shetty, MD,[††] Peter F. Aziz, MD, FHRS[‡‡]

El-Assaad, I et al: Use of dofetilide in adult patients with atrial arrhythmias and congenital heart disease: A PACES collaborative study. Heart Rhythm 2016 Oct; 13(10): 2034-9.

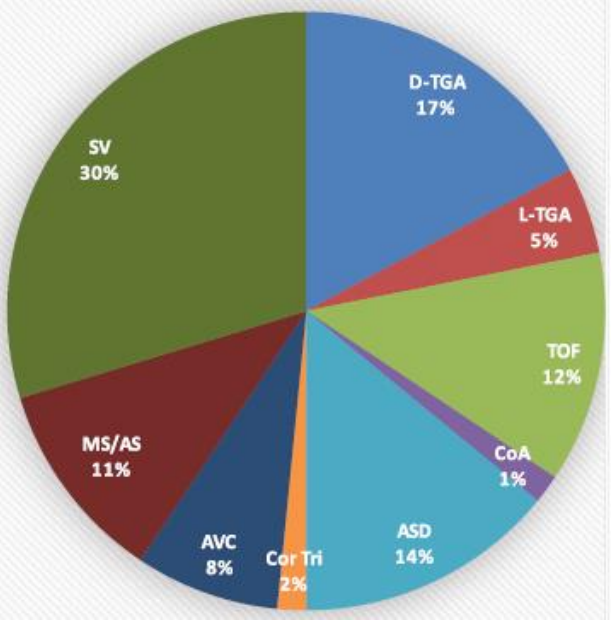
- Dofetilide is a class III anti-arrhythmic that blocks rapidly acting delayed potassium rectifier currents and prolongs the effective refractory period of atrial and ventricular myocardial cells
- Dofetilide is widely used in adult patients with atrial fibrillation or flutter
- PACES/HRS expert consensus for atrial arrhythmias in ACHD lists dofetilide as a first-line alternative to amiodarone
- Goal of the study: evaluate inpatient and outpatient utility and safety profile of dofetilide in ACHD patients

Methods

- Multi-center (5) study through PACES; retrospective chart review from 2001-2015 of pharmacy records for dispensing of dofetilide
- Primary outcome: major inpatient adverse events including death at initiation, renal failure, QTc prolongation, torsades de pointes
- Secondary outcomes: percentage of patients with conversion and maintenance of normal sinus rhythm

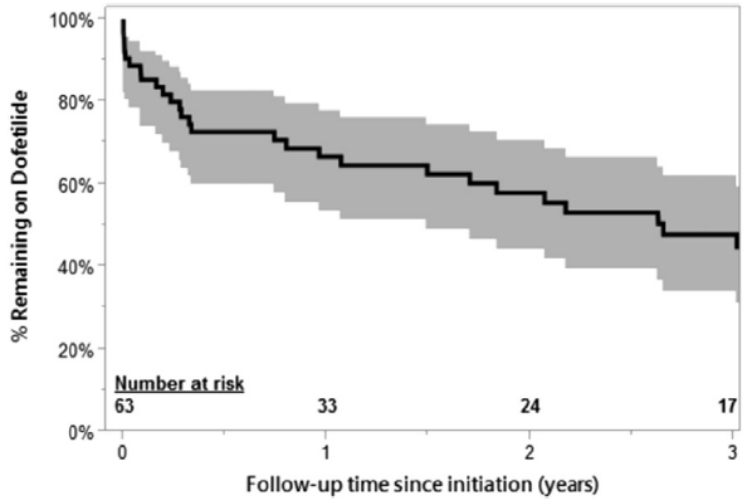
Table 1 Baseline patient characteristics (N = 64)

Characteristic	Value
Age (y)	42 ± 14
Arrhythmia	
Atrial fibrillation	35 (55)
IART	29 (45%)
History of catheter ablation	31 (48)
> 1 ablation	13 (20)
Pacemaker or ICD	32 (50)
Prior antiarrhythmic medications	
β-Blocker	53 (83)
Amiodarone	23 (36)
Digoxin	21 (33)
Sotalol	15 (23)
Propafenone	7 (11)
Flecainide	3 (5)
Others	6 (9)
Average number of medications	2 ± 1
Starting dofetilide dose	
125 μg twice daily	3 (5)
250 μg twice daily	23 (36)
500 μg twice daily	38 (59)



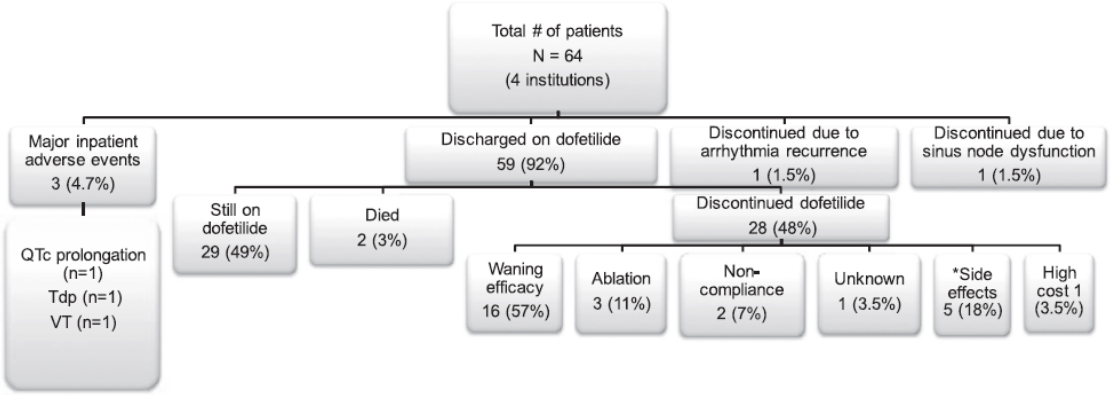
Results

- 3 inpatient adverse events: QTc prolongation, VT and TdP (both in setting of significant QTc prolongation)
- 13 patients (20%) required dose reduction secondary to QTc prolongation
- 59 patients (62%) discharged on dofetilide; 40 patients (68%) had adequate and 19 (32%) had partial rhythm control
- Over median follow-up of 3 years, 29 patients (49%) remained on dofetilide and had resolution or improvement in AF/IART
- Reasons for discontinuing: waning efficacy and side effects (anxiety, palpitations, diarrhea, VT, TdP most common)
- QTc 461 ± 37 ms → 490 ± 39 ms (P<0.001); no statistically significant difference between starting doses
- 2 deaths during follow-up period: out-of-hospital deaths without significant change in creatinine or QTc



Conclusions:

- At 3 years of follow-up, nearly half of patients remained on dofetilide with complete or partial rhythm control
- Pro-arrhythmic events (4.7%) similar to other studies; though 2 deaths may have been related to sudden cardiac death
- Dofetilide was associated with significant QTc prolongation which did not differ based on initial dosage
- Initial loading and dose adjustments should ideally be performed on an inpatient basis
- Creatinine clearance and electrolytes need to be monitored closely



Reviewer Comments:

- Overall there are small numbers and the group is heterogeneous
- 2 out-of-hospital deaths are concerning despite stable creatinine and QTc

Fhf2 gene deletion causes temperature-sensitive cardiac conduction failure.

Nature Communincations. 2016 Oct 4;7:12966.
David S. Park, Akshay Shekhar1, Christopher Marra, Xianming Lin, Carolina Vasquez, Sergio Solinas,
Kevin Kelley, Gregory Morley, Mitchell Goldfarb & Glenn I. Fishman.

Background:

The association between increased core body temperature and arrhythmias, in particular in Brugada Syndrome patients, have been well documented but poorly understood mechanistically. While there has been much investigation into SCN5A, the pore-forming subunit of the cardiac sodium channel Na_V 1.5, no single unifying mechanism for fever-induced arrhythmias has been uncovered.

Voltage-gated sodium channels also assemble with a variety of other proteins, such as FHF2 (Fibroblast growth factor Homologous Factor 2) which help to modulate channel activation, thus providing another potential mechanism for fever-induced rhythm disturbances.

