Cardiac Symptoms of Myotonic Dystrophy

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Disclosures

- Grant Funding
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  - ImriCor
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  - CardioSolv
  - Circle Cardiovascular Imaging

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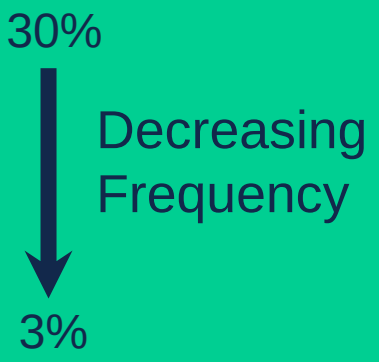
Myotonic Dystrophy and the Heart: Overview

- Cardiac manifestations physiologically due to
  - Myocardial fatty infiltration
  - Fibrosis
- Typical Cardiac clinical manifestations
  - Conduction disturbances and block
  - Atrial Tachy-arrhythmias
  - Cardiac Dysfunction
  - Ventricular Tachy-arrhythmias



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Genetic Basis of DM

- Type I
  - CTG repeat expansion in 3’ untranslated region of the Myotonic Dystrophy Protein Kinase (DMPK) gene on chromosome 19
    - Normal: 5-35 repeats
    - In DM
  - Serine-threonine protein kinase
- Type II
  - Mutations of the CCTG repeat on the zinc finger protein 9 gene on chromosome 3
    - Normal: 11-26 repeats

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Mechanism of Cardiac Manifestations

- Repeat sequences are transcribed to RNA but not translated
- The RNA accumulates in the cellular nucleus and disrupts the splicing of pre-messenger RNA into mature mRNA
  - Muscle specific chloride channel
  - Insulin receptor
- MDPK in the myocardium is localized to the intercalated discs

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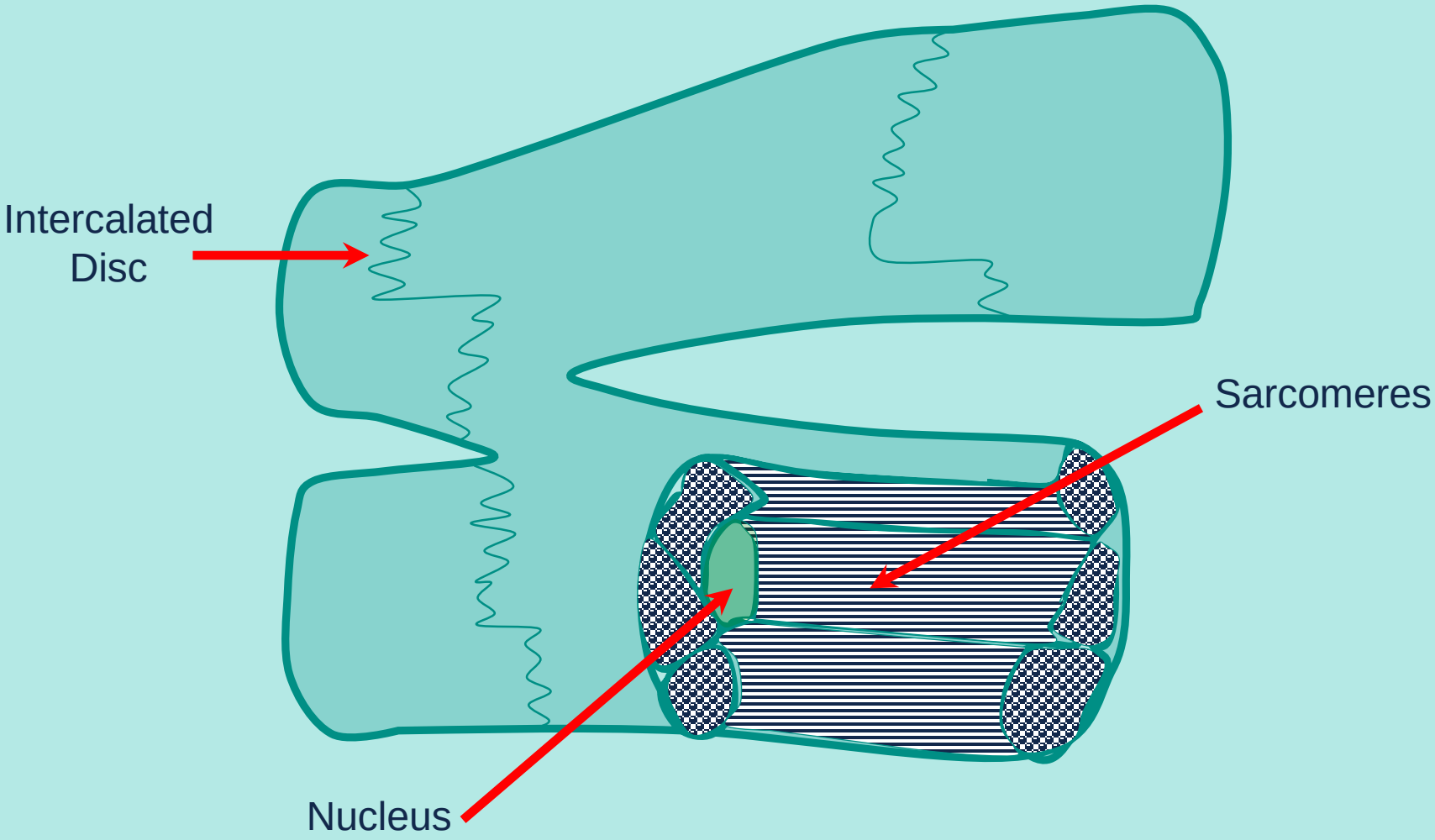
Myocardial Cells



