CryoCor™ Cardiac Cryoablation System for the Treatment of Cavo-Tricuspid Valve Isthmus-Dependent Atrial Flutter

Protocol Number: GL-AFL-02

PMA Number: P050024

June 27, 2007

CRYOCOR, Inc.

Introduction

Helen S. Barold, M.D., M.P.H.

Chief Medical Officer

CRYOCOR, Inc.

Indications for Use

The system consists of the CryoCor™ CryoBlator$_x$™ Cryoablation Catheters and the Model 2020 Console

The CryoCor Cryoablation System's intended use is in the Ablation of Isthmus-dependent Atrial Flutter in patients 18 years of age or older

Regulatory Events

- July 15, 2005- Initial submission
  - Modular submission
- October 12, 2005- Major Deficiency Letter
- January 26, 2006- Letter concerning chronic effectiveness
- November 28, 2006- Resubmission with new core lab
- March 1, 2007- Amendment
- June 27, 2007- Panel Date

Data to Support Approval

- Pre-clinical Data
  - CryoCor lesion sizes as large as RF
- US Pivotal Trial
- OUS Confirmatory Clinical Study
- Pain study
  - Demonstrates a unique advantage of Cryoablation over RF

Demonstrates a Reasonable Level of Safety and Effectiveness

Device Description

Eric Ryba

Director, Intellectual Property

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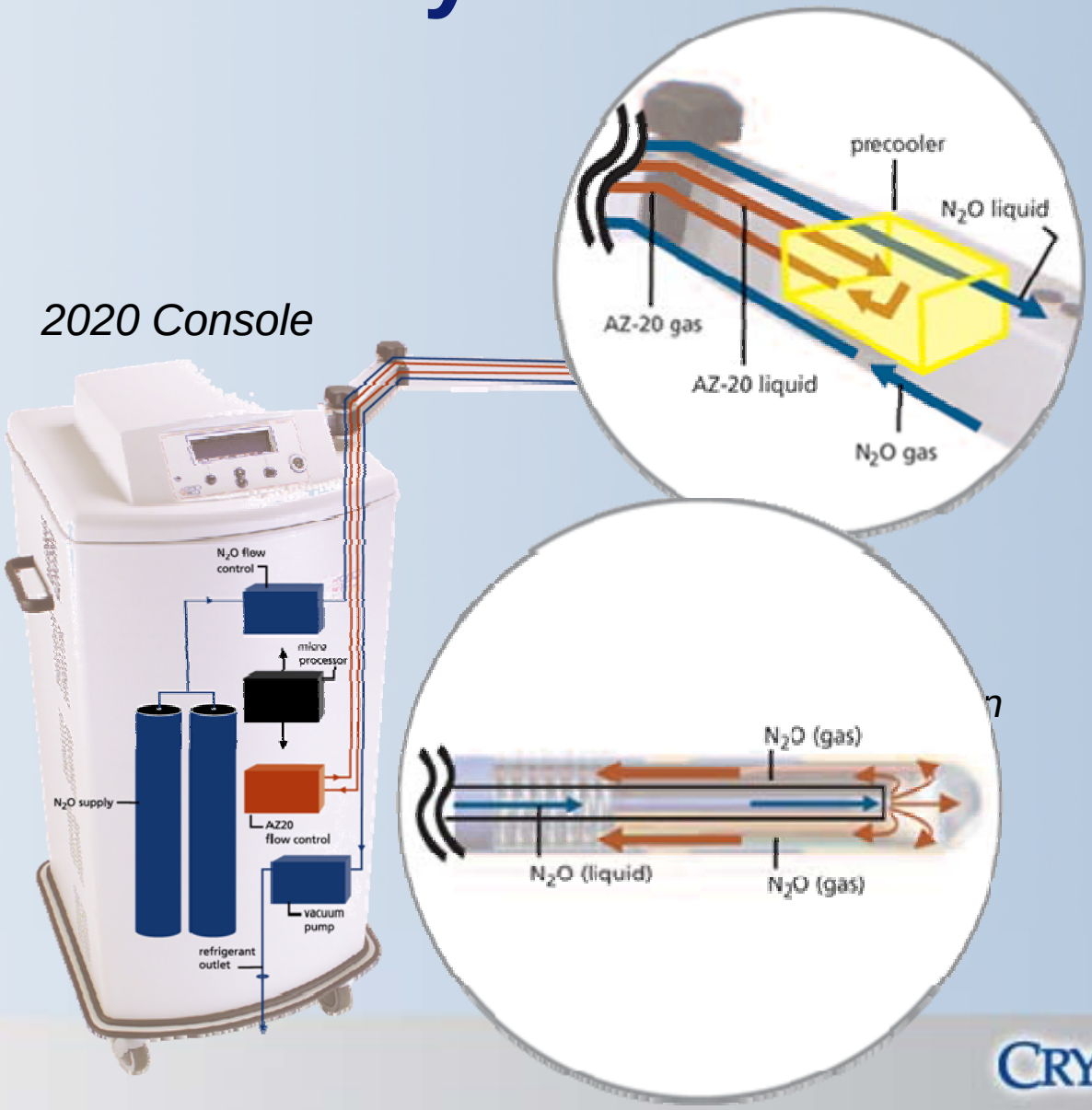
CryoCor Console and Catheter System

2020 Console



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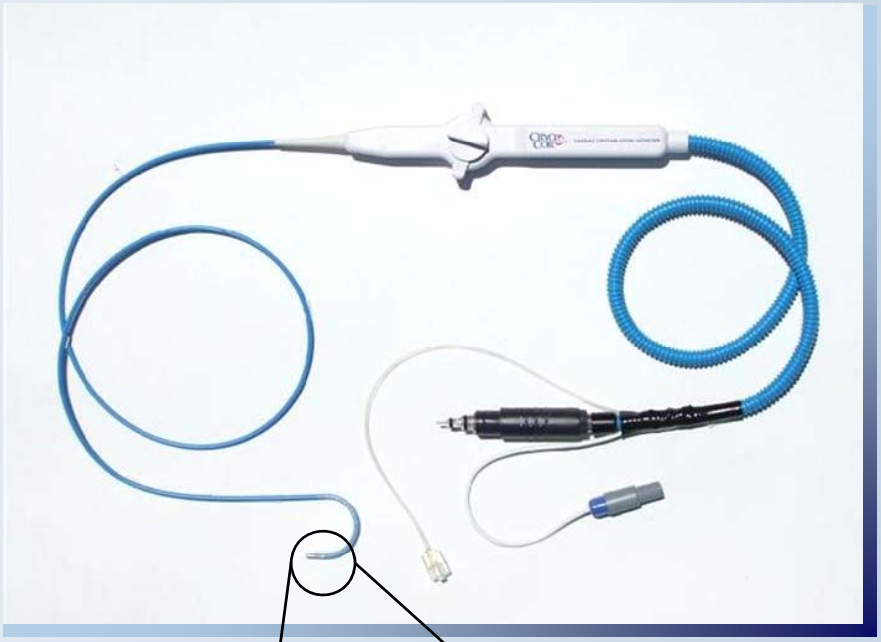
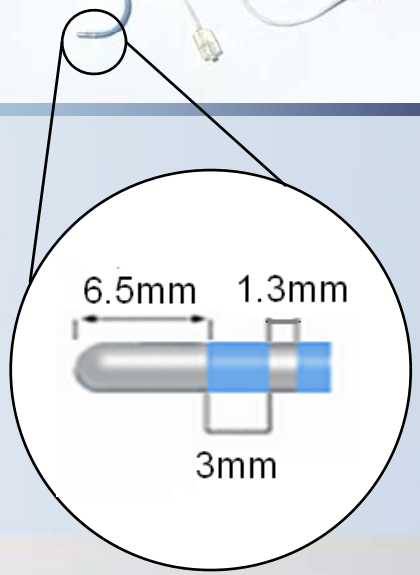
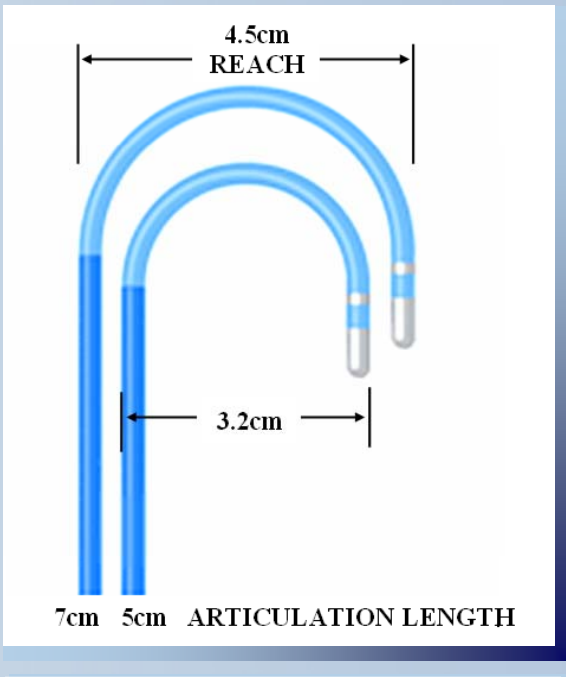
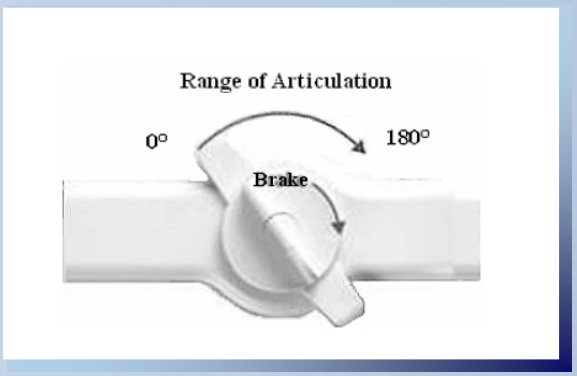
CryoCor 1200 Catheter Product Line









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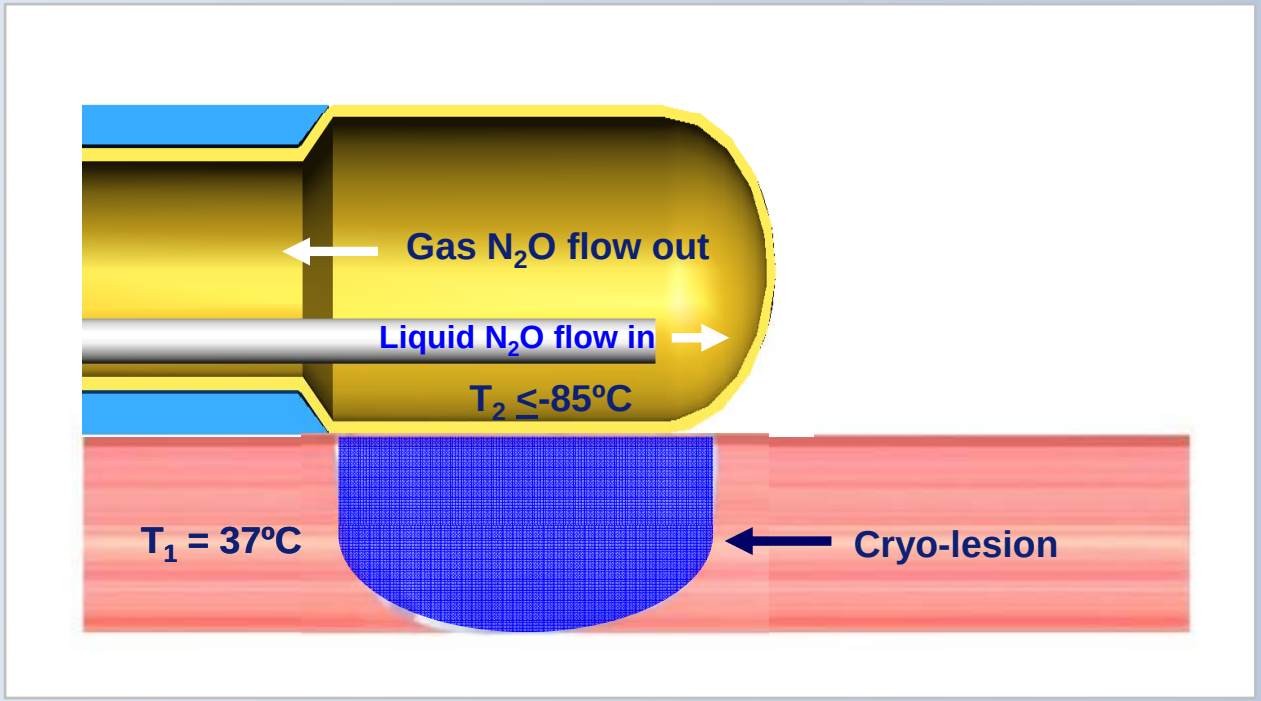
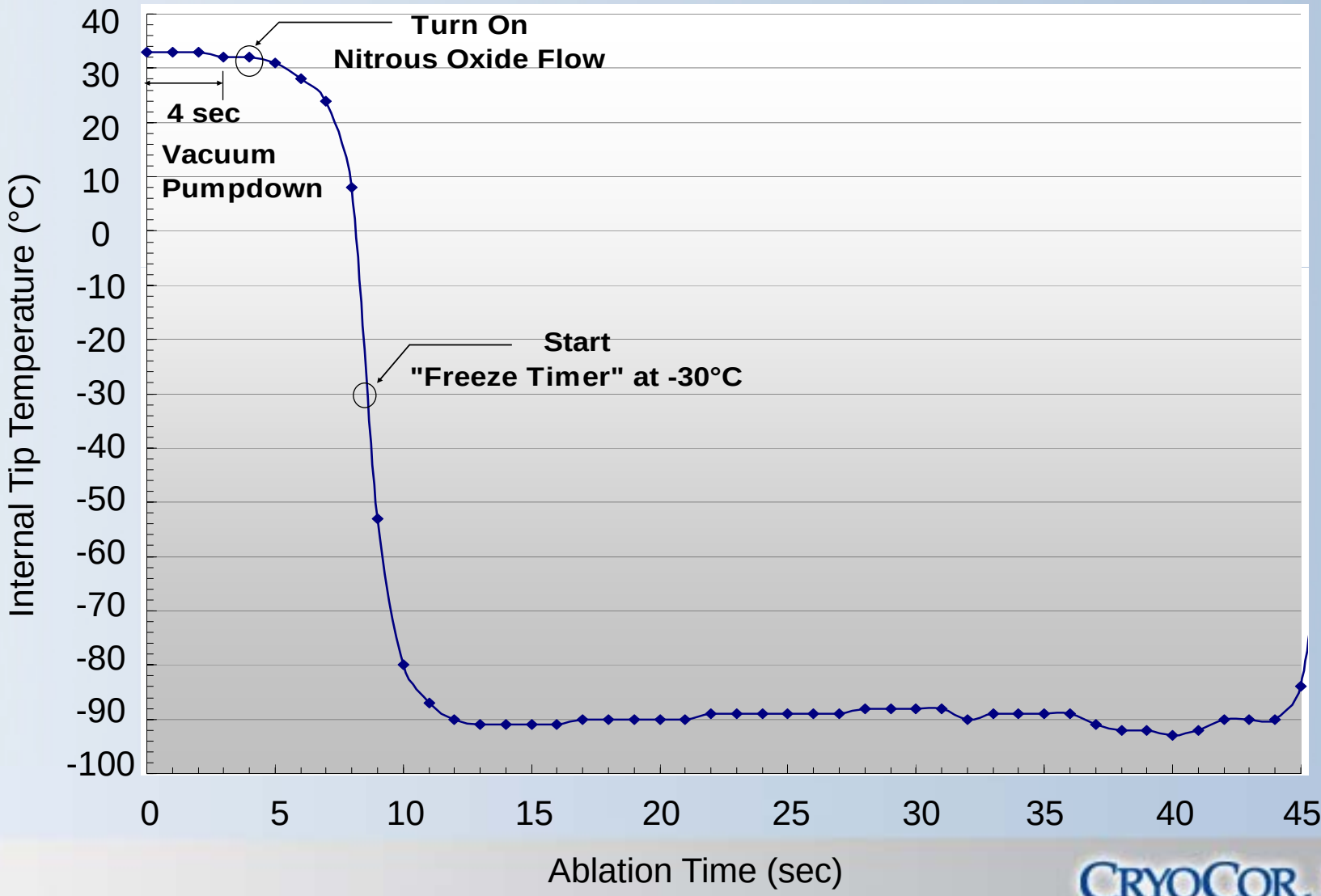
Cryoablation Process