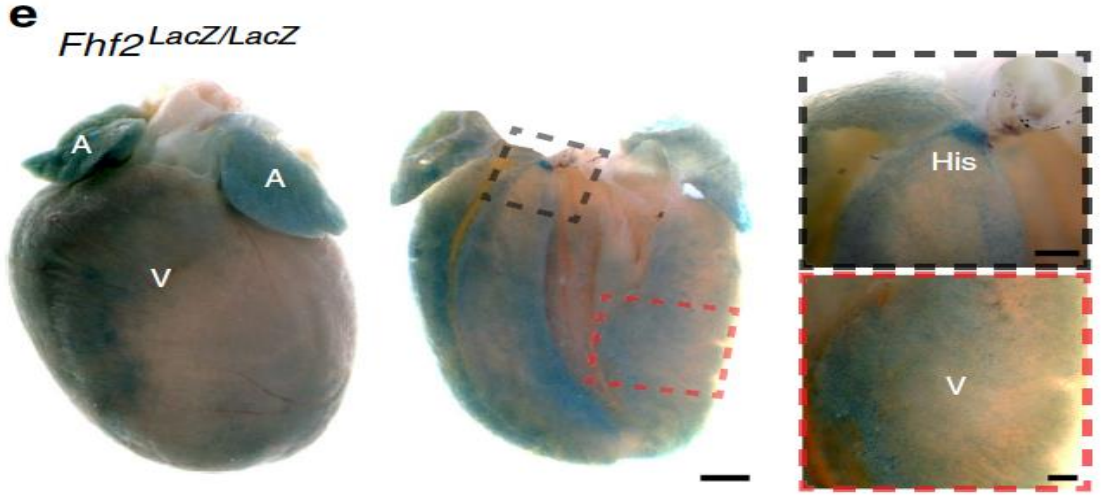


Figure 1e. Whole-mount X-Gal staining of a Fhf2LacZ/LacZ heart. LacZ was detectable throughout the heart, including atria (A), ventricles (V) and bundle of His (His).

Summary:

In this study, *Park et al.* demonstrate that mice with systemic loss of fibroblast growth factor homologous factor 2 (Fhf2KO), while similar to controls in euthermic conditions (37°C), demonstrate hyperthermia (40°C)-induced conduction defects resulting in progressive P and QRS wave prolongation and coved-type ST elevations with T wave inversions, reminiscent of the Type 1 Brugada EKG pattern. This phenotype was completely reversible with temperature normalization and, consistent with the Brugada phenotype, Fhf2KO mice also demonstrate increased sensitivity to Flecainide. The authors go on to show that the observed phenotype is intrinsic, at least in part, to defective cardiomyocyte excitability at elevated temperatures through explantation, patch-clamp and additional transfection experiments. Specifically, loss of Fhf2 results in faster open-state and closed-state Na_v 1.5 inactivation within cardiomyocytes; with the Fhf2 mutation and hyperthermia combining to show a more severe reduction in channel availability. Finally, *Park et al.* validated their *in vivo* phenotype by incorporating their observed data into a previously generated mouse ventricular cardiomyocyte computational model.

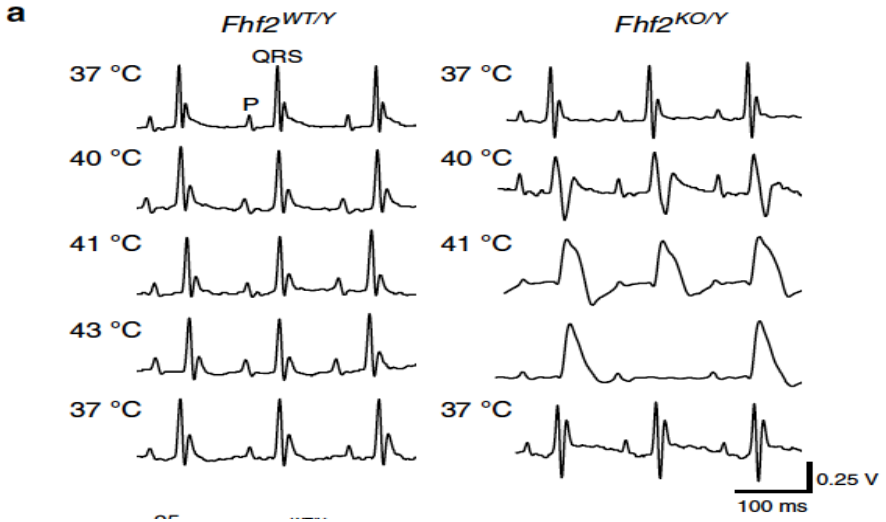


Figure 2a. Representative surface ECG traces of adult (8–12 wk) Fhf2WT/Y and Fhf2KO/Y mice at different core temperatures. Fhf2KO/Y mice, while comparable to WT at room temperature, demonstrated coved-type ST-elevations and high degree AV block with periods of ventricular asystole at above 40C.

Significance:

The data by *Park et al.* support a crucial role for *Fhf2* in maintaining cardiac excitability through a range of body temperatures and, in doing so, provide a novel mechanism for fever-induced arrhythmogenesis. Future studies investigating compound *Scn5a* and *Fhf2* mutant mice as well as human genetic mutation analyses of *Fhf2* and other *Fhf* family members in Brugada Syndrome patients may provide additional insight.

Irx3 is required for postnatal maturation of the mouse ventricular conduction system.

Sci Rep. 2016 Jan 20;6:19197
Kim KH, Rosen A, Hussein SM, Puviindran V, Korogyi AS, Chiarello C, Nagy A, Hui CC, Backx PH

Background:

The ventricular conduction system (VCS), entailing the His-bundle, bundle branches and Purkinje fibers, allows for efficient ventricular contraction through rapid and coordinated electric propagation. Prior studies have demonstrated a role for *Irx3*, a member of the Iroquois (Irx) family of transcription factors, in VCS function through the regulation of gap junction genes, specifically *Gja5* (Cx40) and *Gja1* (Cx43) (*Kim et al 2012*). However, it remains unclear whether the relatively mild changes in these gap junction genes could explain the *Irx3* mutant phenotype, including significant conduction delay, right bundle branch block and propensity for ventricular tachyarrhythmias observed in both mouse and humans alike[1,2,3]

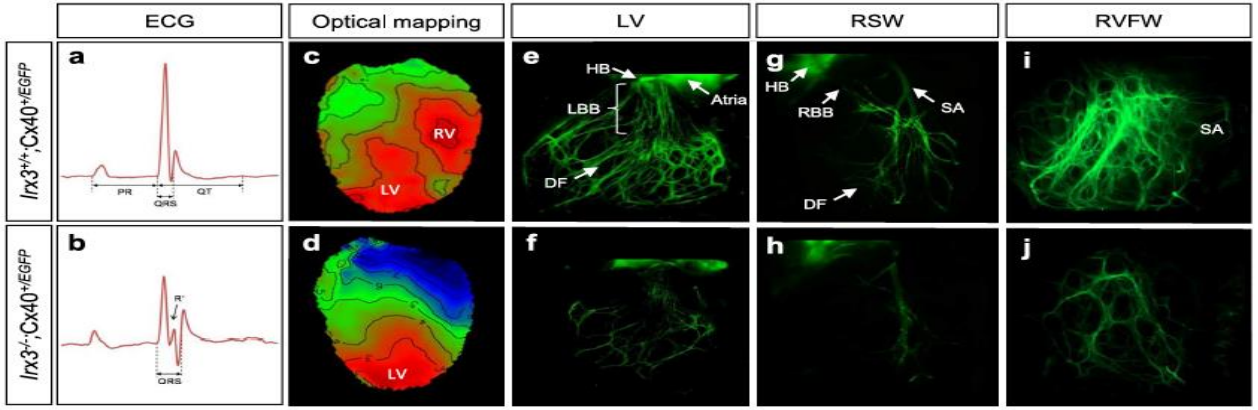


Figure 1. Loss of Irx3 leads to abnormal electrical activation of the ventricles and morphological defects of the VCS.

[1]Kim, K. H., et al. 2012. Iroquois homeodomain transcription factors in heart development and function. Circ Res 110, 1513–1524.
[2]Gaborit, N. et al. 2012. Cooperative and antagonistic roles for Irx3 and Irx5 in cardiac morphogenesis and postnatal physiology. Development 139, 4007–4019.
[3]Koizumi, A. et al. 2015. Genetic defects in a His-Purkinje system transcription factor, IRX3, cause lethal cardiac arrhythmias. Eur Heart J, May 7;37(18):1469-75.