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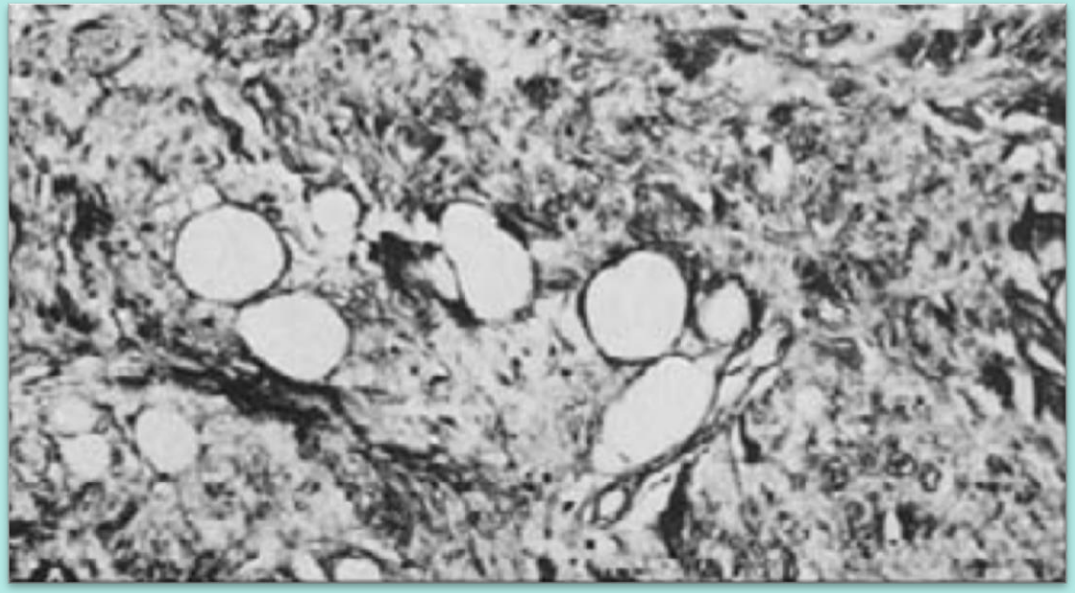
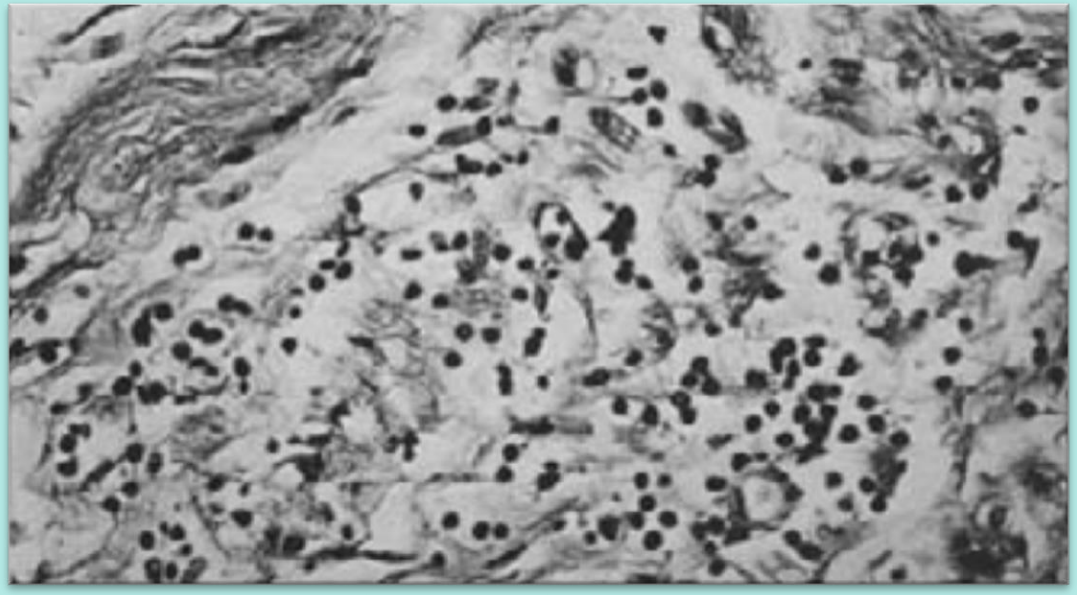
Sinus Node Histology