Internal Tip Temperature



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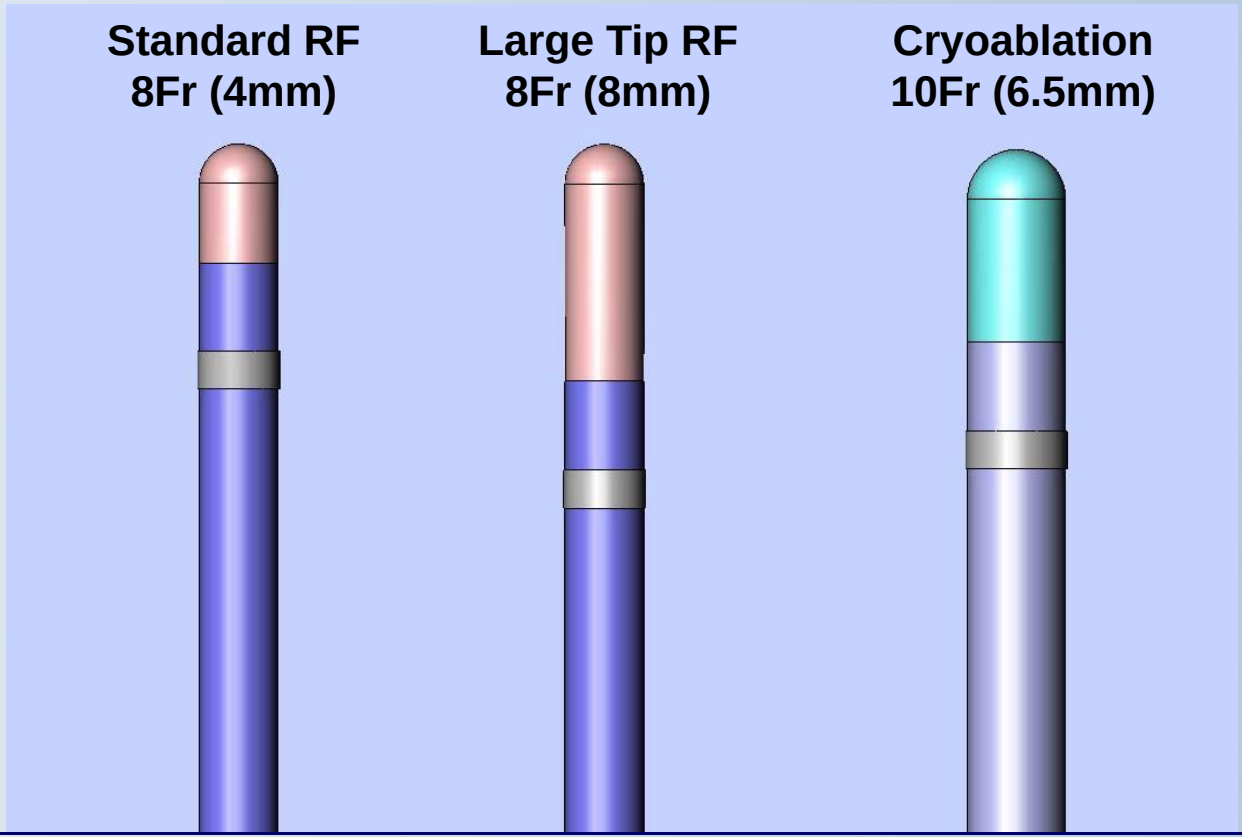
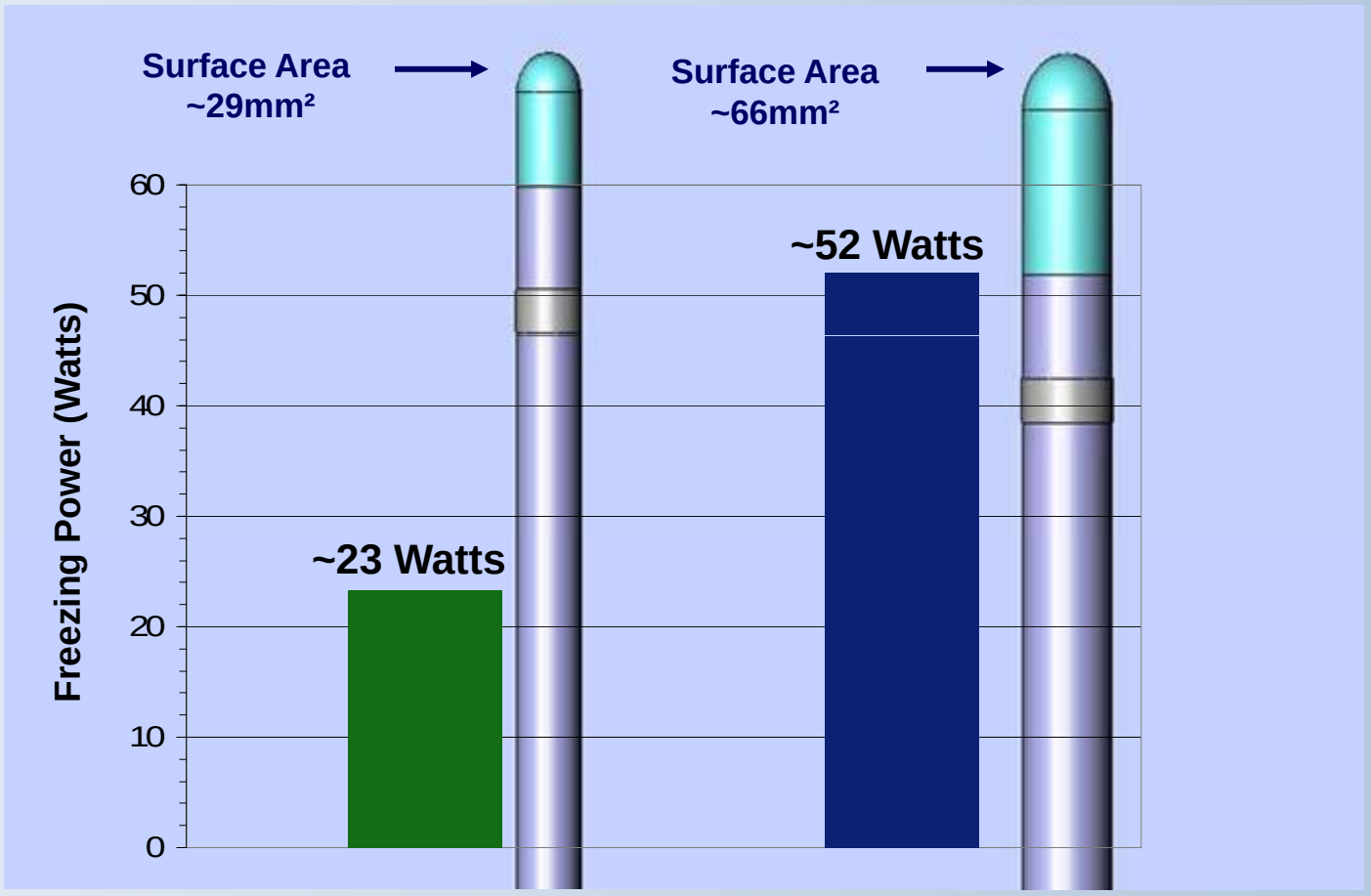
Cryo & RF Catheter Ablation Surface Area Comparison



ABLATION SURFACE AREA		
RF - 8Fr (4mm)	RF – 8Fr (8mm)	Cryo - 10Fr (6.5mm)
~34 mm²	~68 mm²	~66 mm²

Surface Area Comparison and Approximate Heat Transfer Values



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Pre-Clinical Data

Gregory Feld, M.D.

Professor of Medicine
Director, Cardiac Electrophysiology Program
University of California San Diego

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Cryoablation

- Cryosurgery in the 1970's
- Large volume of published literature characterizing cryoablation
  - Safe
  - Preserves tissue architecture
    - Maintain good tensile strength
  - Limited risk of thrombus
  - No steam pops
  - Clearly demarcated, homogeneous lesion formation
  - No pulmonary vein stenosis, atrio-esophageal fistulas when used on the left side
  - Less painful- several studies

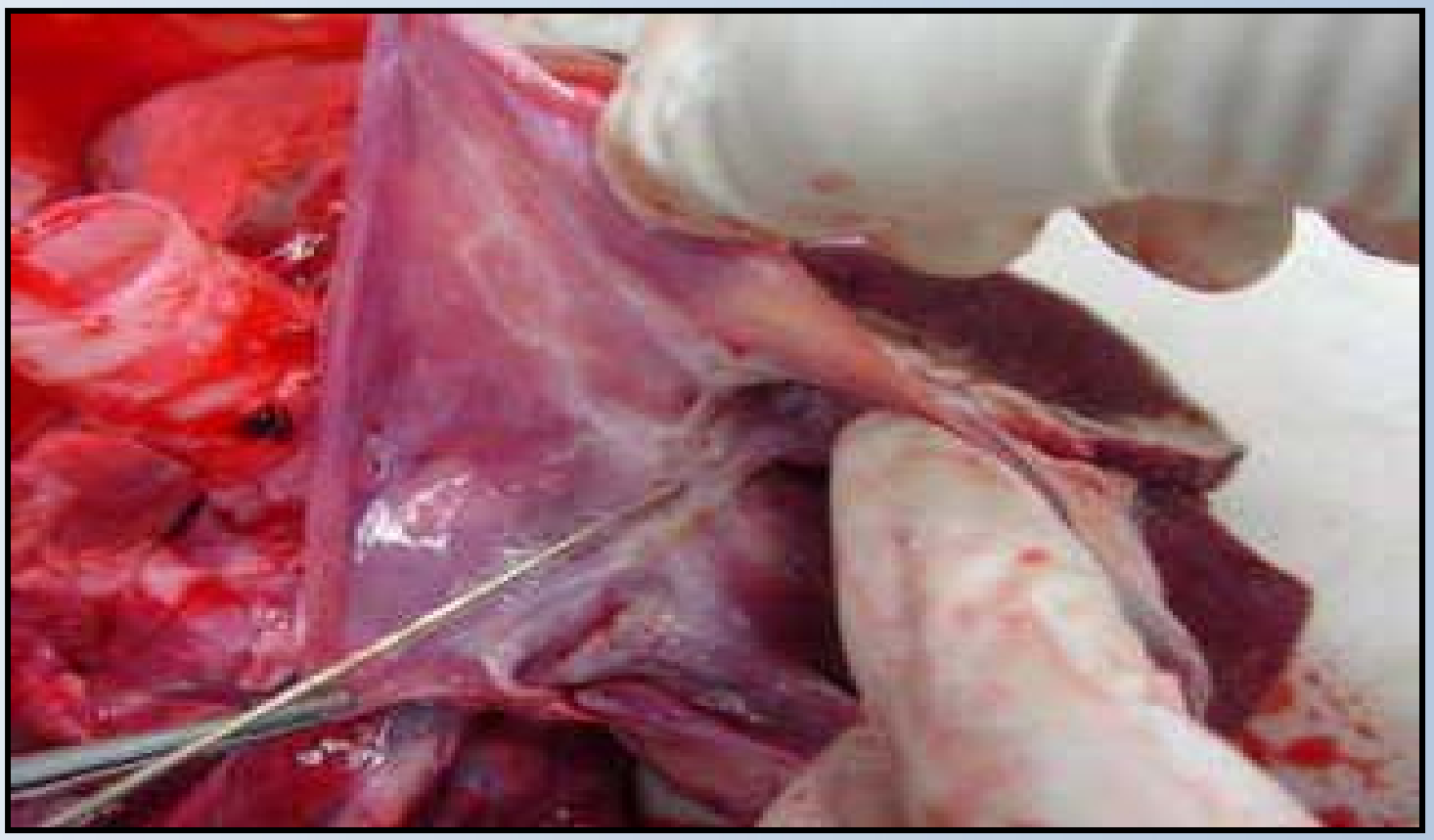
Primary Mechanisms of Cell Injury

- An iceball is formed at the tip of the catheter or along a defined surface
- Cells within the iceball are irreversibly damaged and eventually replaced with fibrotic tissue
- There is cell death, but the extracellular matrix remain largely intact.

Factors that Affect Lesion Size

- Contact with tissue
- Electrode size
- Power
- Regional blood flow
- Freeze time (lesions form at 30 seconds)

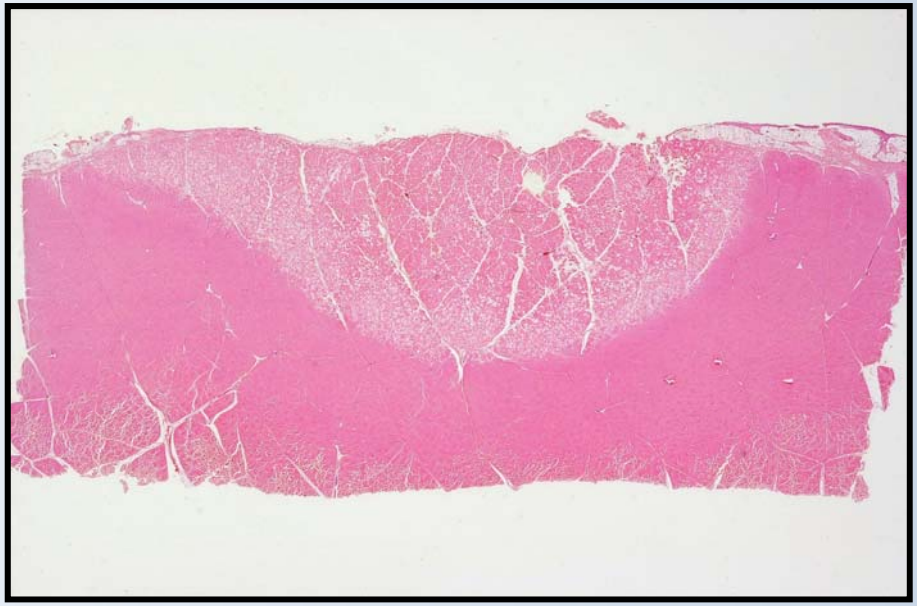
Cryoablation Lesions at Canine Isthmus



Compare Lesion Size for CryoCor vs. RF

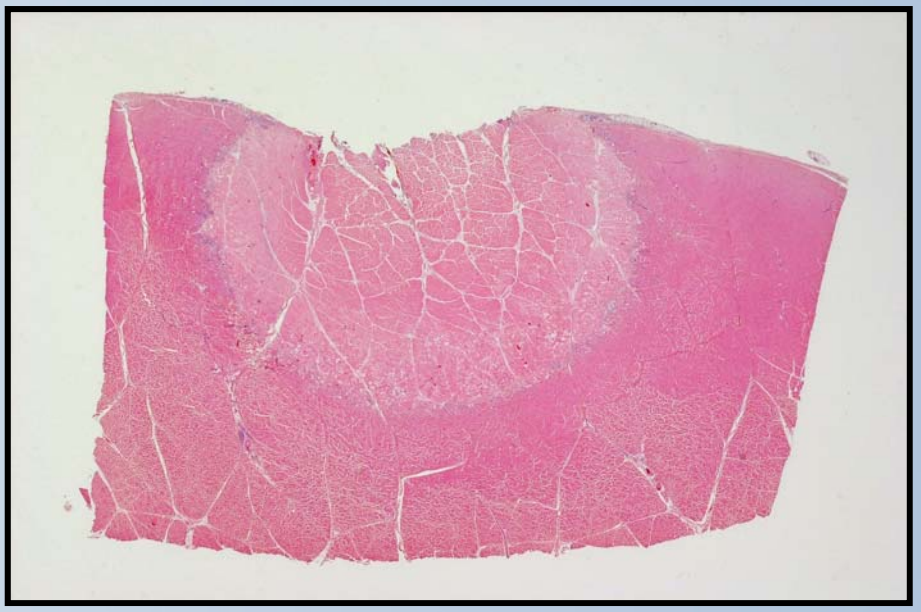
- 10 swine
- Standard thigh muscle preparation
  - constant force of 10gm of pressure on all catheters
- Cryo
  - CryoCor, 6.5 mm tip, 5 minute applications
- Standard RF (SRF)
  - 7F; 4mm tip; 60 sec at 50 watts, temp 50°C
- Irrigated RF (CRF)
  - 7F; 3.5mm tip; 60 sec at 50 watts, saline infusion at 15 ml/min; externally irrigated
- Both vertical and horizontal tip orientations were used

Examples of Lesions Created with Cryo and RF



CryoCor- 5 minutes

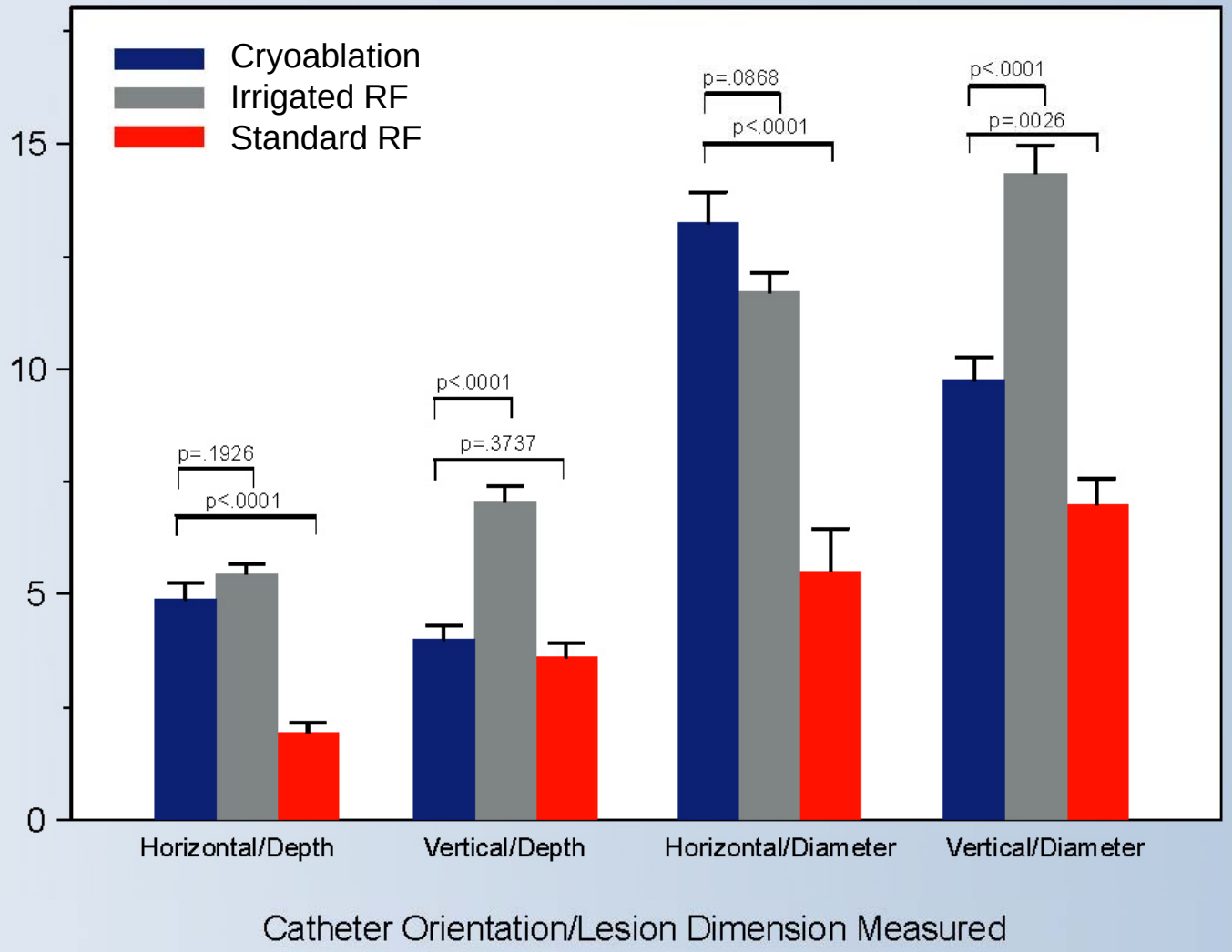
Horizontal Tip Orientation



Irrigated RF- 1 minute

Vertical Tip Orientation

Comparison of Lesion Sizes



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Conclusions

- Cryoablation is able to produce lesions that are larger than standard RF and as large as irrigated RF
- The CryoCor System can make lesions that are large enough to treat atrial flutter

Pre-Clinical Data

Hein Wellens, M.D.
Emeritus Professor of Cardiology
University of Maastricht, The Netherlands

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Catheter-Based Cryoablation Produces Permanent Bidirectional Cavotricuspid Isthmus Conduction Block in Dogs

C. Timmermans, L. Rodriguez,
R. Suylen, J. Leunissen, M. Vos,
G. Ayers, H. Crijns, H. Wellens

JICE 2002 7, 149-155.