Summary: In this study, *Kim et al.* unveil a role for *Irx3* in the early postnatal formation of the VCS. In addition to the previously demonstrated decreased expression of Cx40 and ectopic Cx43 expression within the VCS, Irx3 knockout (KO) mice exhibit a hypoplastic VCS. Specifically, Irx3KO mice had reduced number and density of fibers in bundle branches and distal purkinje fiber networks, largely occurring in the early postnatal period. Notably, the hypoplastic VCS was not associated with significant differences in proliferation nor apoptosis within the VCS cells themselves. Given the phenotypic resemblance to Nkx2.5 and Tbx5 haploinsufficient mice as well as the known interaction between Irx3 and Nkx2.5, the authors investigated a possible co-regulatory role for Irx3 with these other two transcription factors. They went on to show protein interaction with Tbx5 by co-immunoprecipitation and a series of *in silico* studies revealed Irx3 binding motifs present in proximity to the DNA binding sites of both Nkx2.5 and Tbx5. While validation of possible gene targets was not provided using their Irx3KO model, overexpression of Irx3 *in vitro* showed upregulation of several of these candidate genes.

Significance: VCS defects are clinically relevant due to promotion of arrhythmias and/or acceleration of disease processes. In their study, *Kim et al.* have further detailed the molecular mechanisms by which Irx3 is required for normal VCS maturation in the perinatal period. Specifically, the authors provide both direct and indirect evidence that Irx3 may function as a transcriptional co-regulator with Nkx2.5 and/or Tbx5 to mediate the expression of a host of genes responsible for postnatal VCS maturation.

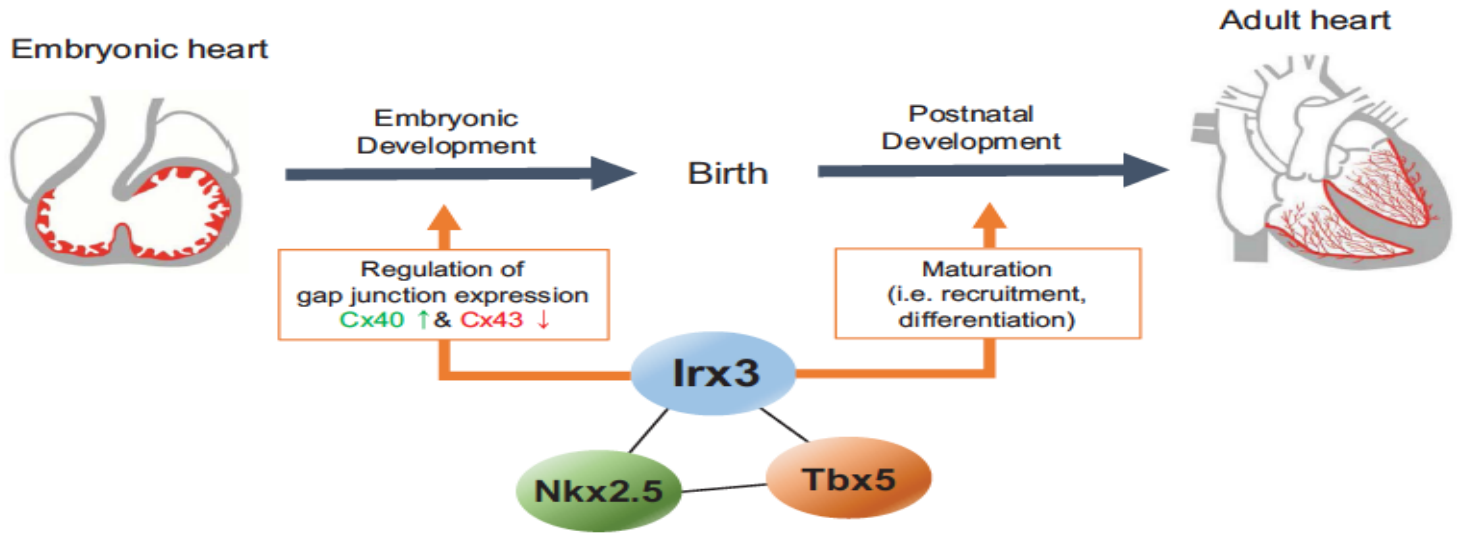


Figure 8. A schematic model of Irx3 cooperating with Nkx2.5 and Tbx5 in the VCS development and function.

EP Case Presentation

PJRT January 2017

A 17 year old previously healthy female presented to the Pediatric EP Clinic for further evaluation and management of an episode of wide-complex tachycardia. She abruptly sensed tachycardia associated with dizziness, light-headedness, shortness of breath and chest pain during dance class. The episode may have been precipitated by an abrupt change in position. The episode lasted approximately 4.5 hours, at which point an ambulance was called and she was brought to the ED. She otherwise has a structurally normal heart and a normal baseline EKG (Figure 1).

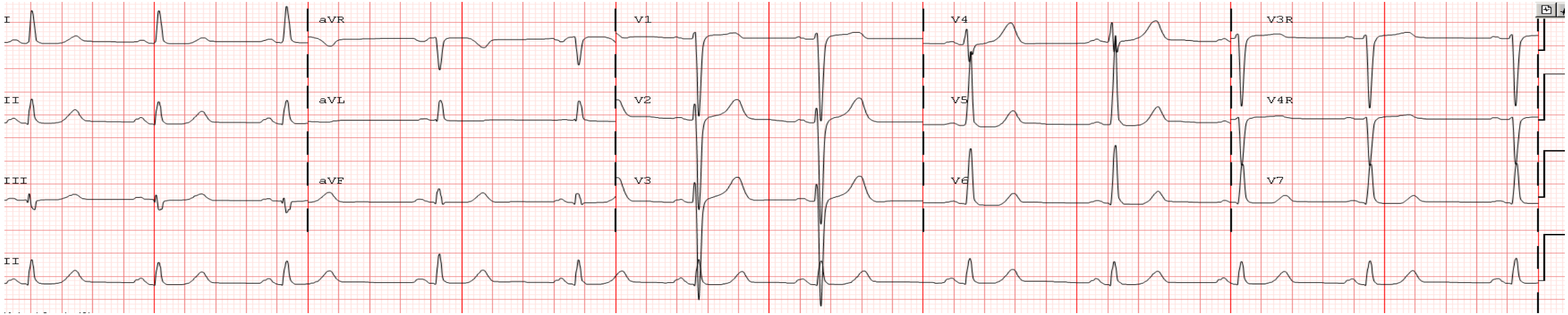


Figure 1. Baseline 12-lead EKG.

The EKG from the emergency department is shown below.
The patient was given adenosine with cessation of the tachycardia.

Figure 2. EKG on arrival to the ED.

Differential Diagnosis?