- Fibro-Fatty Replacement
- Lymphocytic Infiltration





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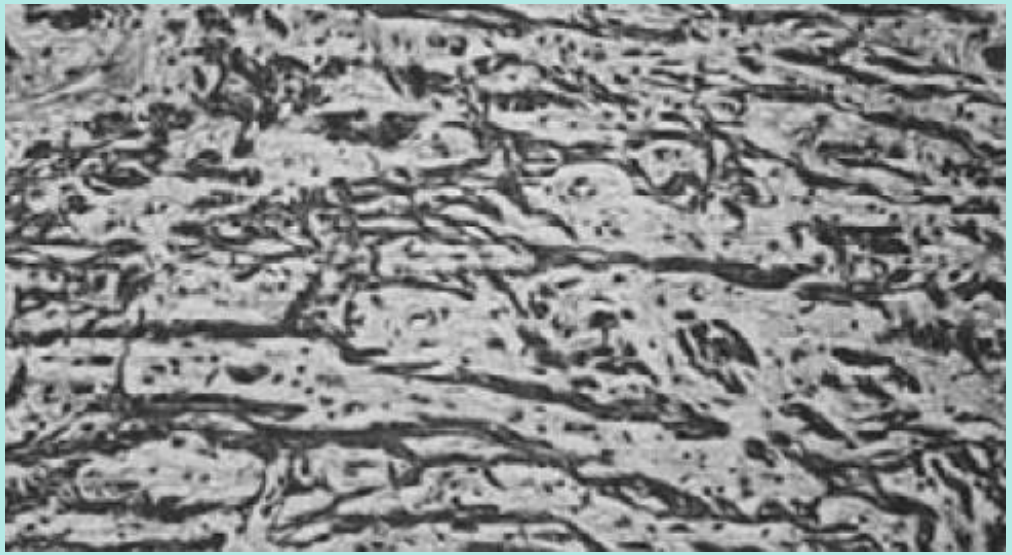
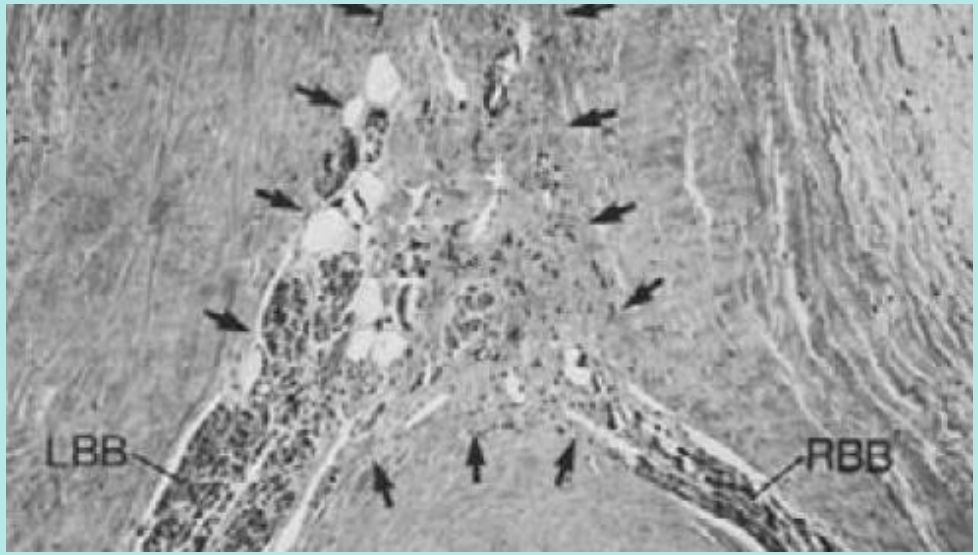
JACC 1988 Mar;11(3):662-71