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Protocol

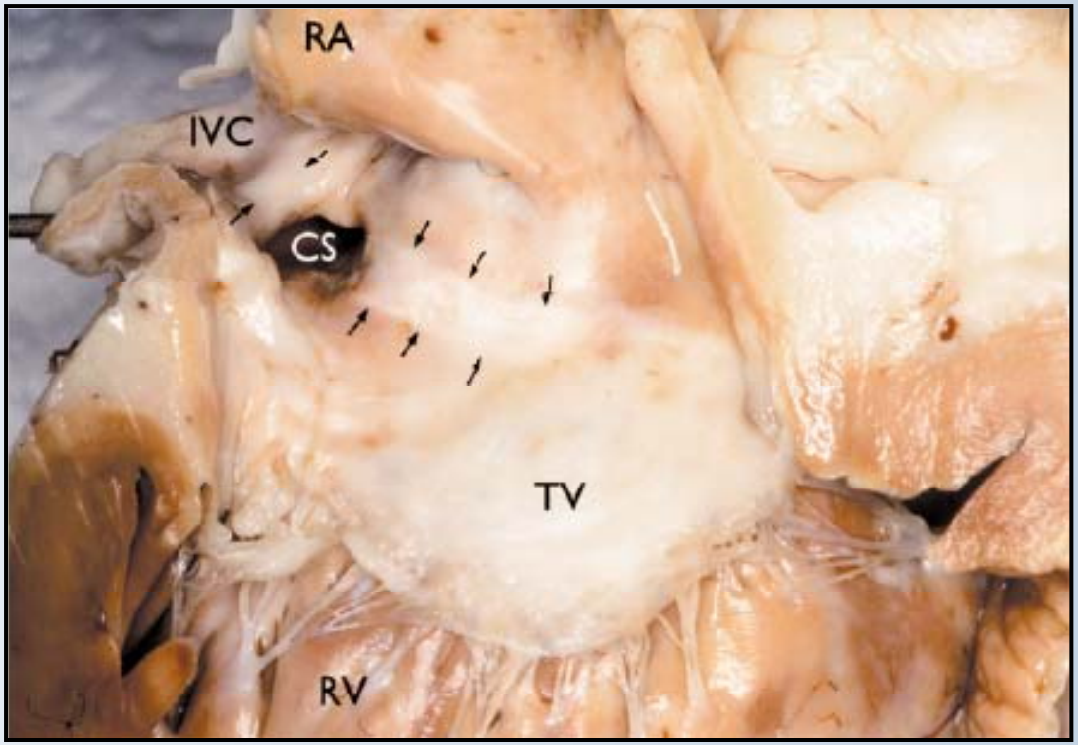
- 7 adult mongrel dogs
- 5 Cryo; 2 RF
- All animals had electroanatomical mapping with CARTO at the time of the procedure and 6 weeks later
- Isthmus Ablation
  - RF 4mm tip; 50W, temp 70°C, 90 second lesions
  - CryoCor 6.5 mm tip, 10F, bipolar, 5 minute lesions

Results

	# Applications	Temp	Procedure time	Application time	Fluoro time	BDB
Cryo	6-10	-65 to -80°C	354 min	2X5 min	81 min	Yes
RF	9	50 to 70°C	340 min	90 sec	52 min	Yes

BDB= Bidirectional Block

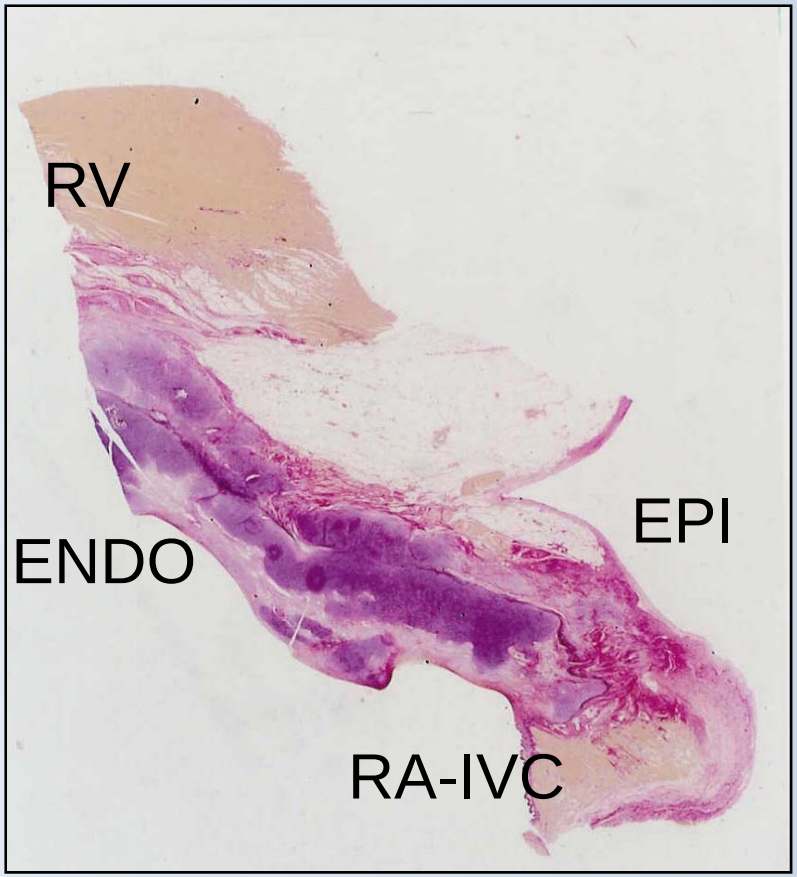
Cryo Lesion Across the Isthmus at 6 weeks



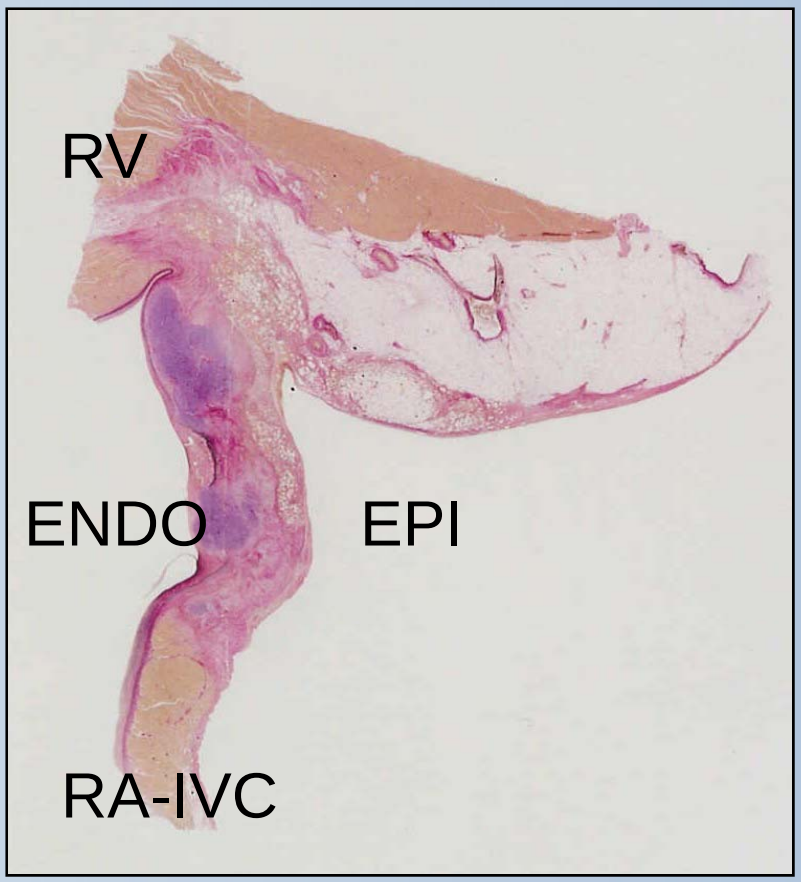
At 6 weeks all animals had permanent bidirectional isthmus block.

One of the animals who underwent RF had endocardial thrombus formation at the transition of the RA to IVC

CryoCor Lesion



RF Lesion



elastica-van Gieson Stain; 6 weeks after ablation of RAI;
ENDO – endocardium; EPI – epicardium; RV – right ventricle
RA-IVC – right atrium – inferior vena cava transition

Conclusions

- Cryo is able to produce chronic bidirectional block with histologic evidence of full thickness lesions
- Cryo adheres well to endocardial surface
  - May be beneficial with uneven surface

Review of Objective Performance Criteria and Published Literature

Hugh Calkins, M.D.

Professor of Medicine and Director of Electrophysiology
Johns Hopkins Hospital

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Cardiac Ablation Catheters Generic Arrhythmia Indications for Use; Draft Guidance for Industry (Objective Performance Criteria)

Table 2: Safety and Effectiveness of RF Ablation Using Conventional RF Ablation Catheters

Arrhythmia	N	Acute Success	Chronic Success	Complications	Comments
Atrial Flutter[1, 6, 8, 10, 11, 16]	1437	72 - 100%	85 – 100%	0 – 6%	Linear lesions across isthmus
Ventricular Tachycardia[10, 11, 16]	1463	66 – 85%	86%	2 – 8%	Right and left ventricles
Atrial Tachycardia [4, 16]	494	91%	85%	3%	Right and left atria

2000

Studies that the OPC are Based on

	# pts	Catheter	Type of F/U	F/U	Chronic Success
Kay JCE 1993	13	4 mm RF	Clinical only	6 mo	90% (9/10)
Saxon AJC 1996	51	4mm RF	Clinical only	166 ±57d	78%
Fisher JCE 1996	200	4mm RF	Clinical only	24 +9 mo	84.5%
Tsai Circ 1999	104	8mm/4mm RF	Clinical only	10±5 mo	100% (22% AFib)

Hendricks EHJ 1995, Scheinman PACE 1995 and PACE 2000 were surveys that reported complications not success rates

Atrial Flutter Ablation Literature Review

- 75 peer-reviewed studies
  - 12 years- Circulation 1994- Circulation 2006
  - 70 using RF
  - 5 using Cryo
- 72 used clinical follow-up at 1,3,6 months with clinic visits and additional visits if symptomatic
  - No event recordings

Long Term Follow-up After RF

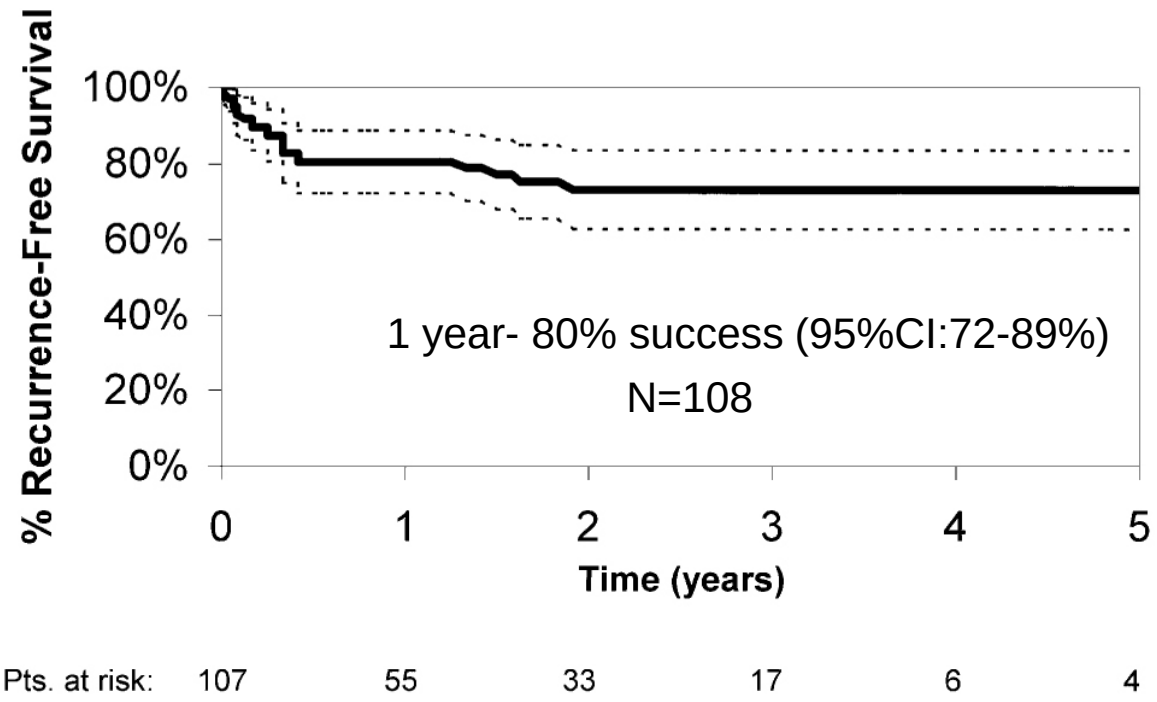

Figure 1. *Kaplan-Meier survival curves (with 95% confidence intervals) for recurrence-free survival from typical atrial flutter following successful radiofrequency ablation of atrial flutter.*

Gilligan, PACE 2003

Long Term Follow-up After RF

Table III.

Studies of Follow-Up Following Radiofrequency A

Authors	Patients	Success	Recurrence: Atrial Flutter	ns)
Cosio et al.[2]	9	78%	42%	
Calkins et al.[10]	16	81%	15%	
Kirkorian et al.[11]	22	86%	14%	
Philippon et al.[12]	59	90%	9%	
Nath et al.[13]	22	97%	23%	
Saxon et al.[14]	51	88%	22%	
Movsowitz et al.[15]	32	97%	15%	
Poty et al.[7]	44	94%	9%	
Fischer et al.[16]	200	95%	15%	
Tai C-T et al.[17]	144	–	10%	
Cosio et al.[18]	28	96%	58%	
Paydak et al.[8]	110	98%	5%	
Anselme et al.[9]	100	83%	1%	
Nabar et al.[19]	82	93%	12%	
Schumacher et al.[20]	56	64%	–	

AF = atrial fibrillation.

Atrial Flutter
42%
15%
14%
9%
23%
22%
15%
9%
15%
10%
58%
5%
1%
12%
–

Gilligan, PACE 2003

Results of Catheter Ablation of Typical Atrial Flutter Calkins, Am J Cardiol 2004

- 150 pts, 17 centers
- 7Fr, 8mm electrode, 100 W RF power generator
- Acute success- 88% (95% LCI: 82.7%)
- 6 month chronic success- 87% (95% CI: 81%; 93%)
  - f/u: office visits at 1,6 months or telephone contact at 1 week, 3,9,12 and 24 months
  - Monthly event recordings with a core lab
- 12 month success rate- 79.7%
- Safety at 1 week- 2.7% device/procedure related events

Results of Catheter Ablation of Typical Atrial Flutter Calkins, Am J Cardiol 2004

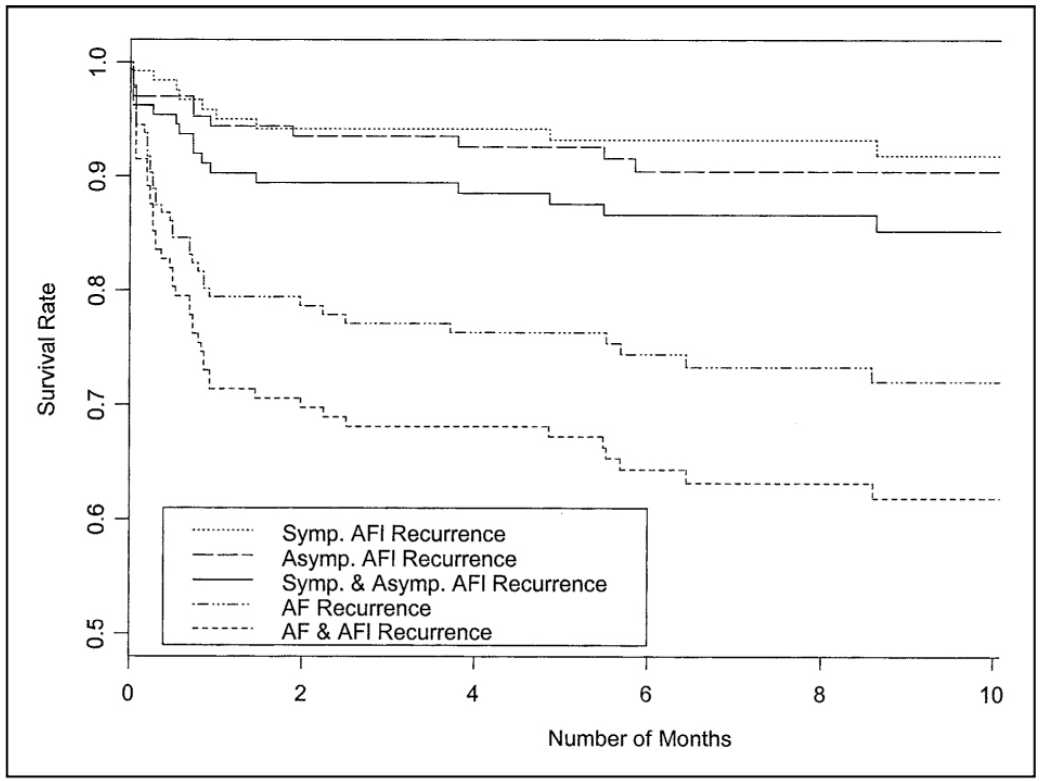

FIGURE 1. Survival rate from recurrent typical atrial flutter (AFl) and atrial fibrillation (AF).