Differential Diagnosis

1. SVT with aberrancy

2. Atriofasicular (Mahaim) tachycardia

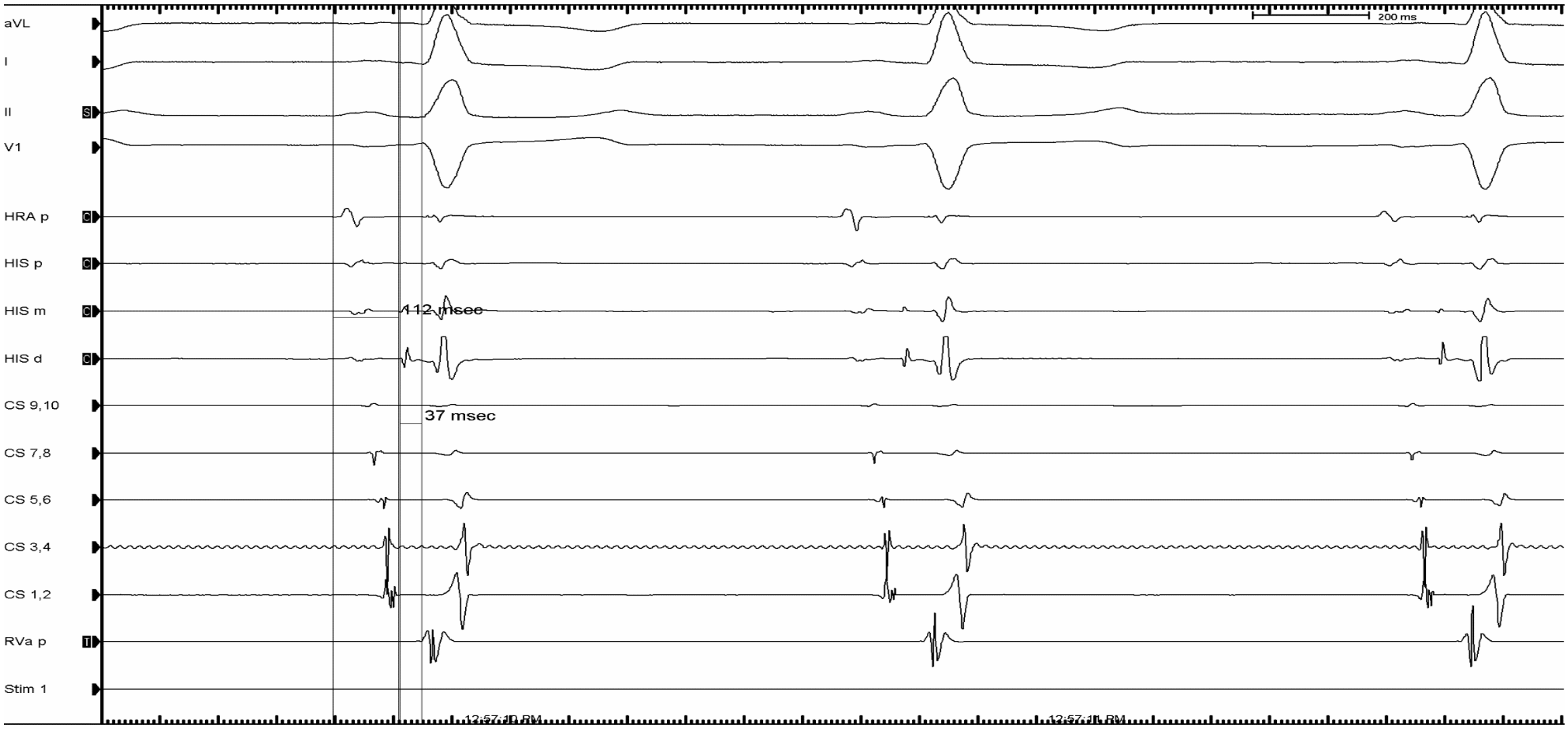
3. Antidromic AVRT

4. Ventricular tachycardia

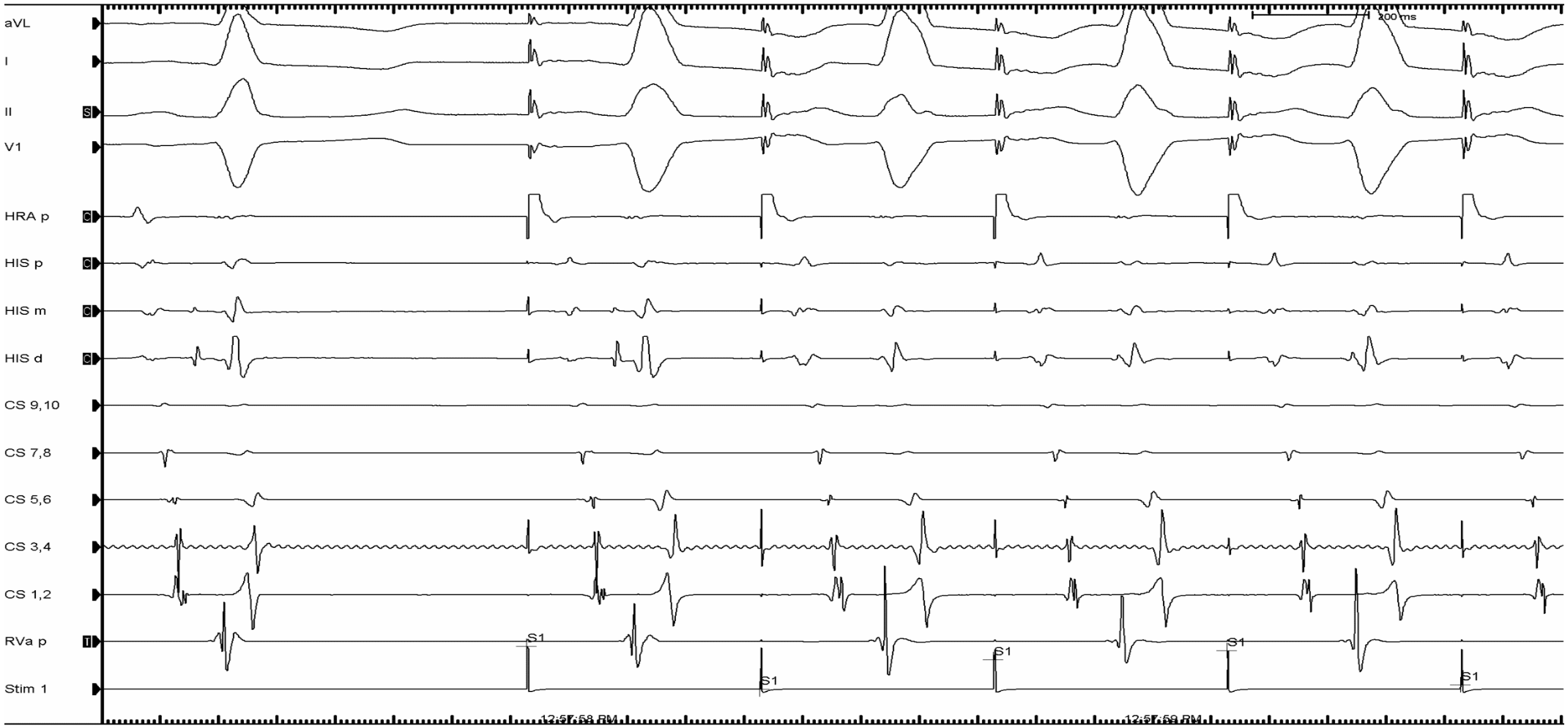
Plan

- Invasive electrophysiology testing with possible ablation

Baseline Measurements



Atrial Overdrive Pacing at 400 msec from the HRA



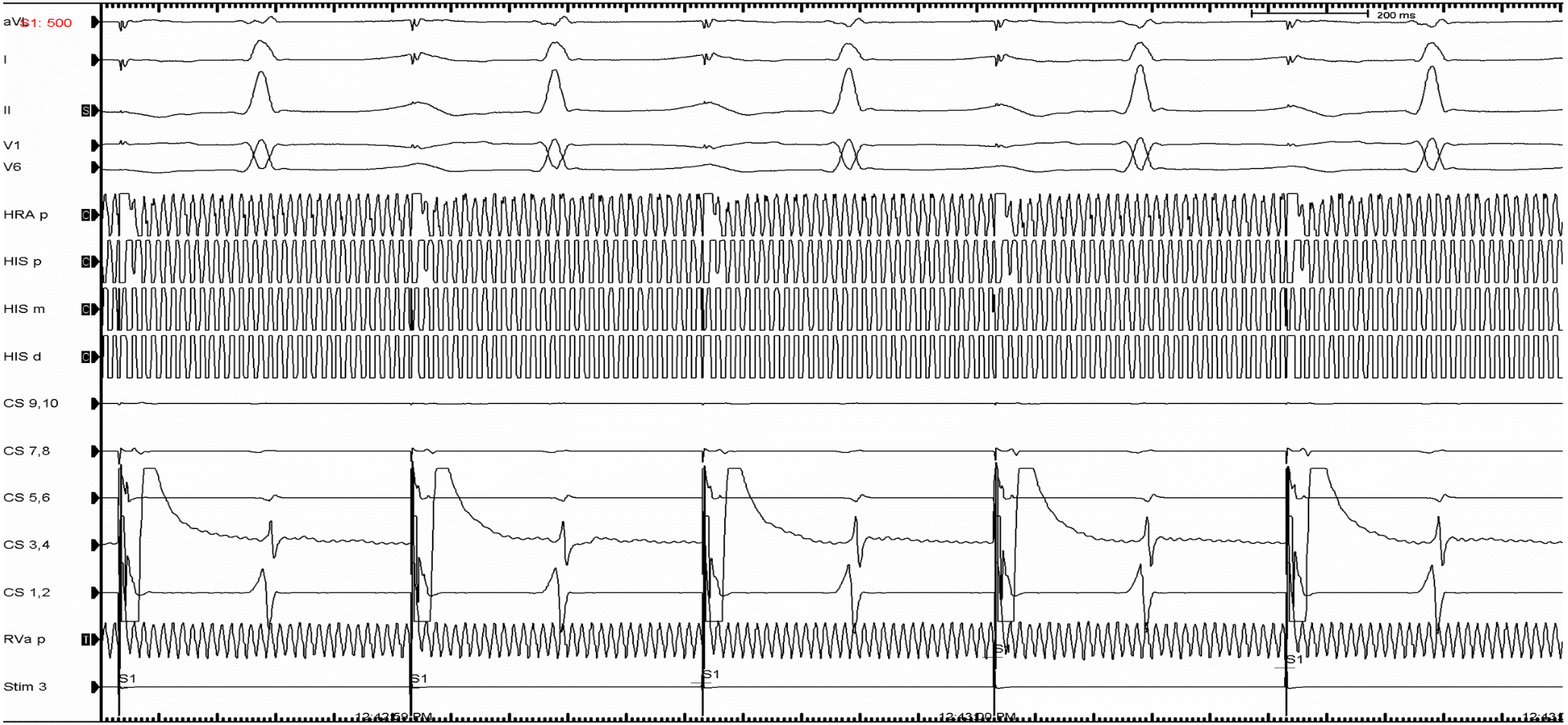
Atrial Pacing Protocol

- With atrial overdrive pacing, the AV block cycle length was 310 msec

- With atrial extrastimulus testing, the atrial effective refractory period (ERP) in the accessory pathway was 290 msec and the AV nodal ERP was > 290 msec.