AV Node Histology

- Fibrosis



- Fibrofatty Infiltration and Atrophy



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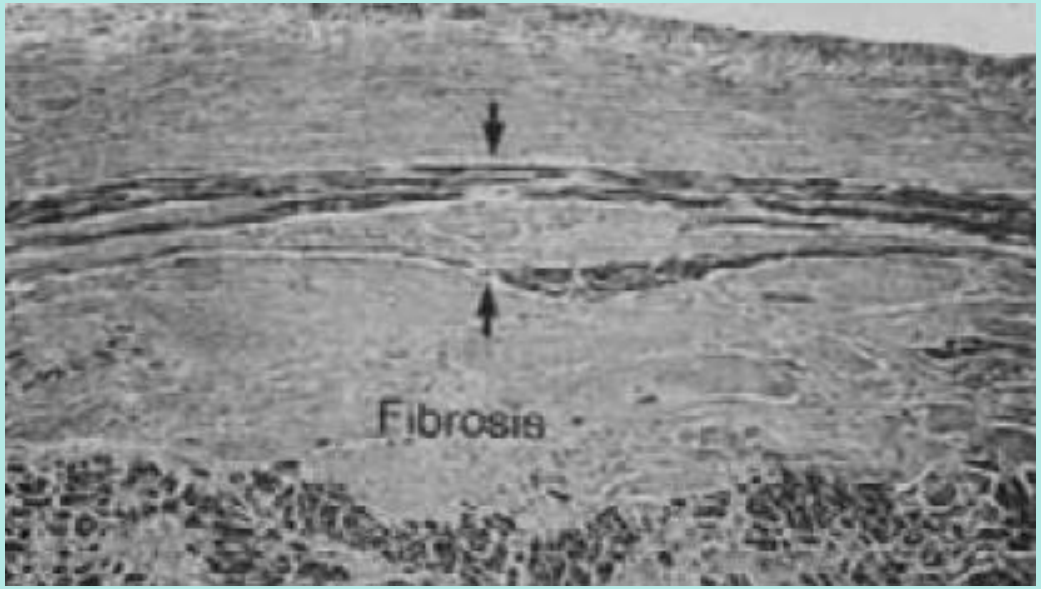
Bundle Branch Histology

- LB Fibrosis



- RB Fibrosis and Atrophy

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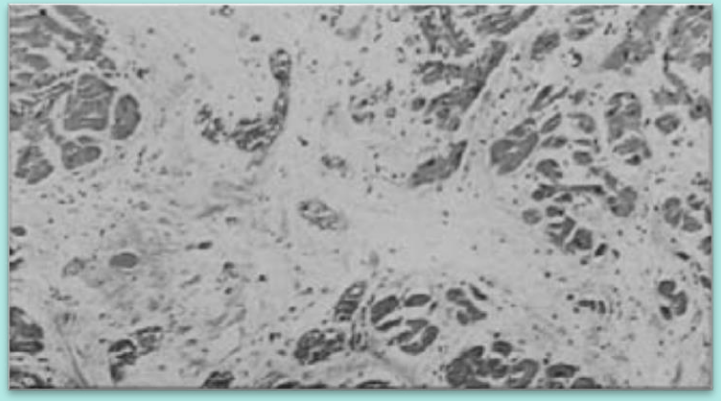
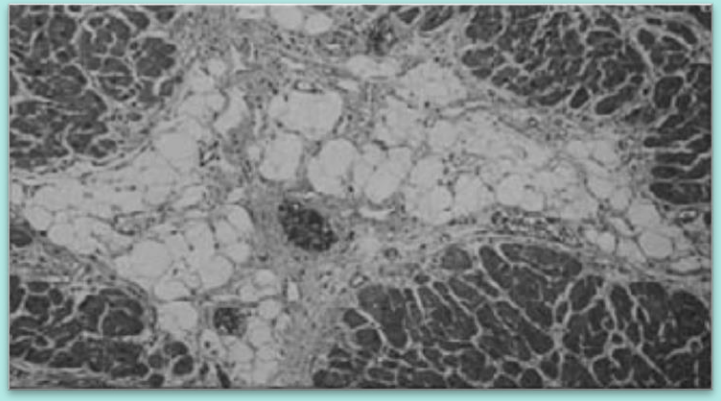
Left Ventricular Histology