- 12 recurrences of typical atrial flutter
- 4 symptomatic
- 8 asymptomatic

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Conclusions

- 96% of prior studies used clinical endpoints; including all the studies used to develop the OPCs
  - Event recording was not routinely employed
- Because of this, the published literature underestimates the true recurrence rate of atrial flutter following RF catheter ablation

Study Design and Endpoints

Gregory Feld, M.D.
Professor of Medicine
Director, Cardiac Electrophysiology Program
University of California, San Diego

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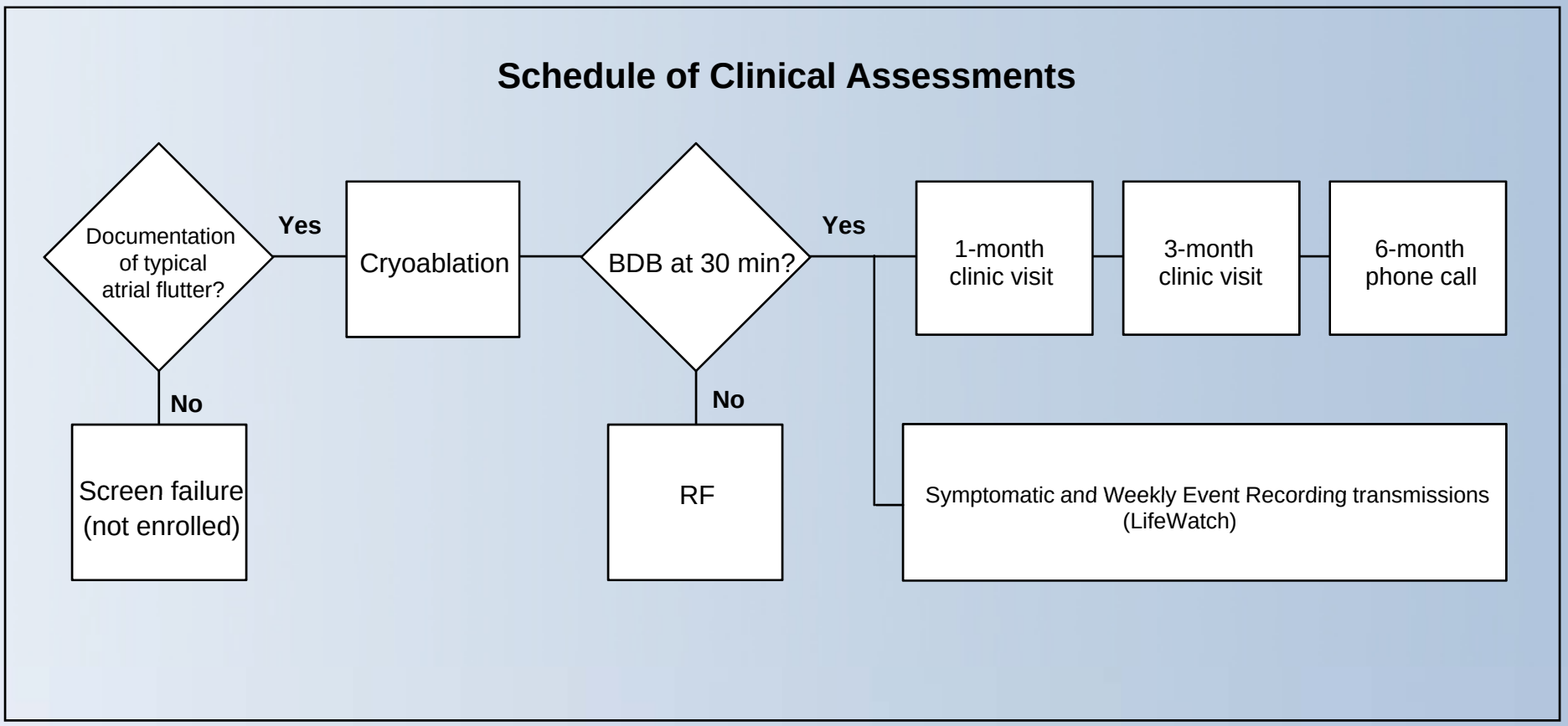
Study Design

- Non-randomized; 24 US sites



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Major Inclusion Criteria

- Age between 18 and 75
- Symptomatic atrial flutter with at least one episode within the last six months, documented on ECG
- Documentation of isthmus-dependent right-atrial flutter as evident from pacing and/or mapping (performed in the EP lab just prior to ablation)
- Willingness, ability and commitment to participate in follow-up evaluations

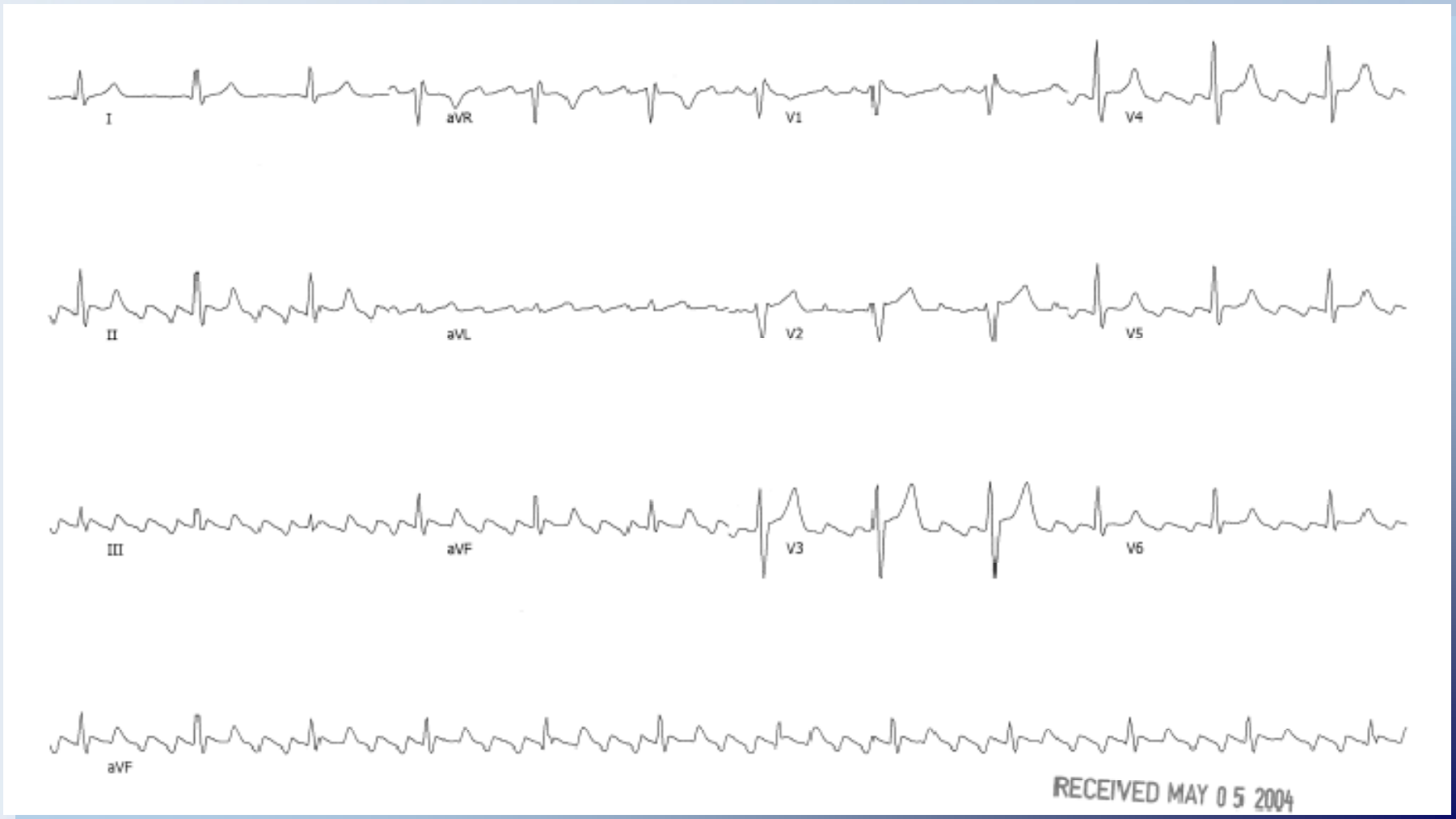
Exclusion Criteria

- Structural heart disease of clinical significance including:
  - Cardiac surgery within six months of screening
  - Unstable symptoms of congestive heart failure (CHF) including NYHA Class III or IV CHF at screening and/or ejection fraction <30% as measured by ECHO or catheterization
  - Right-sided heart valve prosthetics
  - Myocardial infarction (MI) within three months of screening
  - Unstable angina or ongoing myocardial ischemia
  - Corrected or uncorrected atrial septal defect (ASD)
  - Congenital heart disease where either the underlying abnormality or its correction prohibits or increases the risk of cryoablation

Exclusion Criteria (con't)

- Any prior ablation for atrial flutter
- Any prior ablation (other than atrial flutter) within three months of screening
- Concomitant atrial fibrillation requiring AAD treatment other than Class IC or Class III for conversion to atrial flutter
- Any concomitant ventricular arrhythmia requiring pharmacological treatment that would interfere with the interpretation of the results from this study
- Severe electrolyte abnormalities at the time of treatment
- Pregnancy
- Any contraindication to cardiac catheterization
- Poor general health that, in the opinion of the investigator, will not allow the subject to be a good study candidate (i.e. other disease processes, mental capacity, etc.)
- Enrollment in any other ongoing protocol

Typical Atrial Flutter



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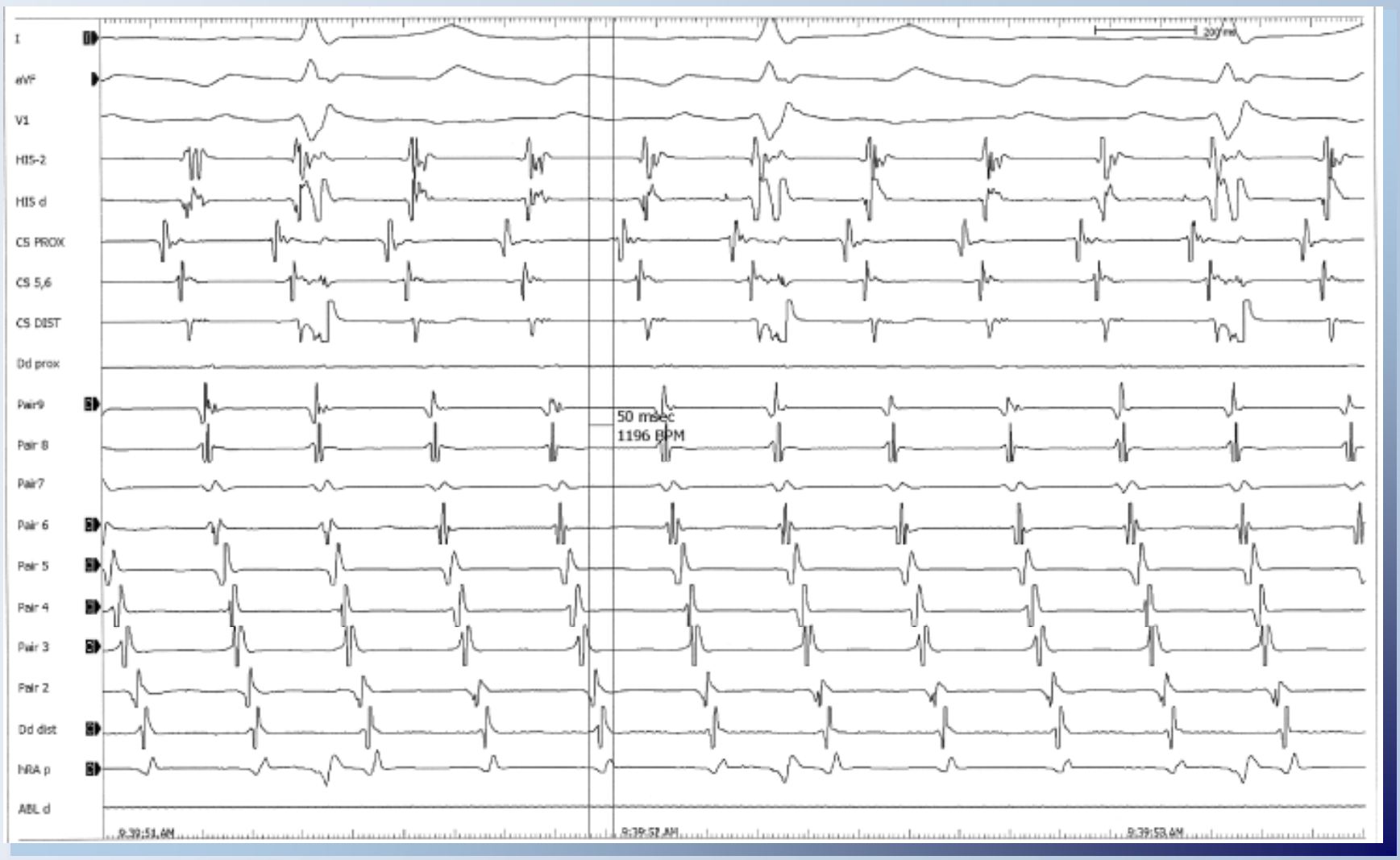
Documentation of Isthmus Dependent Atrial Flutter



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Prior and Concomitant Therapies Allowed

- Subjects with a history of AFib who converted to AFL when placed on anti-arrhythmic drugs were allowed
  - Class 1C and III agents were allowed as treatment for AFib
- Medications changes were at the discretion of the investigator

Acute Endpoints

- Acute Safety- Serious Adverse Events within 7 days of the index procedure
  - Goal: Cryoablation should meet the OPC for safety - upper confidence bound of $\leq$ 7%
- Acute Effectiveness- Bidirectional Block after a waiting period (30 or 60 min)
  - Goal: Cryoablation should meet the OPC for acute effectiveness - lower confidence bound of $\geq$80%

Chronic Endpoints

- Chronic Safety at 6 months
- Chronic Effectiveness - no recurrence of atrial flutter at 6 months, based on OPCs and strict event recordings

Study Endpoint	Target Value	95% Confidence Bound
Acute Success	> 95%	≥ 80%
Chronic Success	>90%	≥ 80%
7 Day SAEs	< 2.5%	≤7%

Sample Size

- Calculated based on primary safety endpoint
- Determined to be 160 patients

Censored Patients

- Compliance was defined as completing at least 3 event recordings per month for at least 5 of the 6 months of observation
- Patients were censored at the point where they became non-compliant with their event recordings

Significant Protocol Changes

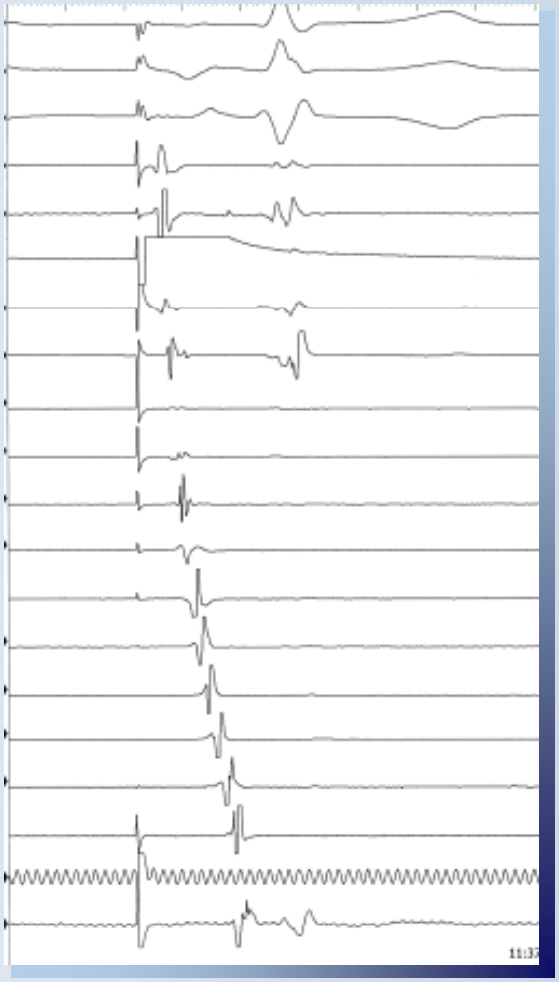
- **60 to 30 minute wait time for BDB**
  - Jan 29, 2004 – involved 109 patients
  - Based on current practice and a review of the literature, the wait to recheck bidirectional block was decreased from 60 minutes to 30 minutes
- **Catheter model change from 1100 to 1200**
  - May 04, 2004 -- involved 71 patients
  - Change made for ease of manufacturing
  - Extensive testing was performed to demonstrate that the lesion sizes were equivalent

Cryoablation Procedure

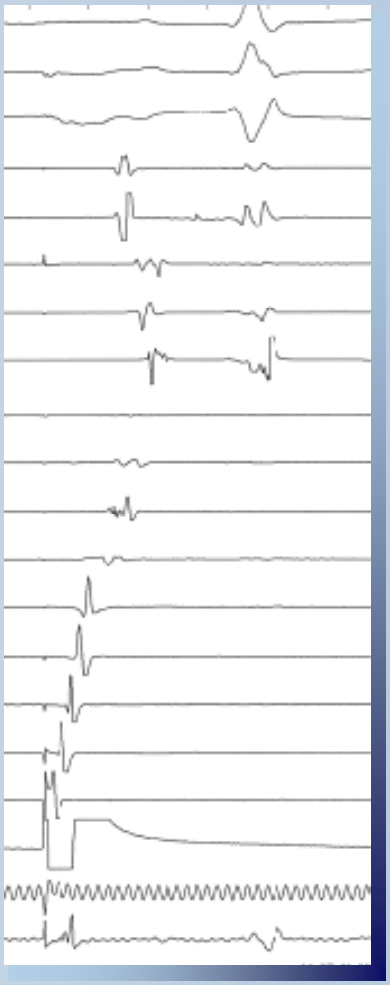
- Standard atrial flutter ablation procedure
- Freezes up to 5 minutes- majority were 2 minutes
- Confirmation of bidirectional block

Example of Bidirectional Block

CS Pacing



LRA Pacing



Initial Submission Issues

Albert Waldo, M.D.