- There was decremental AV conduction with earliest ventricular activation noted in the RVA catheter

CS Pacing from Far Left Lateral Position



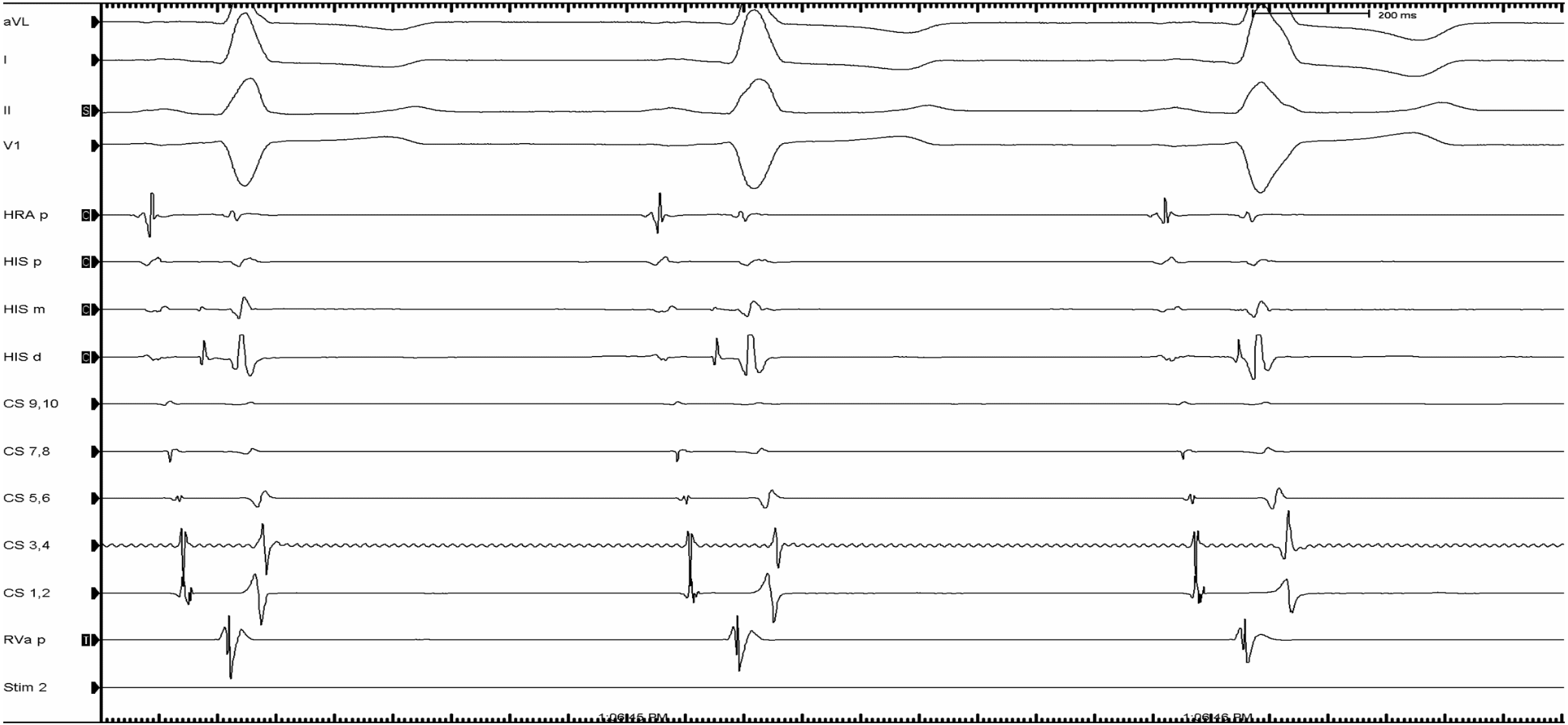
Ventricular Overdrive Pacing at 400 msec

Ventricular Pacing Protocol

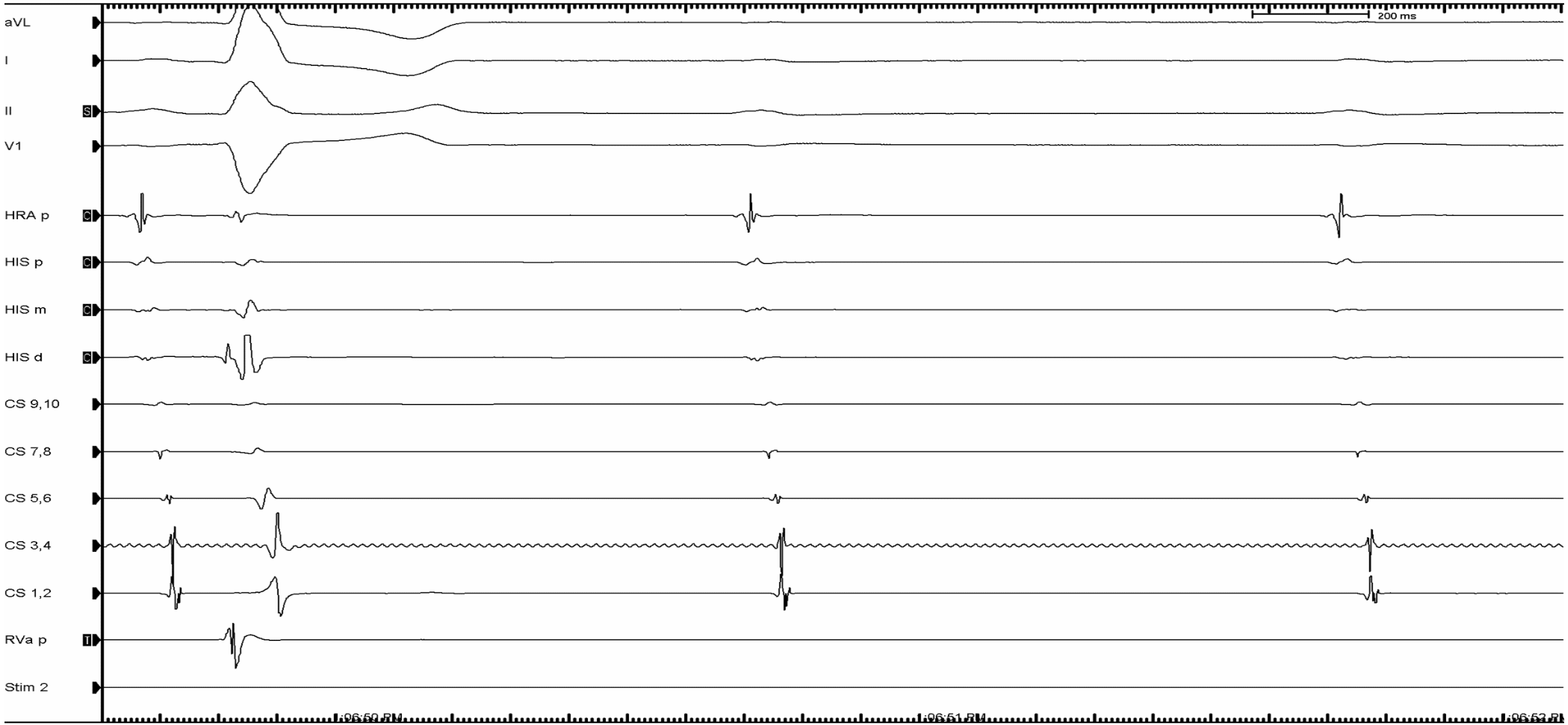
- With ventricular overdrive pacing, there was concentric VA activation sequence with a VA block cycle length of 320 msec