- Patchy Replacement Fibrosis
- Patchy Fibro-Fatty Replacement





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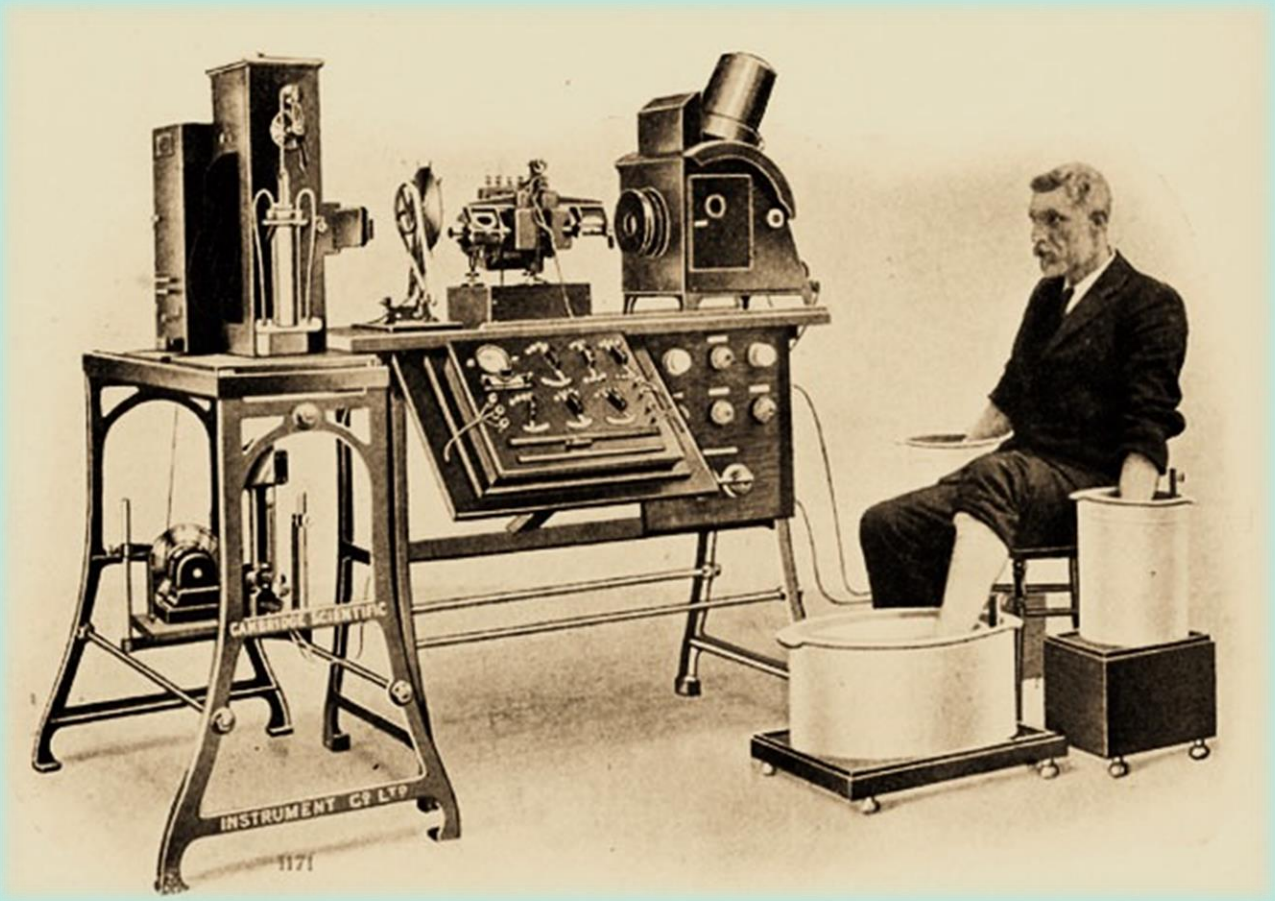
JACC 1988 Mar;11(3):662-71