The Walter H. Pritchard Professor of Cardiology, Professor of Medicine, and Professor of Biomedical Engineering

Case Western Reserve University School of Medicine

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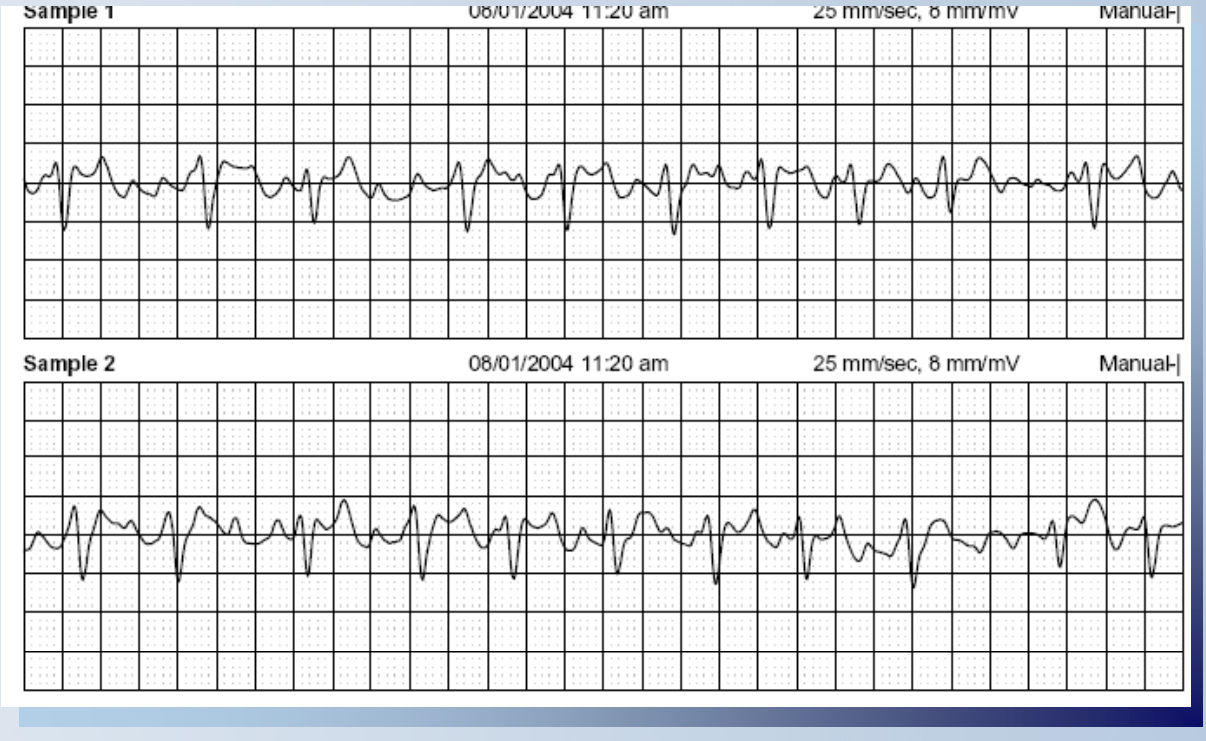
Initial Submission Issues

- Scientific Advisory Board was asked to review the process and make recommendations

Introduction of an Expert Core Lab

- In the initial analysis, the event recordings were not interpreted by an experienced electrophysiologist, but by a technician
- Overall, 41% of patients had atrial fibrillation at some point after the AFL ablation
  - This was one factor that may have led to misinterpretation of the data
- An unbiased and blinded expert core lab was recommended (Dr. Scheinman at UCSF) to accurately interpret the event recordings

Representative Misinterpreted Event Recording



038-03

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Success to Failure

TRANSTELEPHONIC ARRHYTHMIA MONITORING REPORT

DOCTOR INFORMATION	PATIENT INFORMATION
MD: 37	Name: 037CKH003

OVER-READ FINDINGS:

EXPERT CORE LAB: AFL-PRESENT, A TACH VS. AFLUTTER WITH 2:1 AV BLOCK

#	Date	Time		
38	08/02/2004	11:58 pm	MISSED B	
39	08/07/2004	02:13 pm	WEEKLY RECOR	
40	08/09/2004	11:34 pm	NOT FEELING WELL	SINUS RHYTHM, PACS

PRESENT TRANSMISSION (# 41) - 08/12/2004 01:01 am (CST)

Symptoms: NOT FEELING WELL

Patient Activity: DAILY ACTIVITIES

Preliminary Findings: SINUS TACHYCARDIA

Comments: REPORT POSTED TO THE WEB.
FOLLOW UP ECG SHOWS : SINUS RHYTHM.
REPORT FAXED TO MD OFFICE.
PATIENT ASYMPTOMATIC AT THE TIME OF TRANSMISSI

Event Recorder Data: Recorder ID: 209874 Pre-Event Length: 0 sec.
Number of Channels: 1 Post-Event Length: 32 sec.

Tech / RN: sandra steininger, ms

Measu

Rate
117.6 - 119.

PR
0.10 - 0.13 (s)

QRS
0.07 - 0.07 (s)

QT
0.39 - 0.39 (s)

EXPERT CORE LAB: AFL-PRESENT, A. TACH VS. AFLUTTER WITH 2:1 AV BLOCK

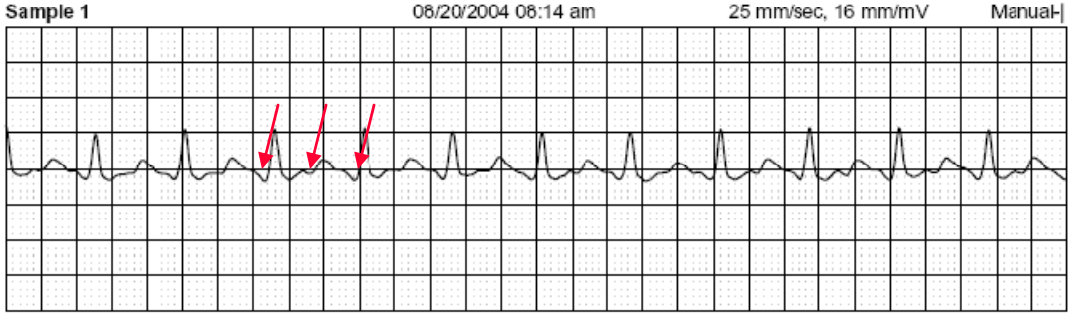
LIFEWATCH: SINUS TACHYCARDIA

MD Signature: _____ **Tech / RN:** sandra steininger, ms

Measurements:

Rate
117.6 - 119.4 (bpm)

PR
0.10 - 0.13 (s)



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Conclusions

- A careful and rigorous approach to have an unbiased, blinded expert core lab evaluate the event recordings

Event Recordings- Core Lab

Melvin Scheinman, M.D.

Professor of Medicine, Emeritus
University of California San Francisco
Walter H. Shorenstein
Endowed Chair in Cardiology

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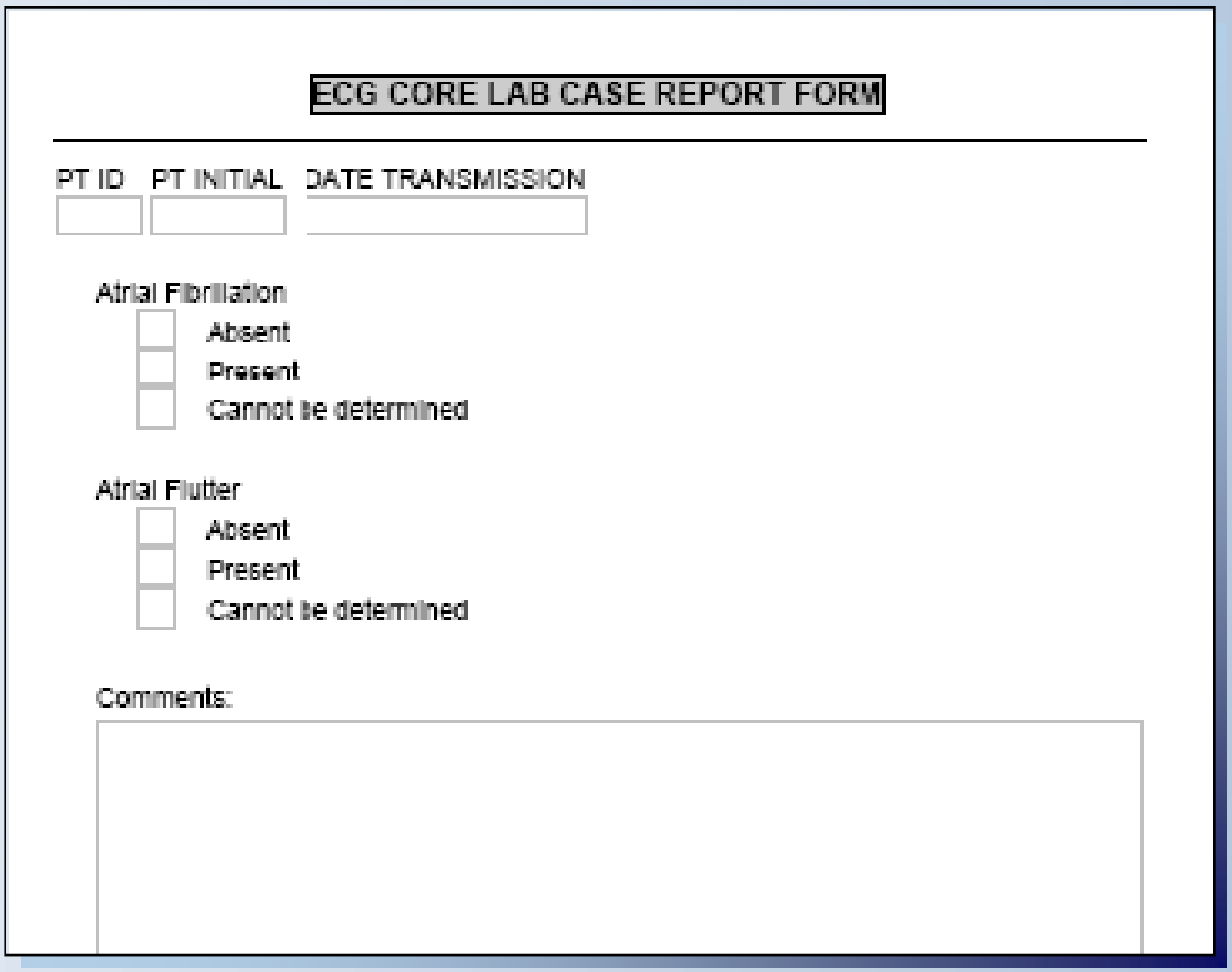
Process

- All event recordings were read independently by Dr. Scheinman and Dr. Yanfei Yang
  - Discrepancies were adjudicated but final decision made by Dr. Scheinman
- Read individual event recordings per patient
- No other ancillary information
- Blinded to the study protocol
- Blinded to original LifeWatch reading

Form Used



ECG CORE LAB CASE REPORT FORM

PT ID | PT INITIAL | DATE TRANSMISSION

Atrial Fibrillation
- Absent
- Present
- Cannot be determined

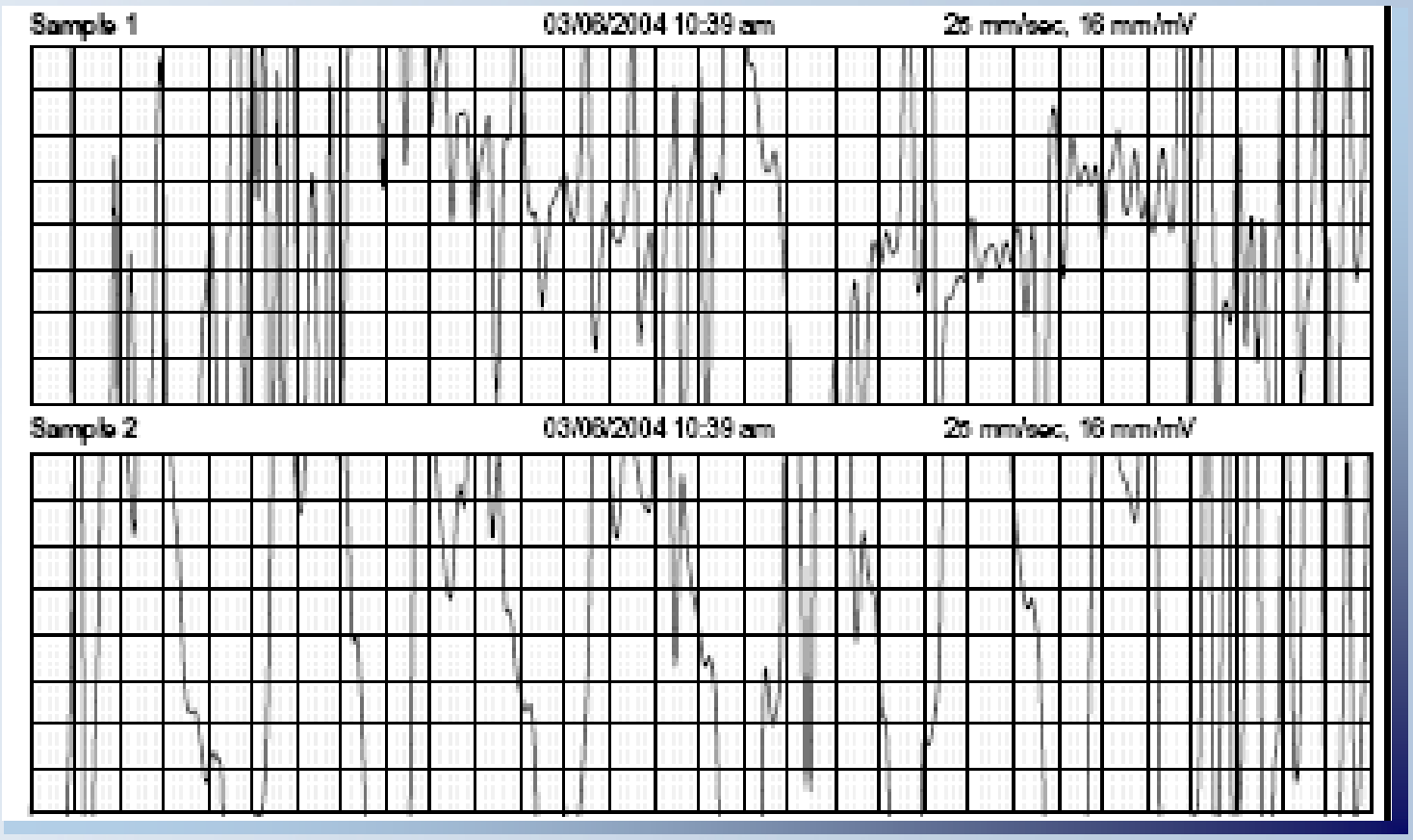
Atrial Flutter
- Absent
- Present
- Cannot be determined

Comments:

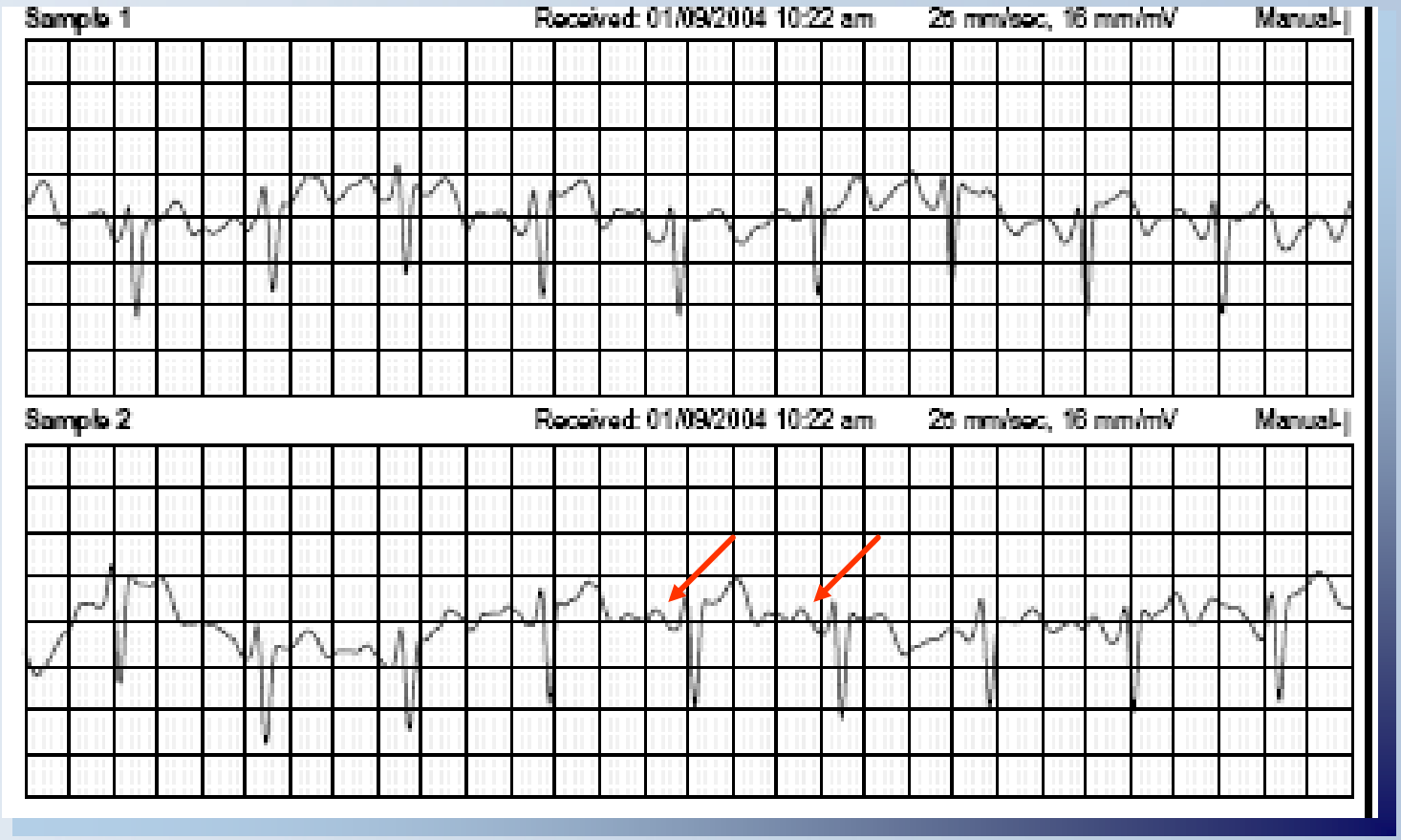
Difficulties of Interpreting Without all the Clinical Information

- Artifacts
- Coarse atrial fibrillation mimicking atrial flutter
- Slow atrial flutter vs. atrial tachycardia