- With ventricular extrastimulus testing, there was decremental, midline VA conduction with a ventricular effective refractory period (ERP) was 250 msec with a VA ERP <260 msec

Adenosine


aVL
I
II
V1
HRA p
HIS p
HIS m
HIS d
CS 9,10
CS 7,8
CS 5,6
CS 3,4
CS 1,2
RVa p
Stim 2
200 ms

Adenosine


aVL
I
II
V1
HRA p
HIS p
HIS m
HIS d
CS 9,10
CS 7,8
CS 5,6
CS 3,4
CS 1,2
RVa p
Stim 2
200 ms
06:50 PM
06:51 PM
06:52 PM

Adenosine


S1: 500
200 ms
aVR
I
II
V1
HRA p
HIS p
HIS m
HIS d
CS 9,10
CS 7,8
CS 5,6
CS 3,4
CS 1,2
RVa p
Stim 2
S1
S1
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1:10:34 PM
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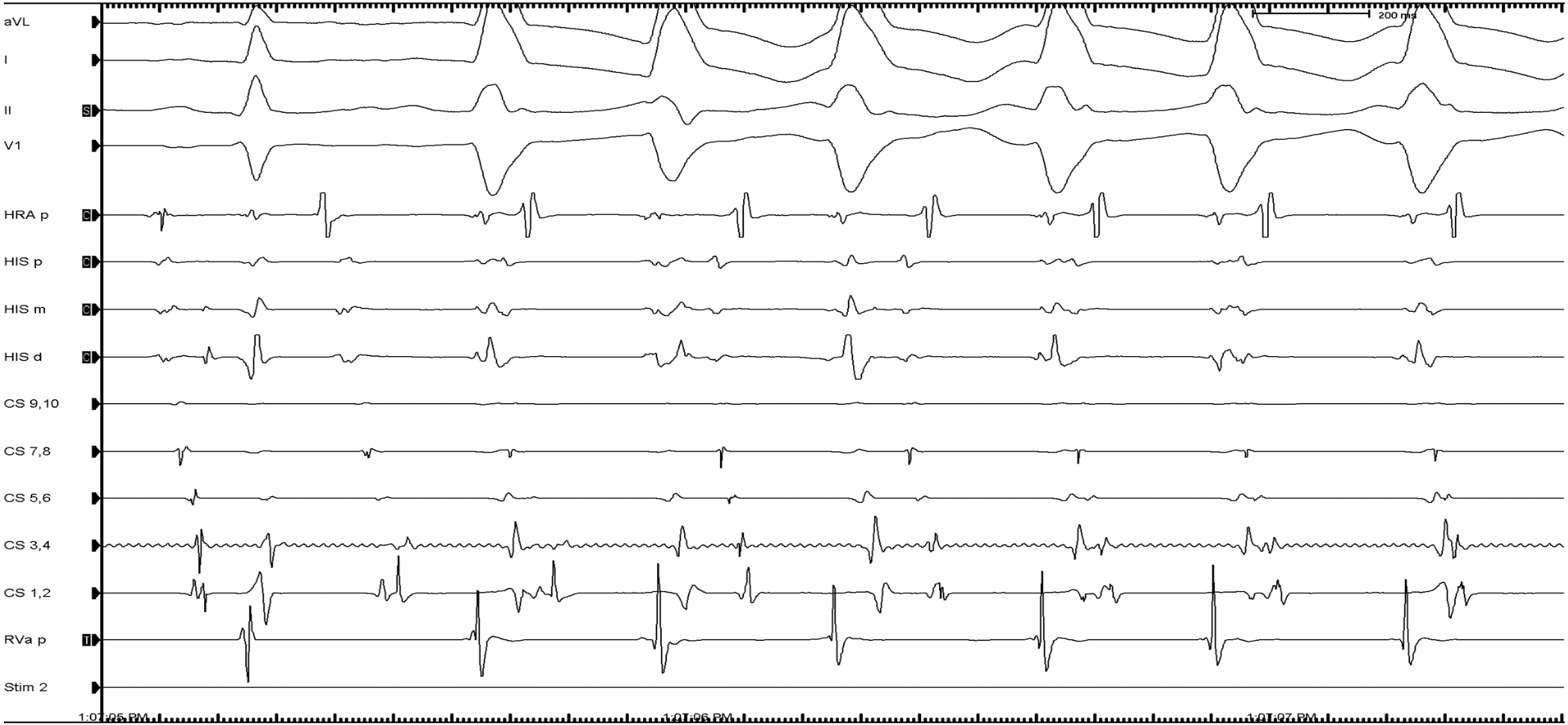
Spontaneous Tachycardia



Spontaneous Tachycardia Intervals

- Tachycardia cycle length 294 msec
- AV interval 236 msec
- VA interval 33 msec
- QRS 125 msec

Diagnosis?