Electrocardiography



William Einthoven's 1901 Electromagnetic String Galvanometer

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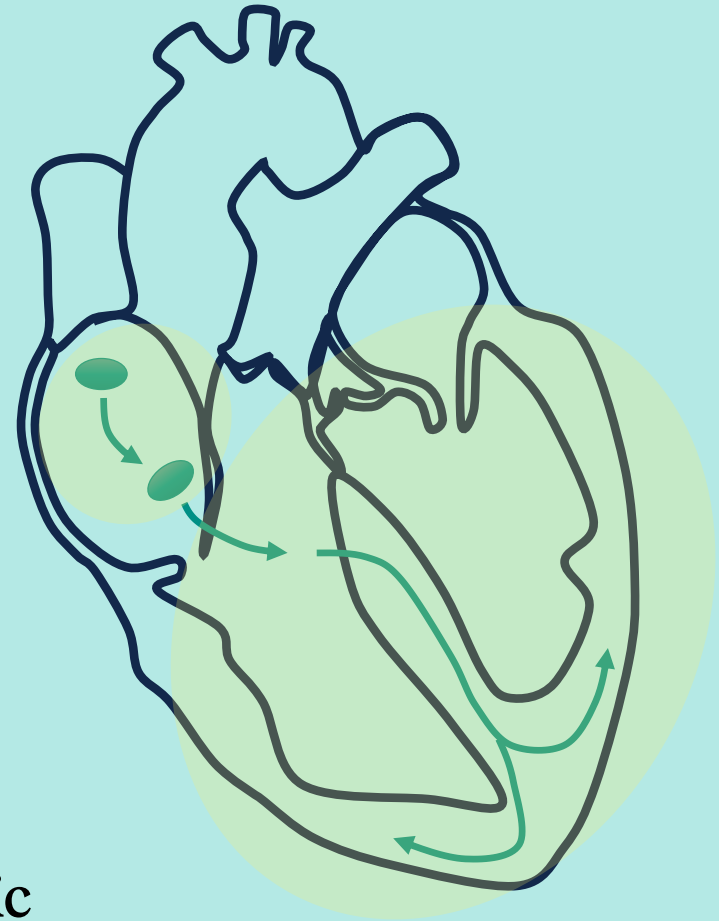
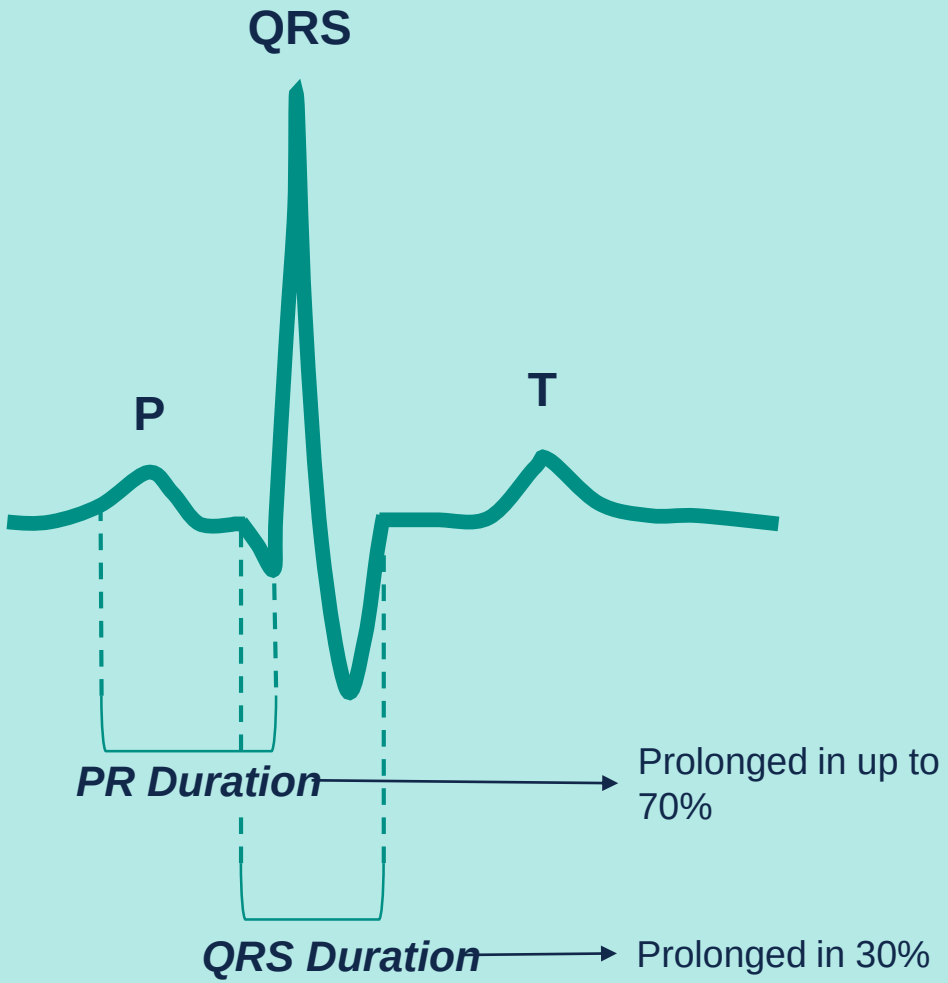
Cardiac Conduction System