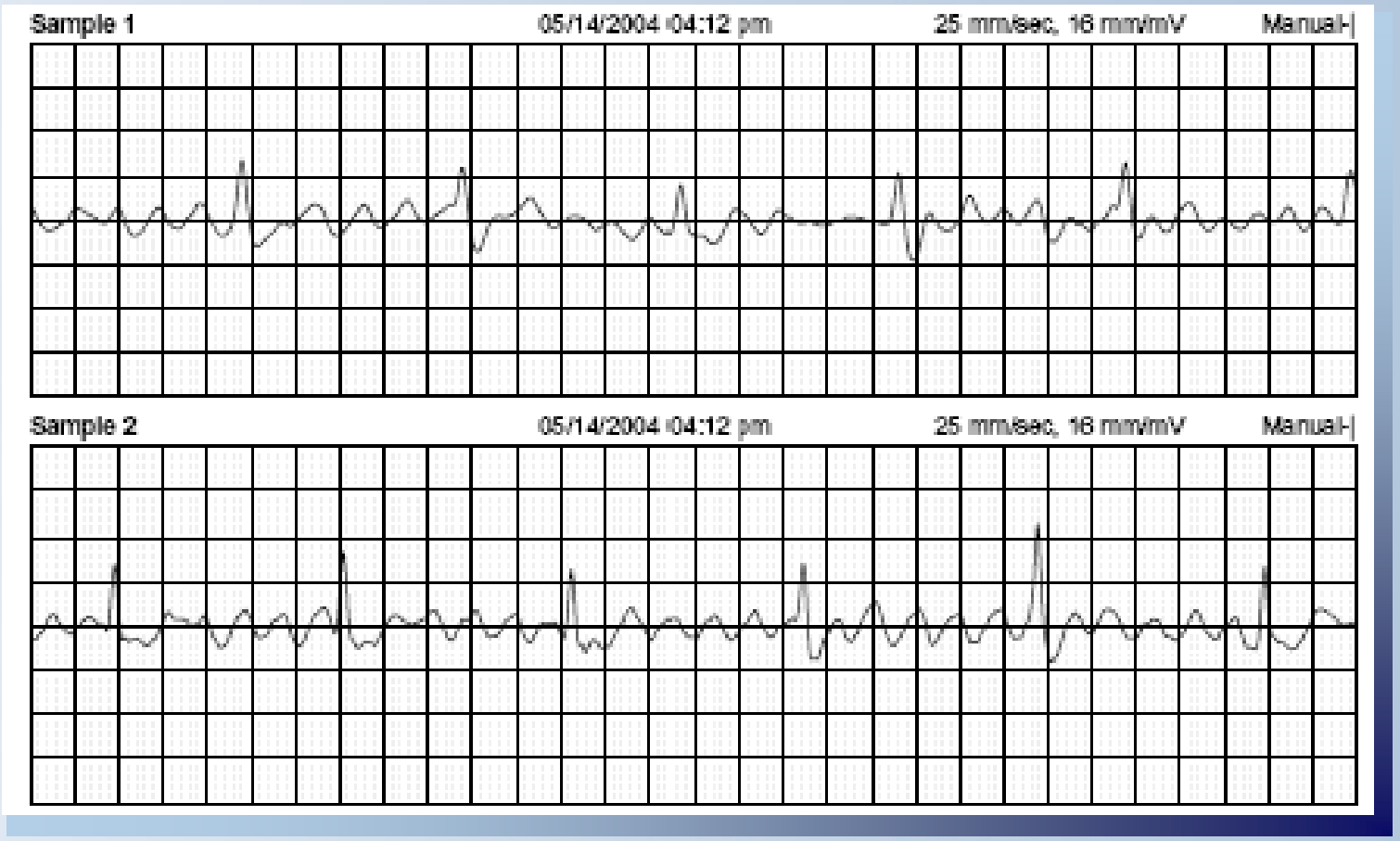
Artifact/Indeterminate



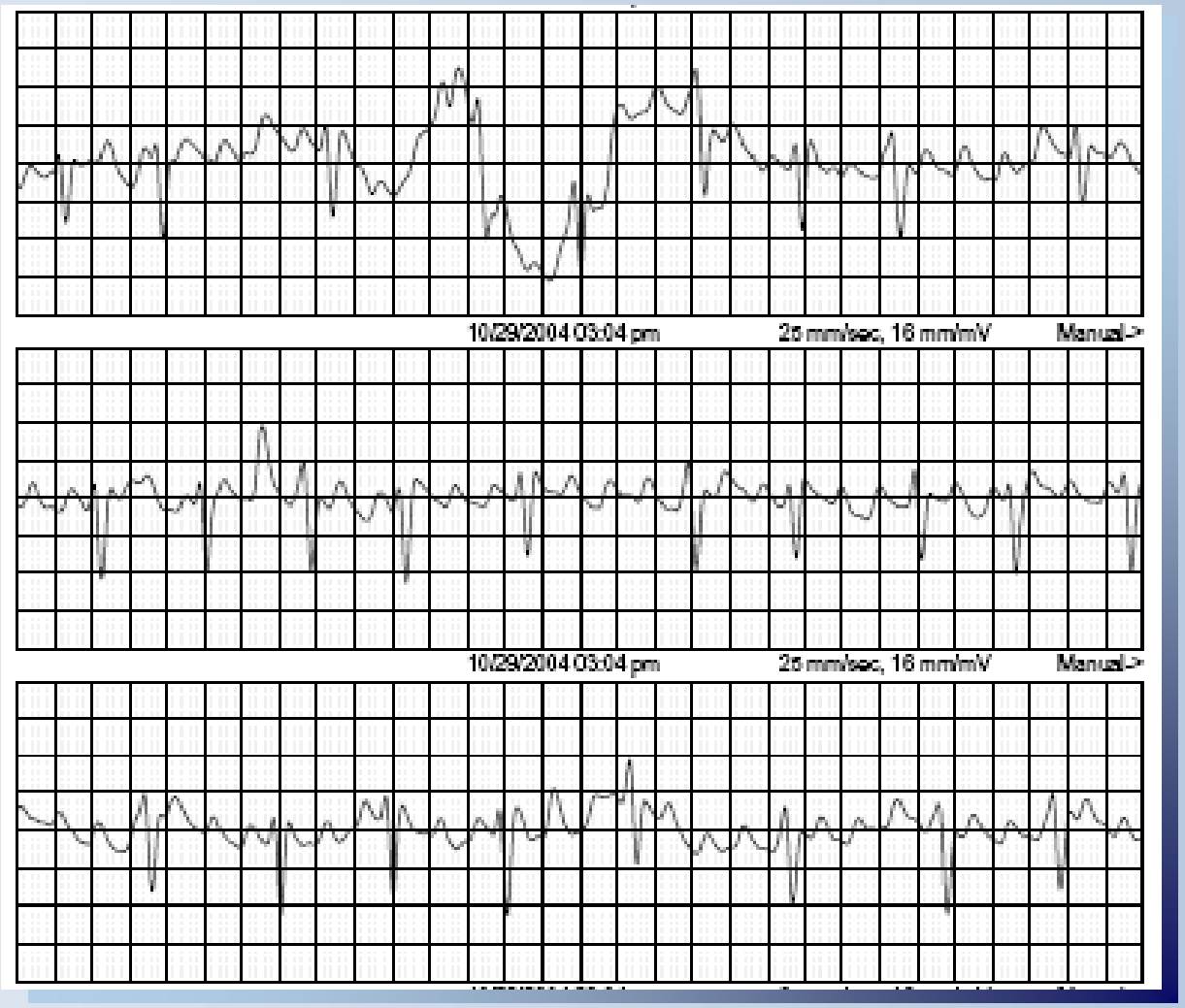
Sinus Rhythm- Artifact



Sinus Rhythm with Artifact



Coarse Atrial Fibrillation



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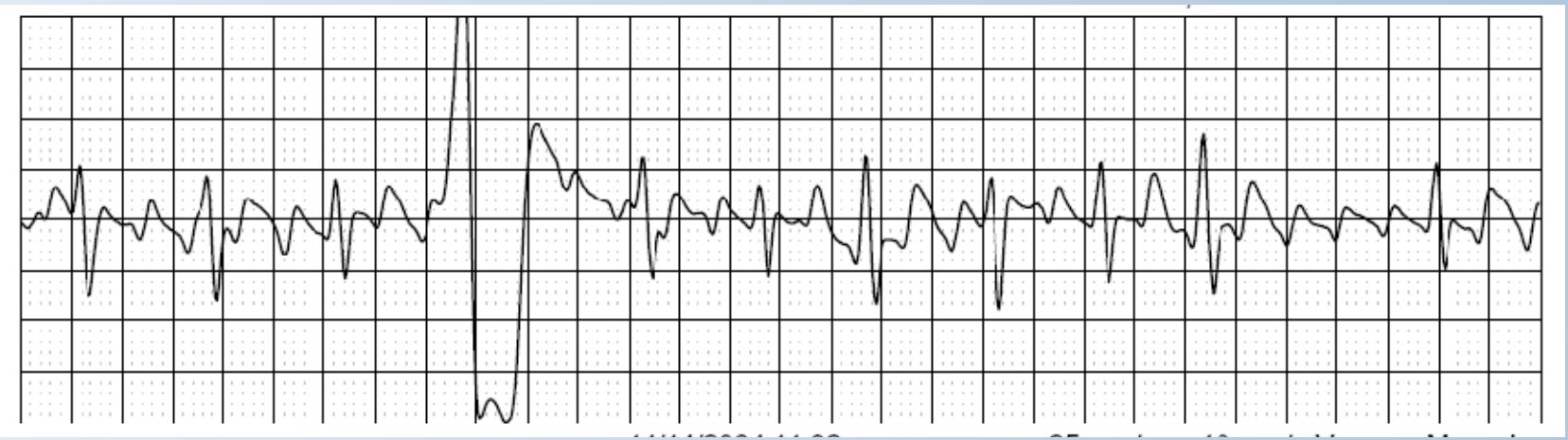
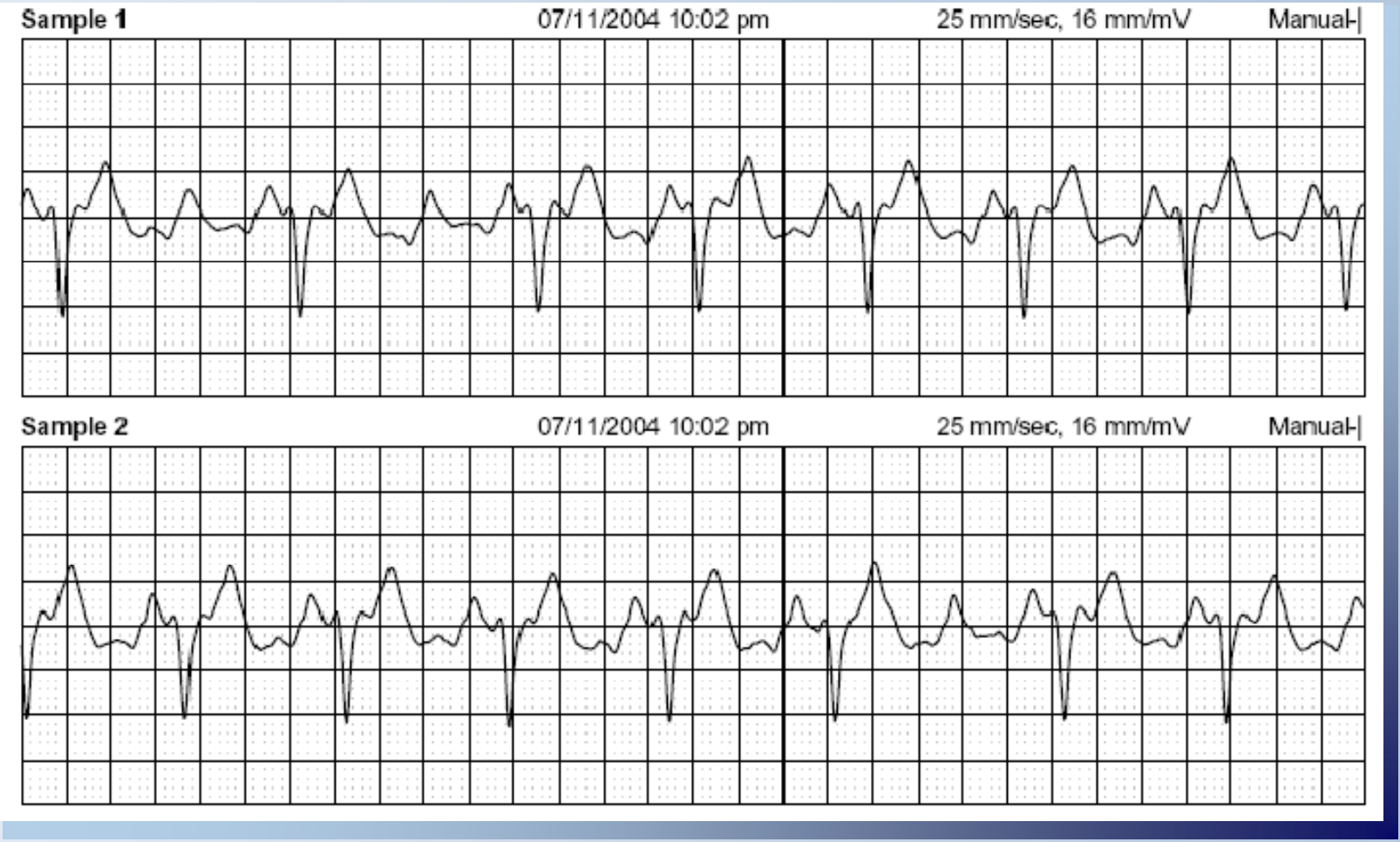
Transient Atrial Flutter
Only seen on one event recording



AT vs Slow Flutter



CryoCor, Inc.

Conclusions

- Event recordings alone can be difficult to interpret
- Sometimes more information is available to make the appropriate clinical evaluation
  - Unable to tell if AFL is CTI dependent
  - If there was only one episode where AFL was unable to be excluded, it was considered a failure
  - Atrial tachycardias- the clinician has pre-ablation data to differentiate AT from AFL

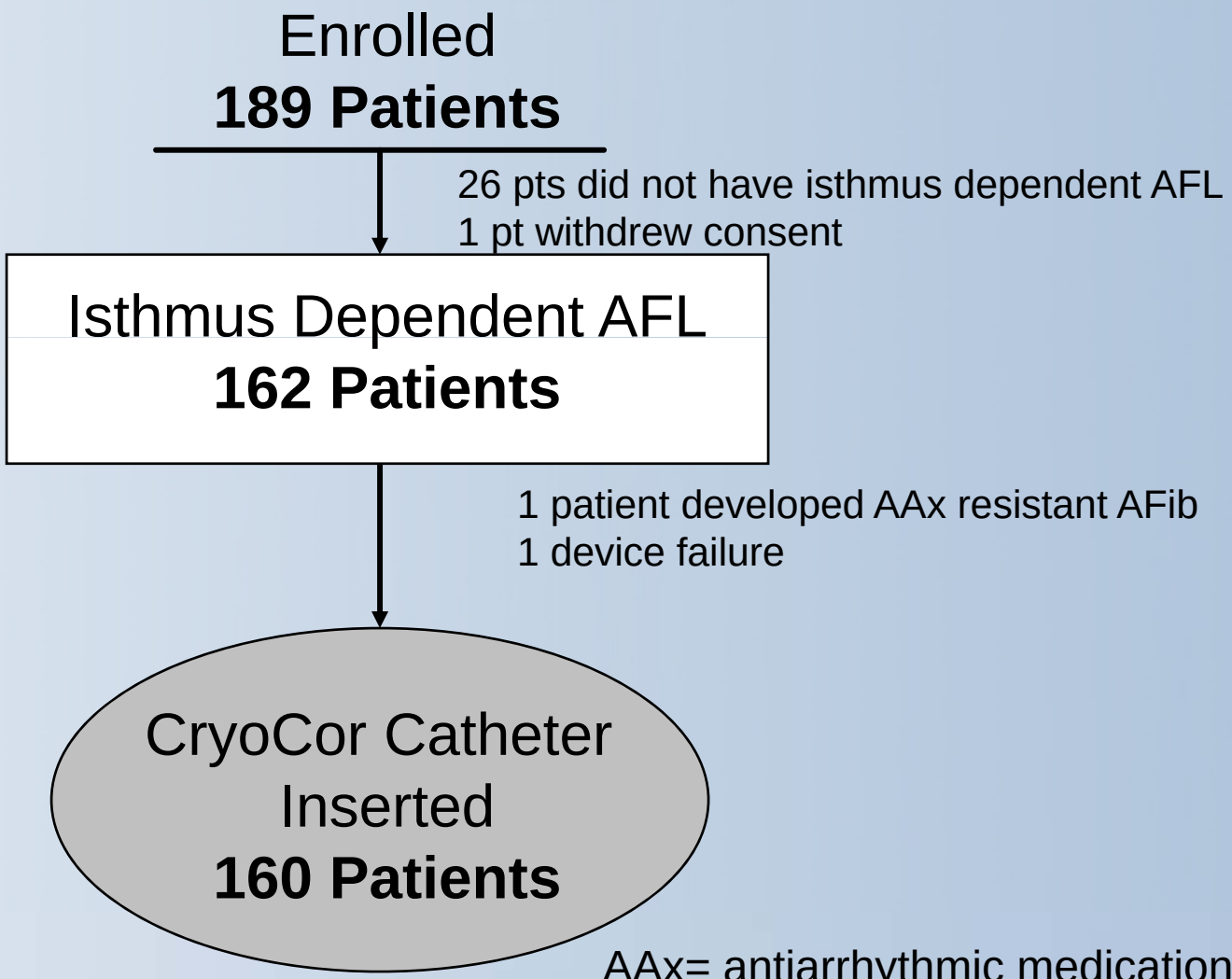
Study Results

James Daubert, M.D.

Associate Professor of Medicine
Director of Electrophysiology Service
University of Rochester Medical Center

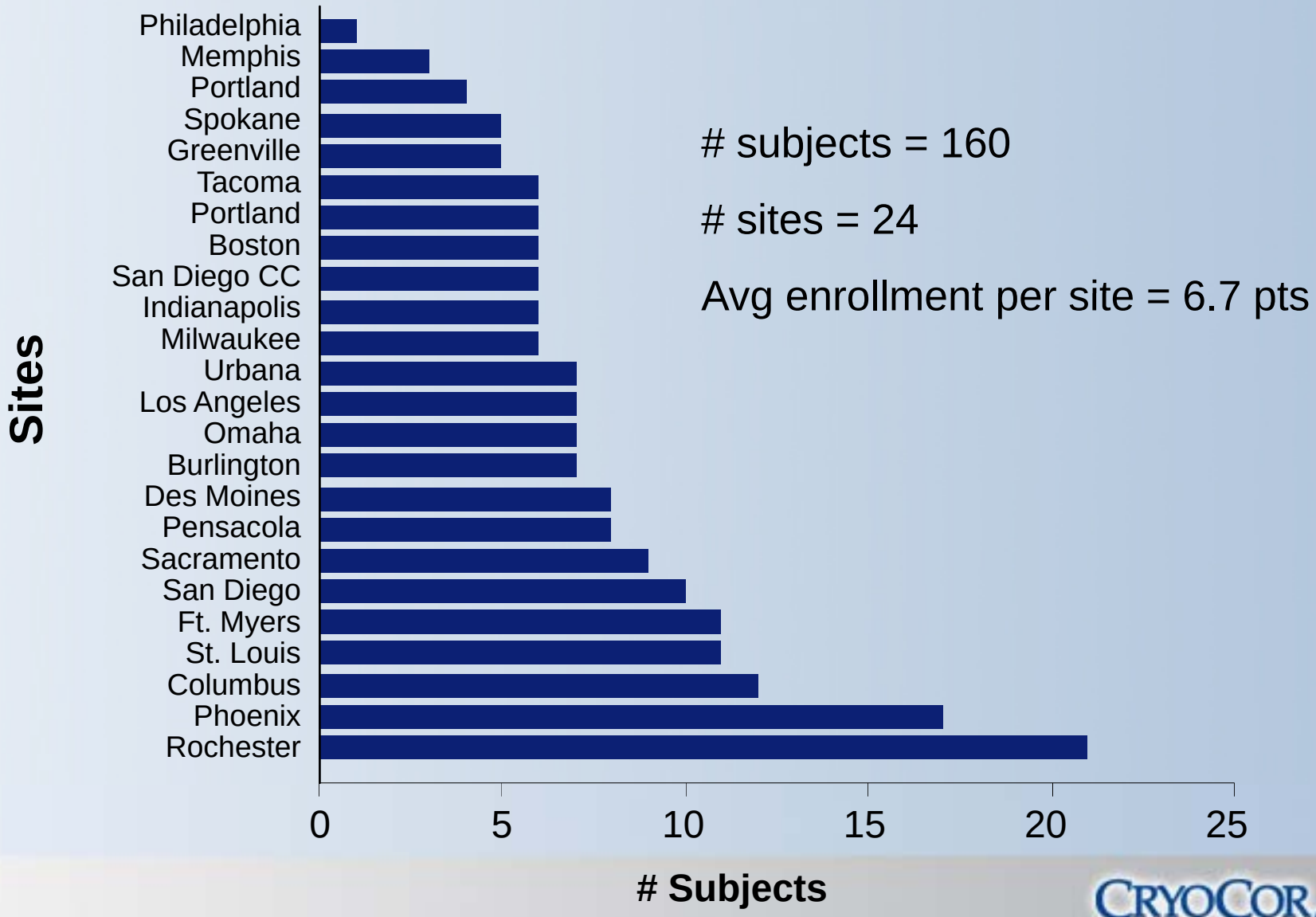
CRYOCOR, Inc.