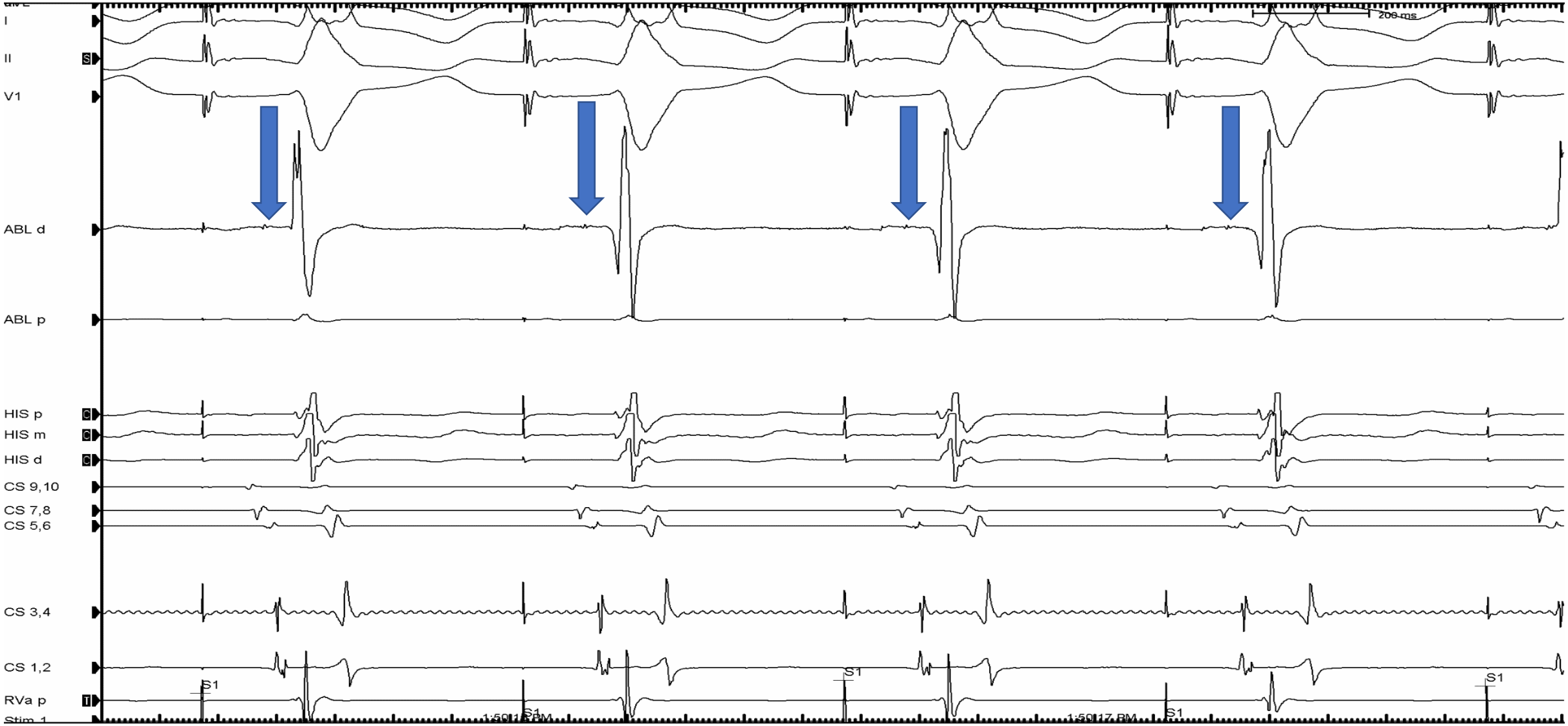
Atriofasicular (Mahaim) Tachycardia

Mapping & Ablation

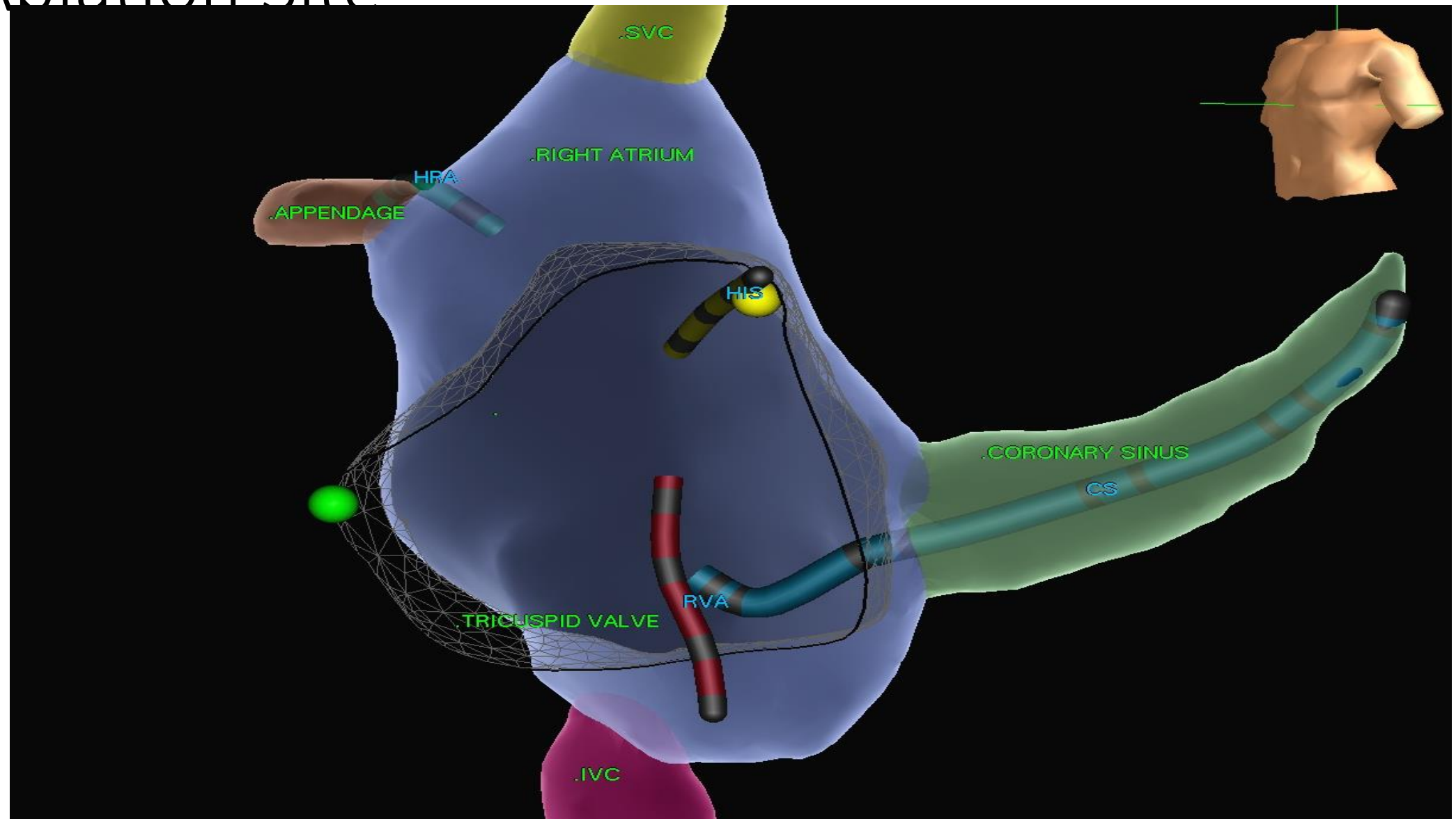
- Mapping of the right lateral position with atrial pacing at approximately 9 o'clock to identify a discrete 'Mahaim potential'

- Radiofrequency ablation in this region resulted in some Mahaim automaticity followed by complete disappearance of the pathway as evidenced by QRS narrowing