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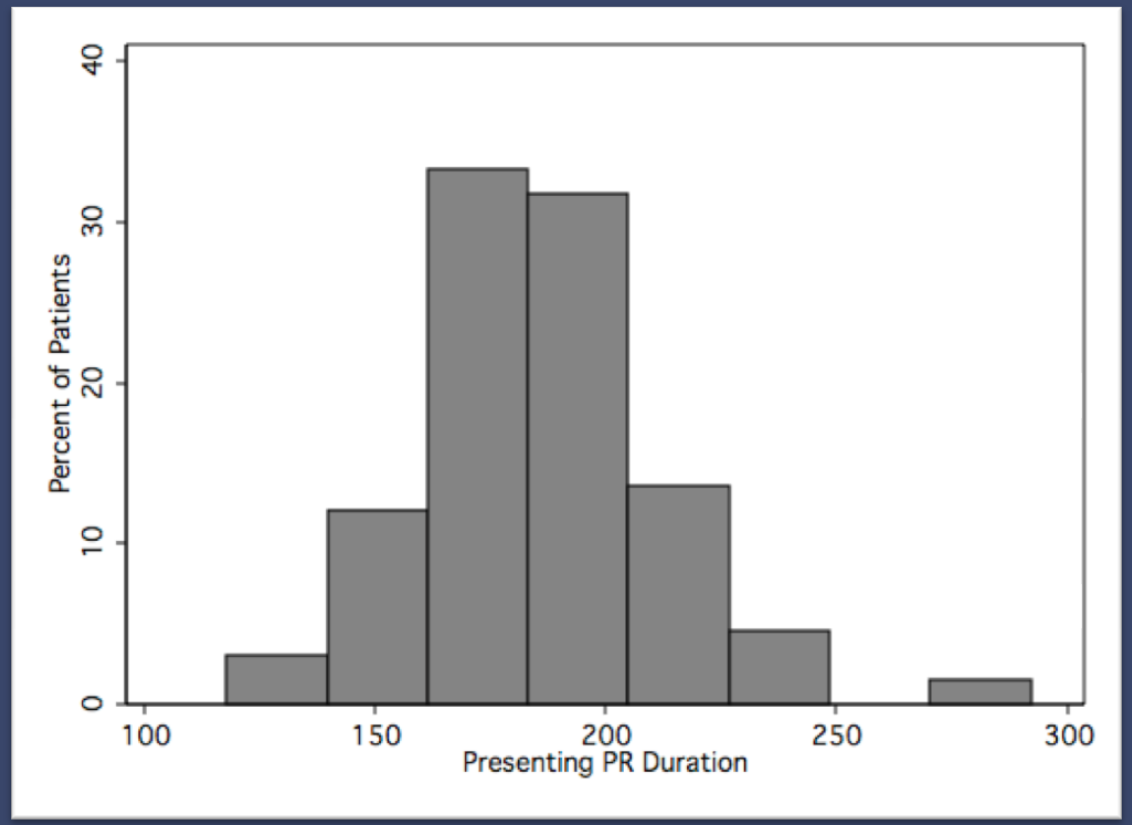
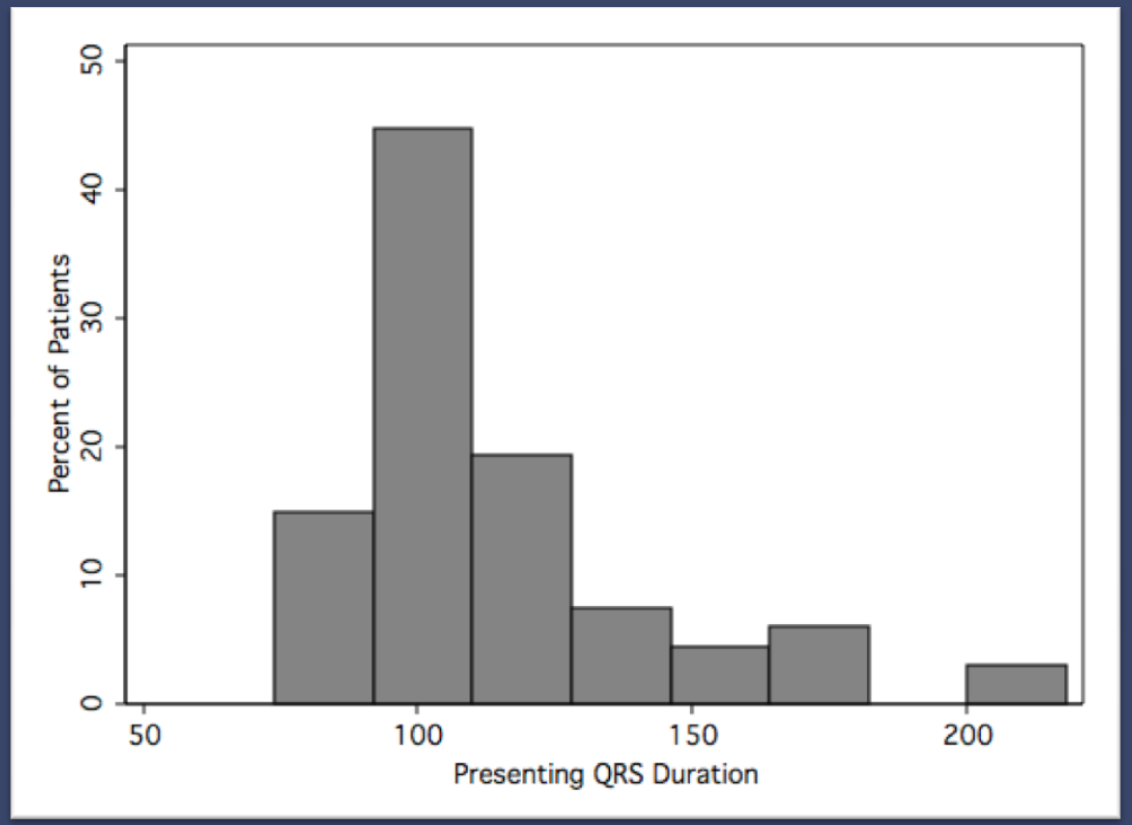