Patient Accountability



AAx= antiarrhythmic medication

Patient Enrollment by Site



subjects = 160

sites = 24

Avg enrollment per site = 6.7 pts

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Subject Demographics

	Subject No. (%)
Male/Female	122/38 (77% male)
Age (mean ± SD)	63.03 ± 9.25 years
AF History	94 (59%)
Cardiomyopathy	16 (10%)
Congestive Heart Failure	27 (17%)
Diabetes	27 (17%)
Hyperlipidemia	84 (53%)
Ischemic Heart Disease	30 (19%)
Obesity	44 (28%)
Previous MI	26 (17%)
Systemic Hypertension	98 (62%)
Tobacco Abuse	18 (12%)
Ejection Fraction <= 40	25 (16%)

2 patients had prior ablations: Afib (PVI) and WPW

Antiarrhythmic Drug Use

- 57 (36%) were on AAx for Afib at time of ablation

	N	%
AMIODARONE	24	15.0%
FLECAINIDE	13	8.1%
PROPAFENONE	9	5.6%
SOTALOL	9	5.6%
DOFETILIDE	1	0.6%
PROCAINAMIDE	1	0.6%
	57	35.6%

Cavo-Tricuspid Isthmus Dependent Atrial Flutter

Counterclockwise	126 (78.8%)
Clockwise	22 (13.8%)
Both	9 (5.6%)
Unspecified	3 (1.9%)

Acute Procedural Data

Description	Mean	SD
# of Freezes	20.45	11.34
# of Effective Freezes	18.61	9.30
Average Freeze Time (min)	2:20	:30
Average Temp °C	-81.52	3.73
Minimum Temp °C	-85.56	3.61
Fluoroscopy Time (min)	35	26
Procedure Time (hrs)*	3:20	1:11

* Includes 30 or 60 minute wait time

Acute Safety (7 day SAE rate)

	Count	Percent	95% One-Sided CL	95% Two-Sided CL
7 Day SAEs	9/160	5.63%	UCL: 9.61%	(3.02%; 10.35%)
7 Day SAEs (D&P)	**4/160***	**2.50%**	**UCL: 5.63%**	**(0.69%; 6.28%)**

*Device and Procedure Related SAEs

- Post Procedural hematoma
- AV block requiring permanent pacemaker
- Tamponade 6 days after procedure
- Acute respiratory failure

All SAEs were adjudicated by the DSMB

Chronic Safety

Study Endpoint	Count	%	95% One-Sided CL	95% Two-Sided CL
SAEs post-7 days	28/160	17.50%	UCL: 23.06%	(12.41%; 24.14%)
There were no device or procedure related events				

There were 3 deaths during the study – 2 suicides and a pulmonary embolus that was unrelated to the procedure

Acute Procedural Success-
Bidirectional Cavo-tricuspid Isthmus Block

Count	Percent	95% One-Sided CL	95% Two-Sided CL
140/160	87.50%	82.36%	(81.36%; 92.19%)

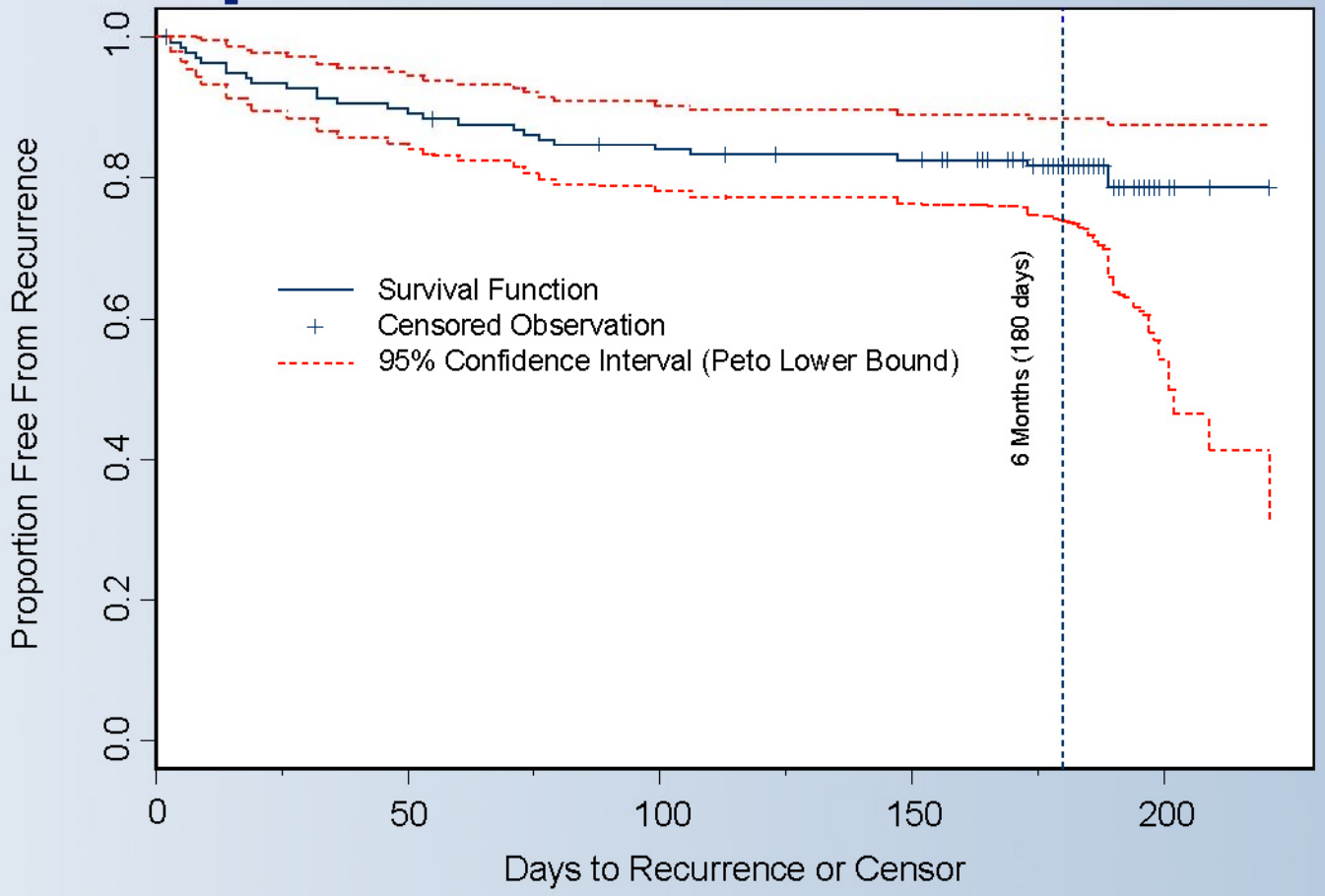
- 19 pts crossed over to RF
- 1 pt had heart block and received pacemaker

Chronic Effectiveness Analysis

Definition: Freedom from atrial flutter recurrence at 6 months

- Expert Core Lab (Primary Analysis)
  - Blinded interpretation by Dr. Scheinman

Chronic Effectiveness Based on Expert Core Lab Outcomes



Survival Estimate	**81.60%**	**LCI: 74.70 % (Peto)**	**OPC ≥80%**
Simple Proportion	**106/132=80.30%**	**LCI: 72.39%**	

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Management of Patients with Recurrence N=26

- 10 subjects underwent re-treatment for atrial flutter
  - 5 with cryoablation
  - 5 with RF
- One electrical Cardioversion for AFL
- 2 started on Amiodarone for AFL
- 13 were as a treated as a “clinical” success

Clinical Determination

- 30-15- one tracing interpreted by Scheinman as AFL. Clinically felt to be PAF. No changes in medication as a result. Clinically felt to be a success.
- 31-07- Scheinman interpretation- AFL with variable AV block, coarse AFib possible. Only one tracing. Other tracings were all afib. Treating clinician reviewed all tracings and interpreted as atrial fibrillation and not atrial flutter. Propafenone was stopped as a result with no further AAx started. Clinically felt to be a success.
- 36-04- only one tracing interpreted as atrial flutter by Scheinman. Clinical interpretation was atrial fibrillation. No AAx changed. Clinically felt to be a success.
- 37-03 only one event recording that was read as Atach vs atrial flutter with 2:1 AV block. According to treating clinician this was non-sustained atrial tachycardia and not atrial flutter. Started the subject on Rhythmol at 6 mo visit. Clinically felt to be a success.
- 37-06- only one tracing with Aflutter. Clinically felt to have PAF and not atrial flutter. Treated with AAx for PAF. Clinically felt to be a success.
- 38-11 only one tracing with atrial flutter. No medication changes. Clinically felt to be a success.
- 39-03 Scheinman interpretations could not rule out atrial tachycardia. Clinically felt to be a success with no recurrence of atrial flutter. No medication changes.
- 40-01 only one tracing with interpretation of atrial flutter. Clinician did not feel it was atrial flutter. No medication changes. Clinically felt to be a success.
- 44-04 -only one tracing with atrial flutter. Clinically felt not to be flutter. No medication changes. Clinically felt to be a success.
- 50-02 Scheinman interpretation was ? on AFL, probably not in view of other tracing could be fortuitous relationship of biphasic T and P wave. Clinically felt to be a success
- 51-03 only one tracing interpreted by Scheinman as atrial flutter. Clinician interpreted tracings as AFib and not atrial flutter with ECGs. Clinically felt to be a success.
- 52-02 Scheinman interpretations as Atrial flutter or atrial tachycardia. Clinically felt to be a success and AAx were stopped.
- 52-05 Clinically felt to be a success and there were no medication changes.

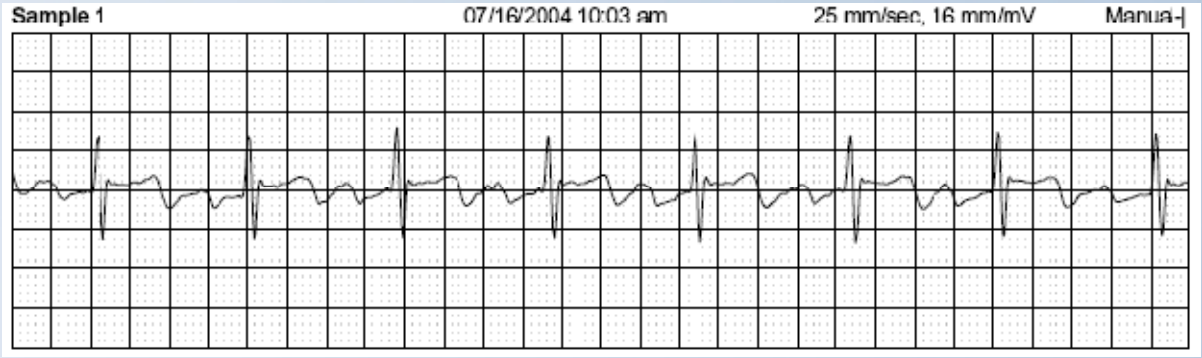
Chronic Effectiveness Analysis

Definition: Freedom from atrial flutter recurrence at 6 months

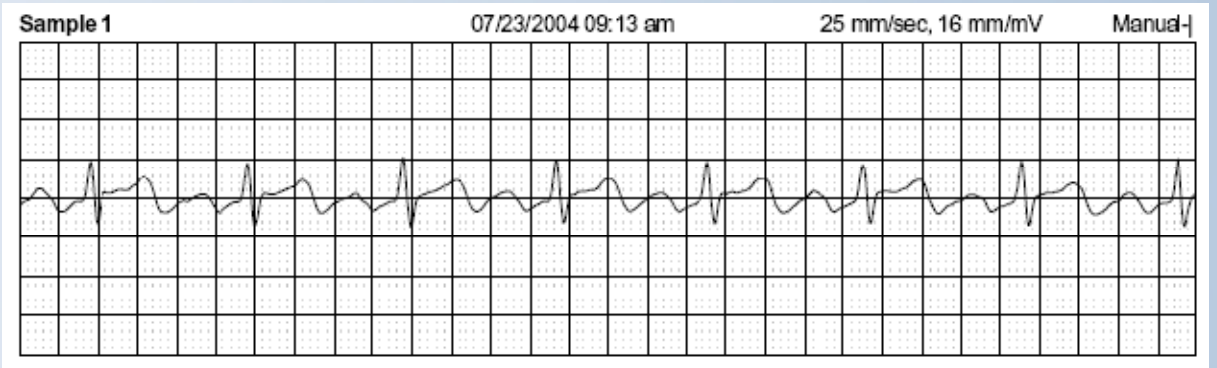
- Clinical Determination (Post Hoc Analysis)
  - All patients were re-evaluated by Dr. Barold
  - Based on clinical interpretation of patient's entire file taking into account treating physician's opinion

Clinical Determination

Sinus Rhythm

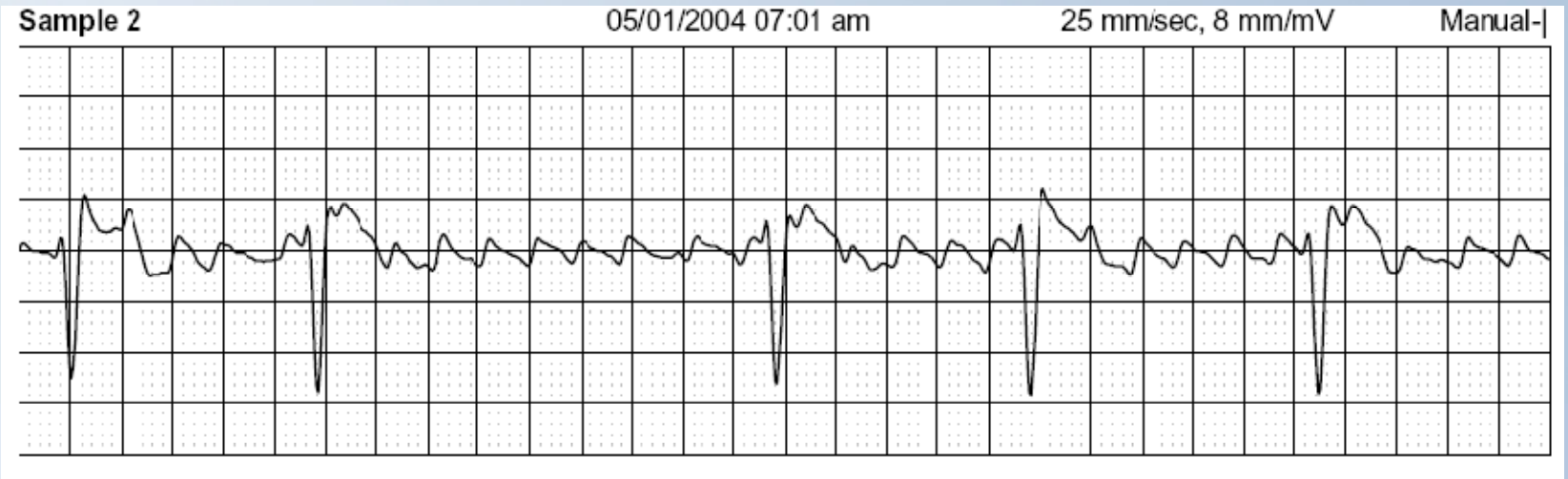


AFL- considered a failure “could be fortuitous relationship of biphasic T and P wave”



Asymptomatic during all event recording, only one tracing was called potentially AFL

- **Expert Core Lab interpretation- AFL with variable AV block, coarse AFib possible. Only one tracing. Other tracings were all afib.**
- **Treating clinician reviewed all tracings and interpreted as atrial fibrillation and not atrial flutter.**
- **Propafenone was stopped as a result with no further AAx started. Clinically felt to be a success.**

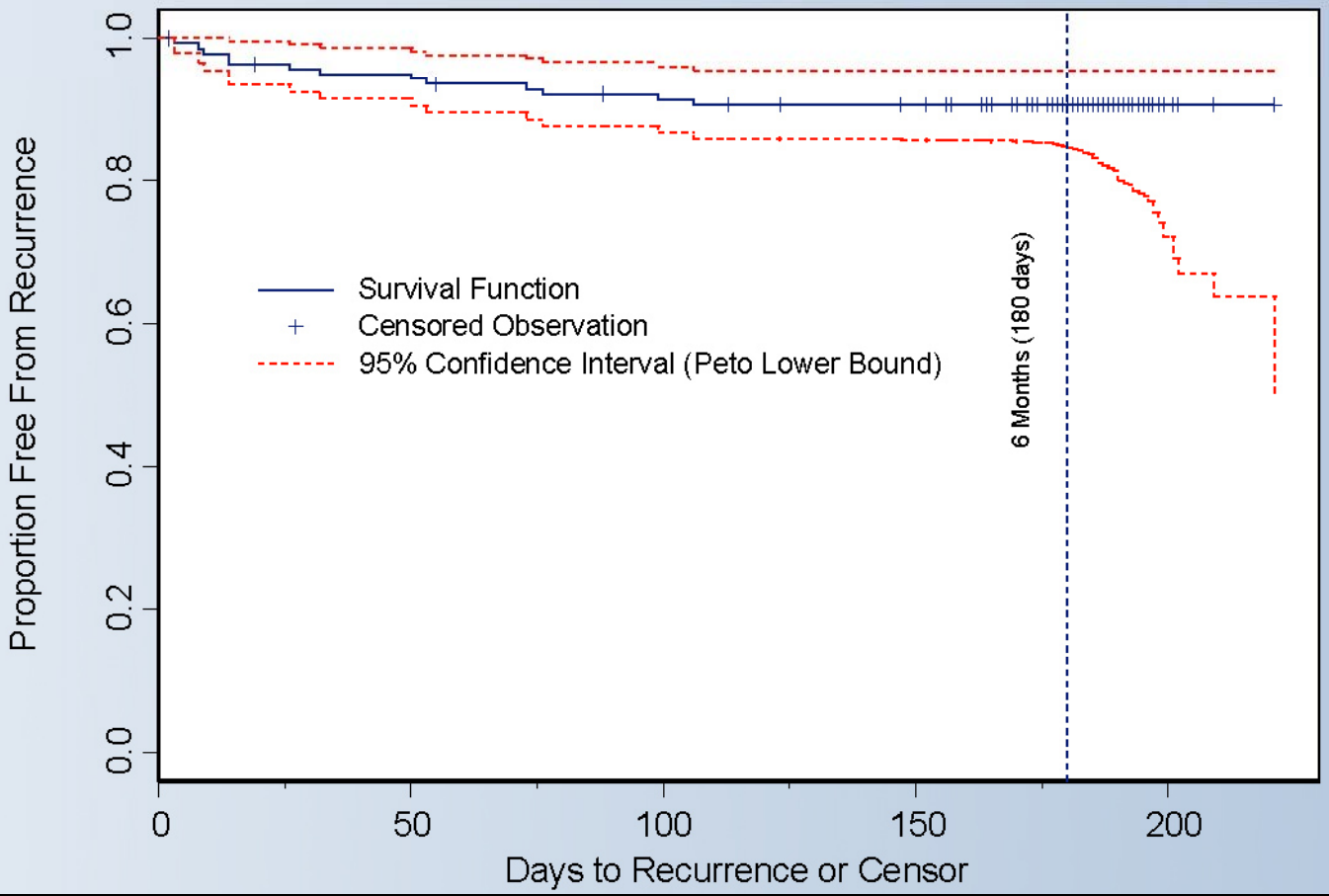


Clinical Determination

5. Additional comments not addressed in previous sections: RECEIVED OCT 18 2004

Patient has symptomatic atrial tachycardia (non-sustained), not atrial flutter. We will begin treatment with Rhythmol SR 225mg BID.