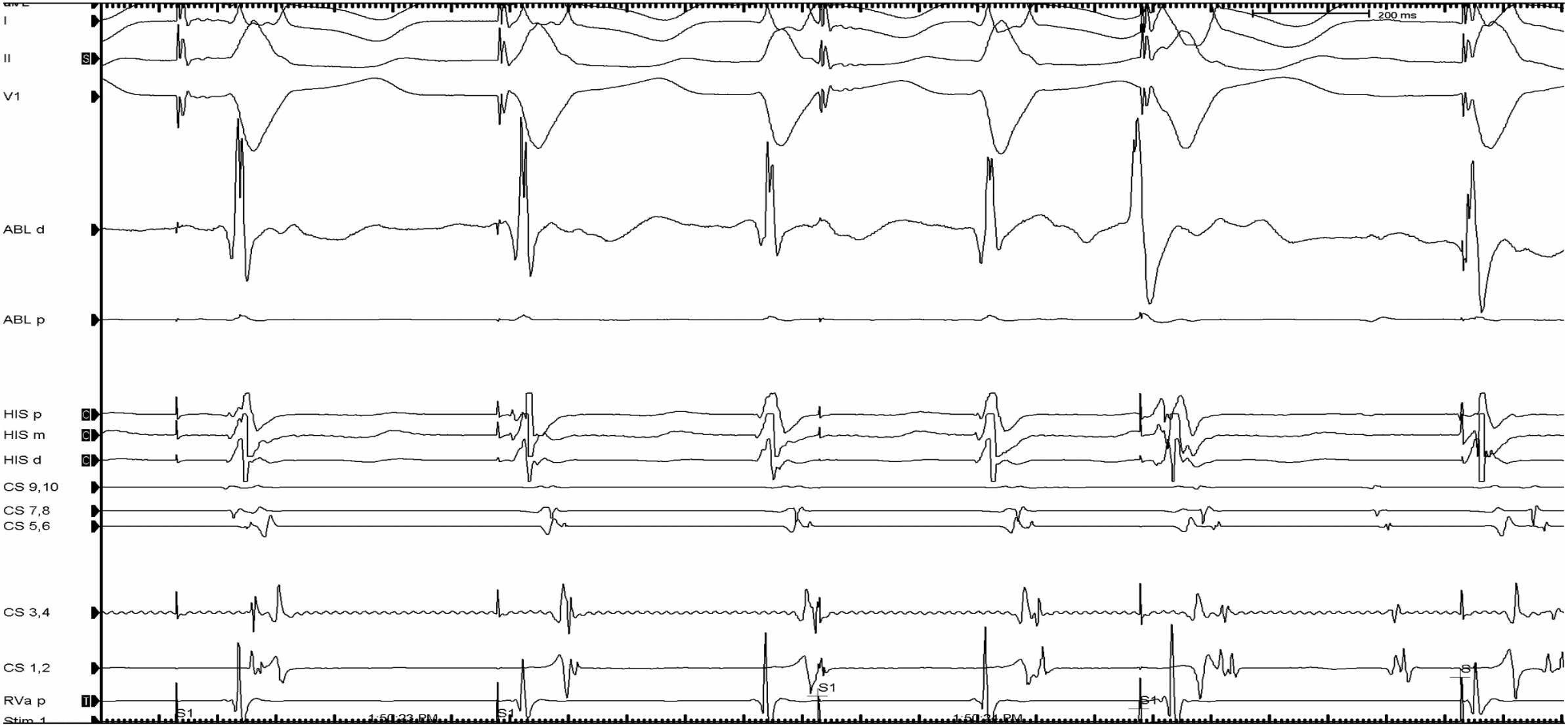
Mahaim Potential on ABL_d



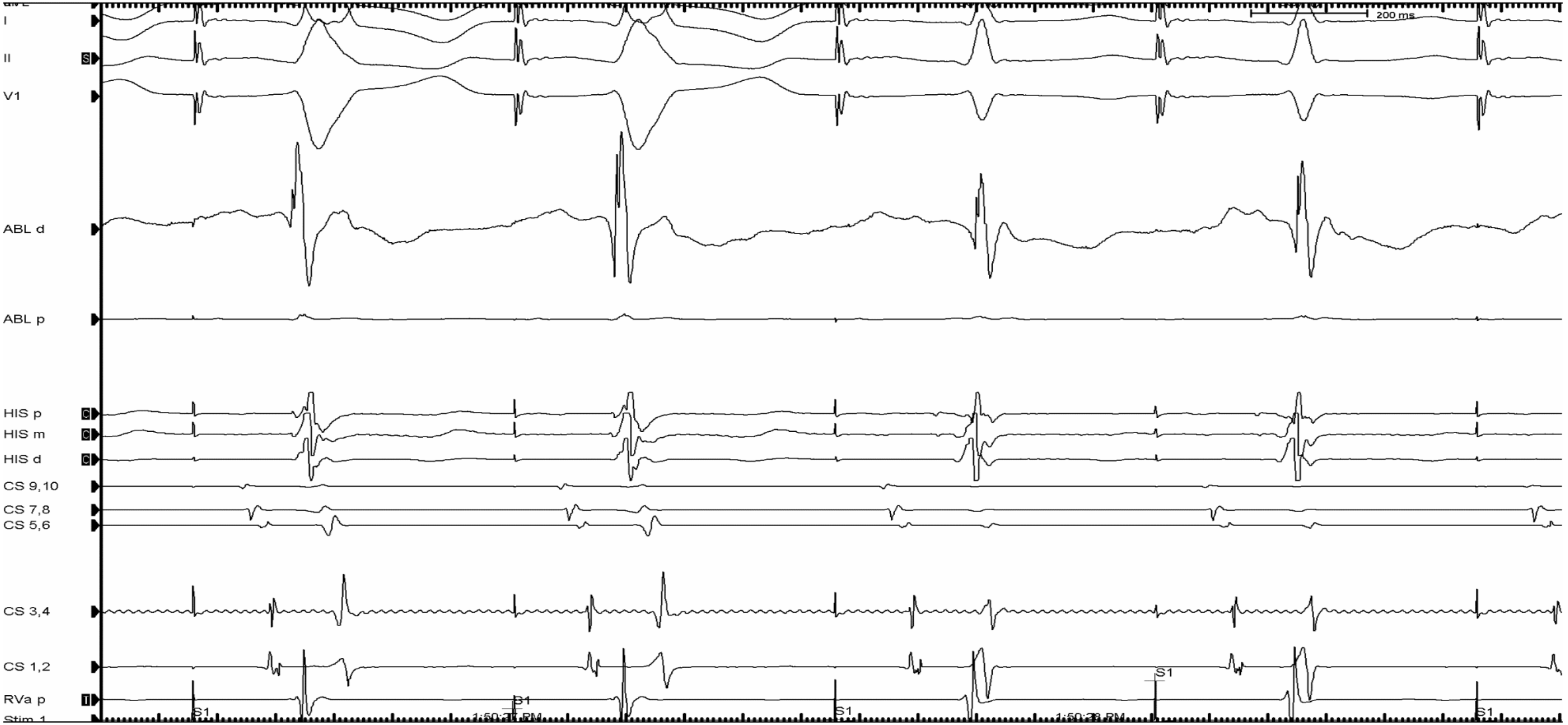
Ablation Site



Mahaim automaticity with RFA



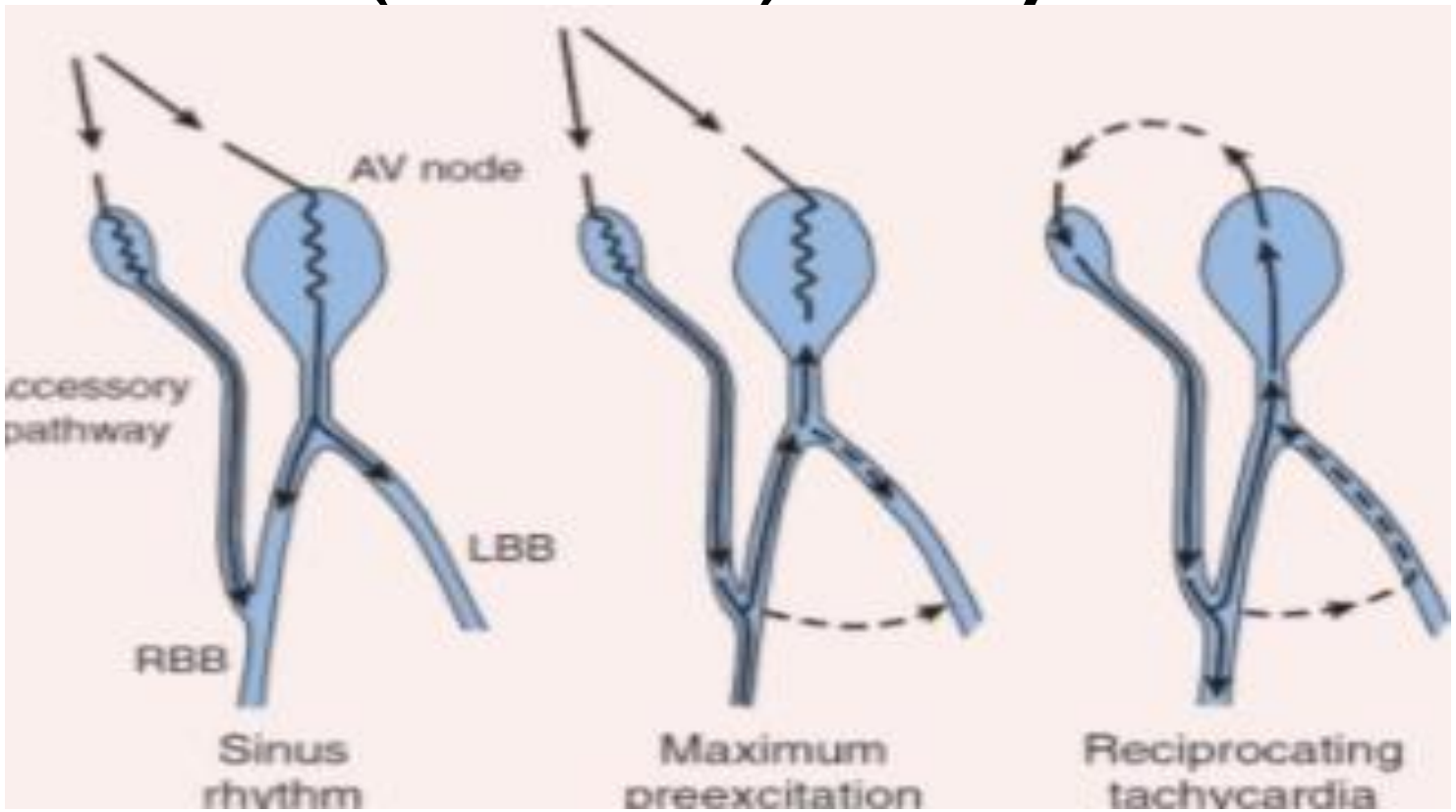
RFA Start and Loss of Mahaim Conduction in 9 seconds



30 min Post-RFA Pacing Protocol

- Narrow QRS with atrial overdrive pacing
- AV block cycle length was 390 msec with QRS 80 msec
- With atrial extrastimulus testing at a drive train cycle length of 600 msec, the AV nodal ERP was 320 msec (eg. 600/320 msec) and there was decremental midline AV conduction
- VA block cycle length was 300 msec
- With ventricular extrastimulus testing at a drive train cycle length of 600 msec, the ventricular ERP was 220 msec with decremental midline VA conduction
- Adenosine resulted in both AV and VA block

Atrio-fasicular (Mahaim) Tachycardia



Mahaim fibers are fibers that transverse from the right atrium to the right bundle branch (i.e. *atriofascicular*)

Mahaim Tachycardia: EKG Criteria

1. QRS axis between 0 and -75°
2. QRS duration <150 msec
3. R wave in limb lead I
4. rS in precordial lead V1
5. Late precordial transition >V4
6. Tachycardia cycle length 220-450 msec

Sternik *et al*. Electrocardiogram during tachycardia in patients with anterograde conduction over a Mahaim fiber: old criteria revisited. Heart Rhythm 2004; 4:406-413.

Mahaim Tachycardia: EP Study

- The Mahaim pathway exhibits *antegrade only decremental* conduction with faster atrial overdrive pacing
- The Mahaim pathway is *adenosine-sensitive*; therefore, there is both AV block and VA block with adenosine
- Mahaim tachycardia has a *LBBB*-like morphology with a *superior* axis and a late precordial transition
- Mahaim fibers are usually mapped antegrade either during tachycardia or at an atrial pacing rate that maximizes preexcitation along the tricuspid valve annulus between His bundle and os of coronary sinus (9 o'clock position)