Chronic Effectiveness Based on Clinical Determination



Survival Estimate	90.50%	85.70% (Peto)	95.60%

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Summary Table

Study Endpoint	Percent	95% Two-Sided CL	OPC 95% CI
Acute Safety	5.63%	(3.02%; 10.35%)	≤7%
Acute Safety (D/P)*	2.50%	(0.69%; 6.28%)	≤7%
Acute Effectiveness	87.50%	(81.36%; 92.19%)	≥80%
Chronic Effectiveness**	81.60%	(74.70%; 88.40%)	≥80%
Chronic Effectiveness ***	90.50%	(85.70%; 95.60%)	≥80%

*Device and Procedure Related
**As per strict electrogram interpretation (primary analysis)
***As per clinical analysis

Maastricht Cryoablation Atrial Flutter Clinical Study

Hein Wellens, M.D.

Emeritus Professor of Cardiology

University of Maastricht, The Netherlands

CryoCor, Inc.

Methods

- All patients who underwent cryoablation with the CryoCor System at the Academic Hospital of Maastricht were prospectively placed into a database from June 2001 to January 2006
- Those patients with isthmus dependent atrial flutter who would have met the inclusion criteria for the US study were evaluated
- Exclusions–
  - underwent second EP study/ablation (PVI) during f/u
  - <3 months follow-up

Methods (con't)

- Procedures performed by 2 experienced electrophysiologists
- Patients did not receive sedation for the ablation
- There was a 30 minute waiting period after the last ablation with the addition of isoproterenol.
- Follow-up: all patients came back to the outpatient clinic at 1,3,6 months and yearly or if symptoms developed
  - 24 hour Holter at 1,3 and 6 months

Catheter-Based Cryoablation Permanently Cures Patients With Common Atrial Flutter

Randy Manusama, MD; Carl Timmermans, MD; Froylan Limon, MD; Suzanne Philippens, RN; Harry J.G.M. Crijns, MD; Luz-Maria Rodriguez, MD

Background—Cryoablation (cryo) has a high success rate in the short-term treatment of atrial flutter (AFL), but evidence of long-term efficacy is lacking. The present study reports the long-term effect of cryo of the cavotricuspid isthmus (CTI) in patients with common AFL.

Methods and Results—Thirty-five consecutive patients (28 men; mean age, 53 years) underwent cryo of the CTI. In 34 patients, the AFL had a counterclockwise rotation (cycle length, 242±43 ms). Eleven patients had structural heart disease. Cryo was performed with a 10F catheter with a 6-mm-tip electrode (CryoCor). Applications (3 to 5 minutes each) were delivered by use of a point-by-point technique to create the ablation line. The acute end point of the procedure was creation of bidirectional isthmus conduction block and noninducibility of AFL. A median of 14 applications (range, 4 to 30) at 10 sites (range, 4 to 19) was given along the CTI with a mean temperature of −80.0±5.0°C. Mean fluoroscopy and procedure times were 40±26 minutes and 3.2±1.3 hours, respectively. Of the 35 patients, 34 were acutely successfully ablated (97%). After a mean follow-up of 17.6±6.2 months (range, 9.6 to 26.1 months), 31 patients (89%) did not have recurrence of AFL. Three of the 4 patients with recurrence had a second successful procedure. One patient had transient ST elevation in the inferior leads during cryoapplication.

Conclusions—Cryo produces permanent bidirectional isthmus conduction block of the CTI. Short- and long-term success rates are comparable to those for radiofrequency ablation. (*Circulation*. **2004;109:1636-1639.**)

Maastricht Cryoablation Atrial Flutter Clinical Study

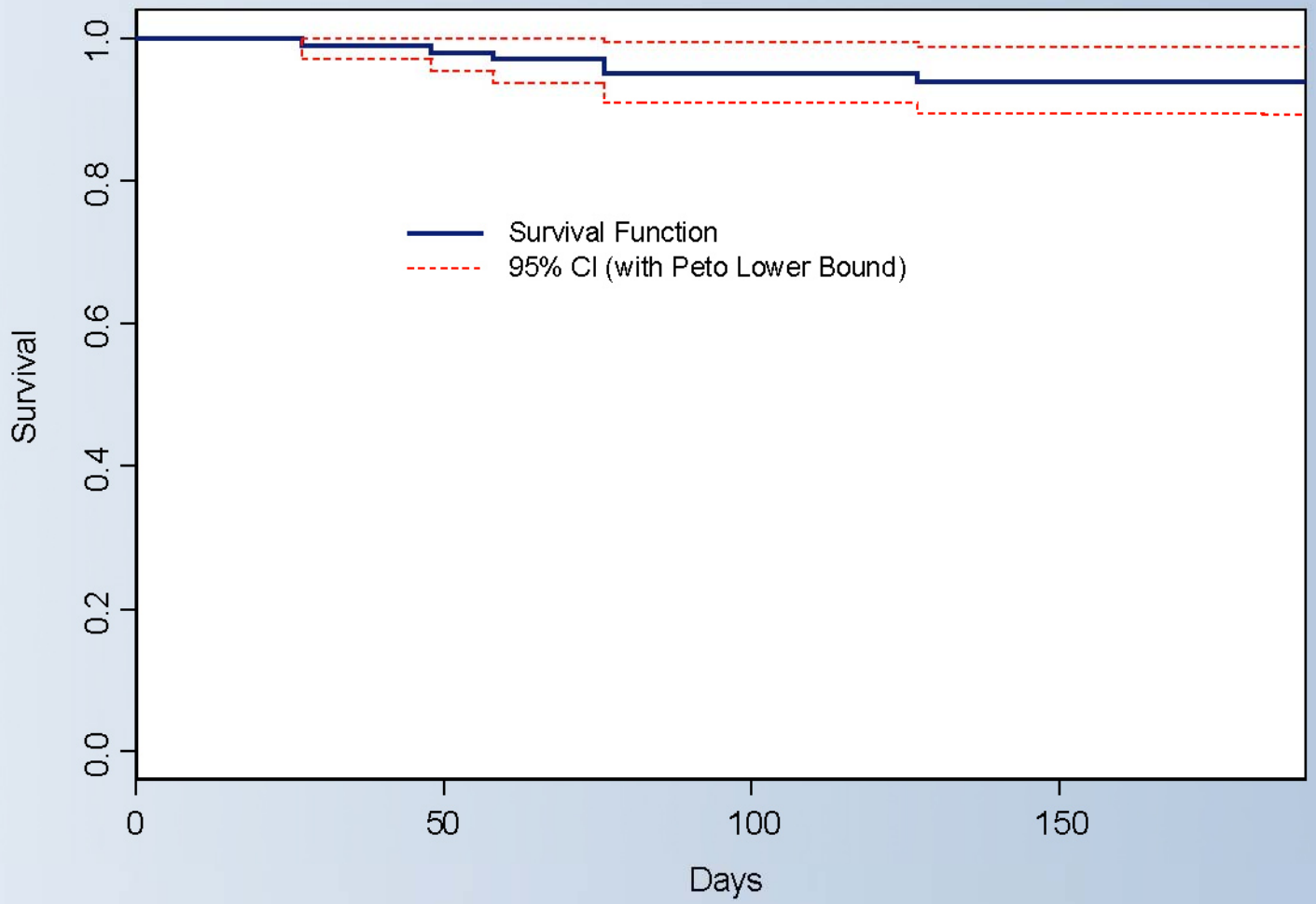
- 111 consecutive patients
  - 77.5% male (86/25)
  - Average age was 56.5 +/- 13.3 years
  - 78.4% had history of AF (87)
- Similar demographics as US pivotal study

Maastricht Cryoablation Atrial Flutter Clinical Study

	Count	95% CI
Acute effectiveness	104/111= **93.69%**	(87.44%; 97.43%)
Chronic Effectiveness at 6 months	91/97 = **93.81%**	(87.02%; 97.7%)

7 patients did not have 6 month follow-up

Maastricht Cryoablation Atrial Flutter Clinical Study



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Conclusions

- CryoCor System has excellent clinical effectiveness
- A similar clinical outcome as the US Clinical Analysis
- Sedation was not necessary during the ablation

Randomized Study Comparing Radiofrequency Ablation With Cryoablation for the Treatment of Atrial Flutter With Emphasis on Pain Perception

Carl Timmermans, MD; Gregory M. Ayers, MD; Harry J.G.M. Crijns, MD; Luz-Maria Rodriguez, MD

Background—Radiofrequency ablation (RF) of atrial flutter (AFL) has a high procedural efficacy, a low recurrence rate, and reports of procedure-related pain. The aim of the present study was to compare RF with cryoablation (cryo) for the treatment of AFL, with emphasis on pain perception during application of energy.

Methods and Results—Fourteen patients (55±11 years, 11 males) with AFL were randomized to receive ablation of the cavotricuspid isthmus (CTI) by either RF or cryo. Cryothermia was delivered with the CryoCor Cryoablation System (10F, 6-mm tip), and radiofrequency energy was delivered with the use of an 8-mm–tip catheter. Pain was evaluated according to a visual analogue scale (VAS; 0 to 100). All patients in the cryo group were successfully ablated with a mean of 18 applications (9 sites), and RF was successful in 6 of 7 patients (not significant) with 13 applications (not significant). The mean temperature was −82°C and 55°C for cryo and RF, respectively. One patient in the cryo group perceived pain, versus all 7 patients in the RF group ($P<0.05$). The proportion of painful applications averaged 75.3% in the RF group and 2.0% in the cryo group ($P<0.05$), whereas the corresponding VAS for pain was 38.3±25.3 and 0.32±0.86, respectively ($P<0.05$). At 6-month follow-up, there were no recurrences of atrial flutter.

Conclusion—Cryo, as compared with RF, produces significantly less pain during application. Although in the present study there was no significant difference in efficacy, larger studies will be needed to definitively compare efficacy. **(*Circulation*. 2003;107:1248-1250.)**

Key Words: atrial flutter ■ catheter ablation ■ arrhythmia

Methods

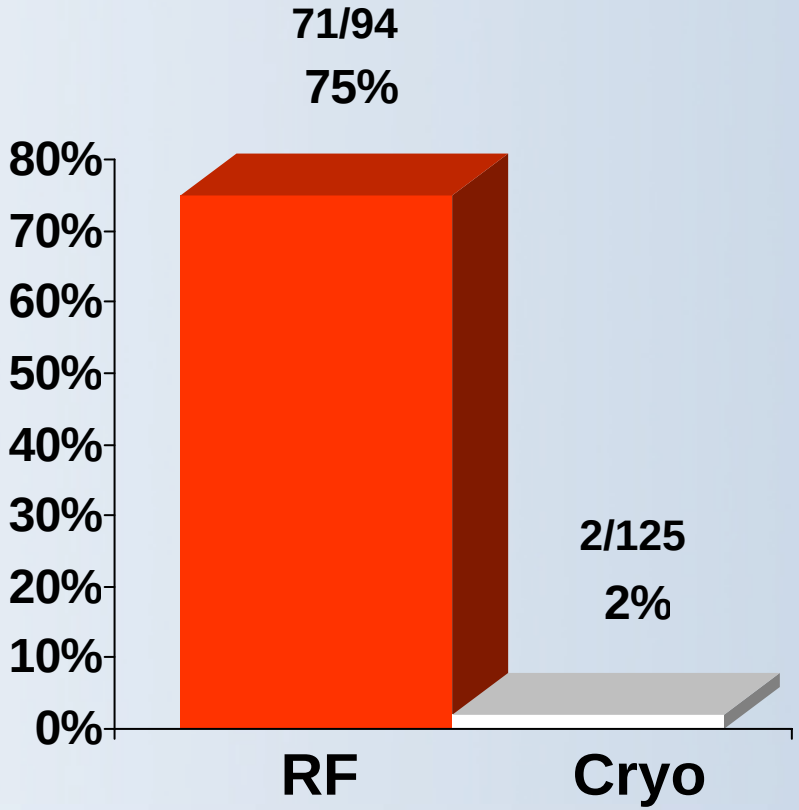
- 14 consecutive patients with isthmus dependent atrial flutter
- Randomized to RF or Cryo (CryoCor System)
  - Patients were blinded to the energy source
- Pain was evaluated using a Visual Analogue Scale (VAS) from 0 to 100 at the end of each application

Results

	RF	Cryo
# applications	94 (13 ± 11)	125 (18 ± 4)
Ave Temp.	55±4°C (50-60°C)	-82±5°C (-69 to -89°C)
Isthmus block	6/7	7/7
# patients who experienced pain	7/7	1/7
Application Time	90 sec	4 min

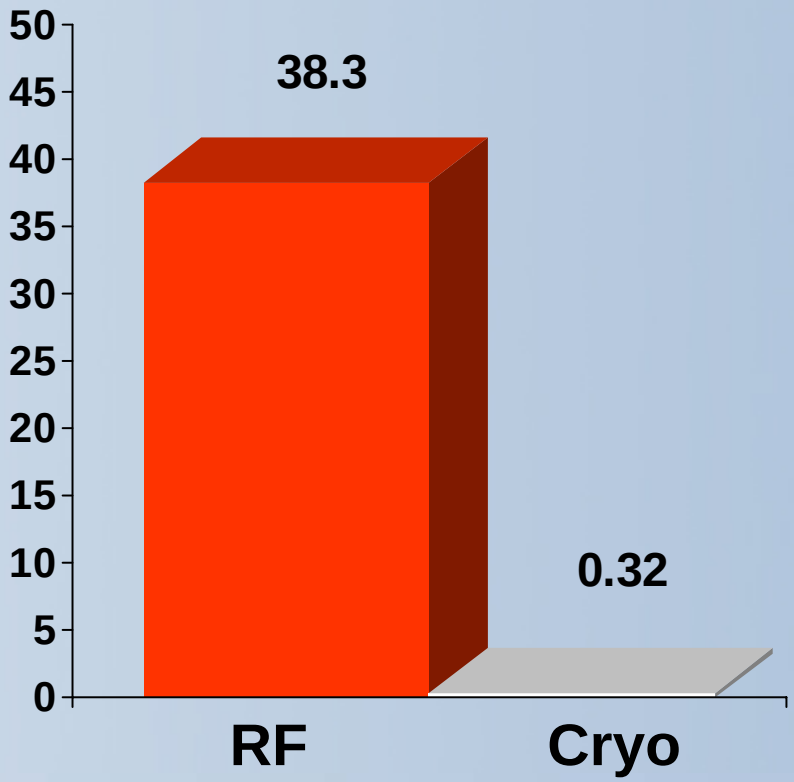
Results

% of Painful Applications



p value <0.0001

Mean Pain Score (1-100)



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Conclusions

- Cryoenergy was significantly less painful than RF
- Cryoenergy is more patient friendly than RF
- Avoids the complications of sedation
  - Especially in certain patient populations- i.e.: COPD; sleep apnea; morbid obesity
- Less patient movement due to pain

Conclusions

Albert Waldo, M.D.

The Walter H. Pritchard Professor of Cardiology, Professor of Medicine, and Professor of Biomedical Engineering

Case Western Reserve University School of Medicine

CRYOCOR, Inc.

Data to Support Approval

- Pre-clinical Data
  - Lesion sizes as large as RF
- US Pivotal Trial
  - Provided data demonstrating a reasonable level of safety and effectiveness
- Maastricht Confirmatory Clinical Study
- Pain study
  - Demonstrated a unique advantage of Cryoablation over RF

Summary

- Results with the CryoCor System are comparable to published RF ablation literature
- Objective Performance Criteria were based on 4 studies using RF ablation where chronic success was determined by routine clinical follow-up alone without the use of event recordings
- Using event recordings can lead to an increased detection of atrial flutter, but may also pick up other atrial arrhythmias that are not endpoints of the study
  - Atrial fibrillation
  - Non-isthmus dependent atrial flutter
  - Clinically insignificant atrial arrhythmias

Summary

- There may be important populations where Cryoablation provides a distinct advantage
- There is no other approved cryoablation device for the treatment of atrial flutter

Conclusion

We Believe this Study Demonstrated a Reasonable Level of Safety and Effectiveness