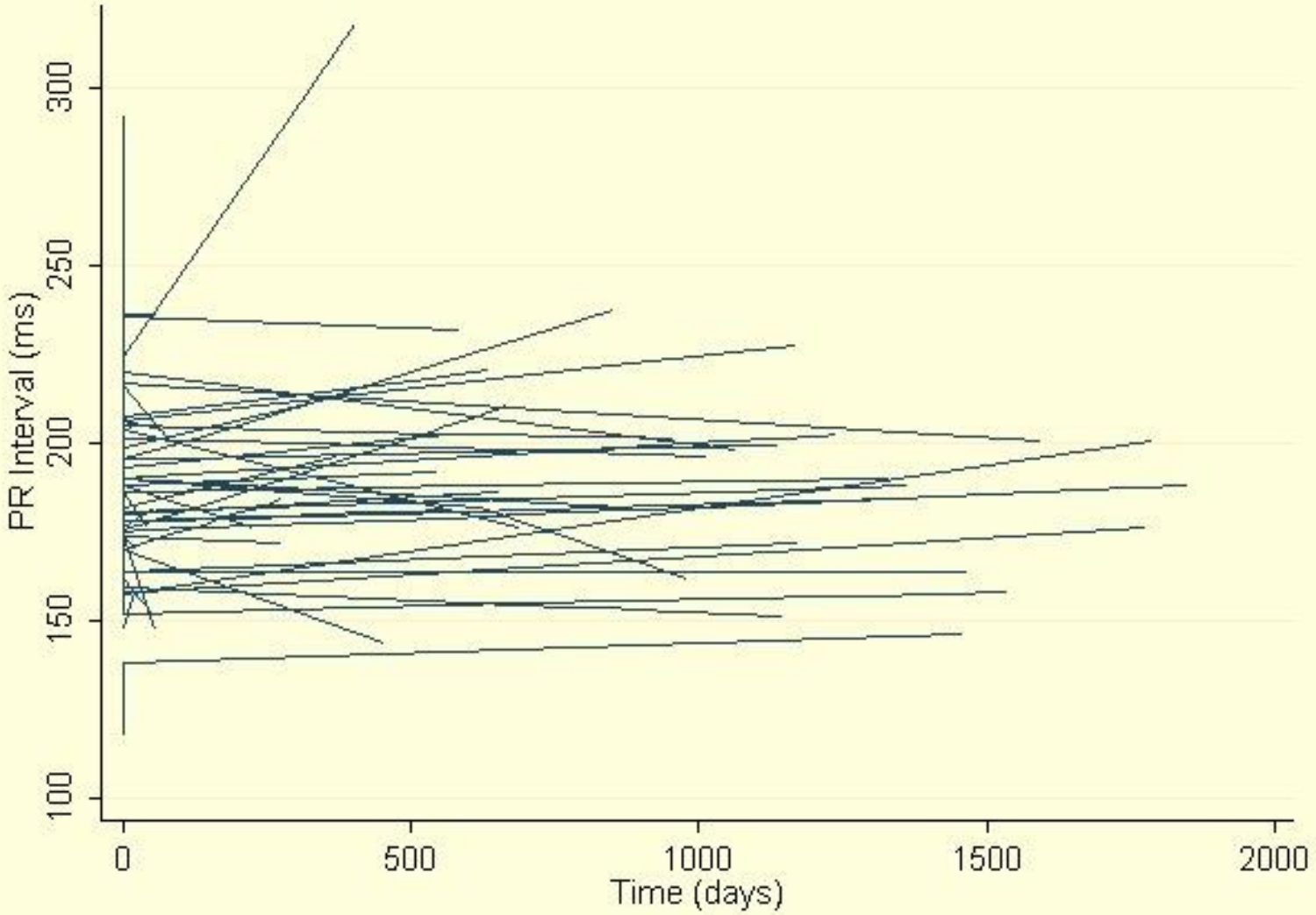




ECG Abnormalities at Presentation

Longitudinal Trends in PR Interval



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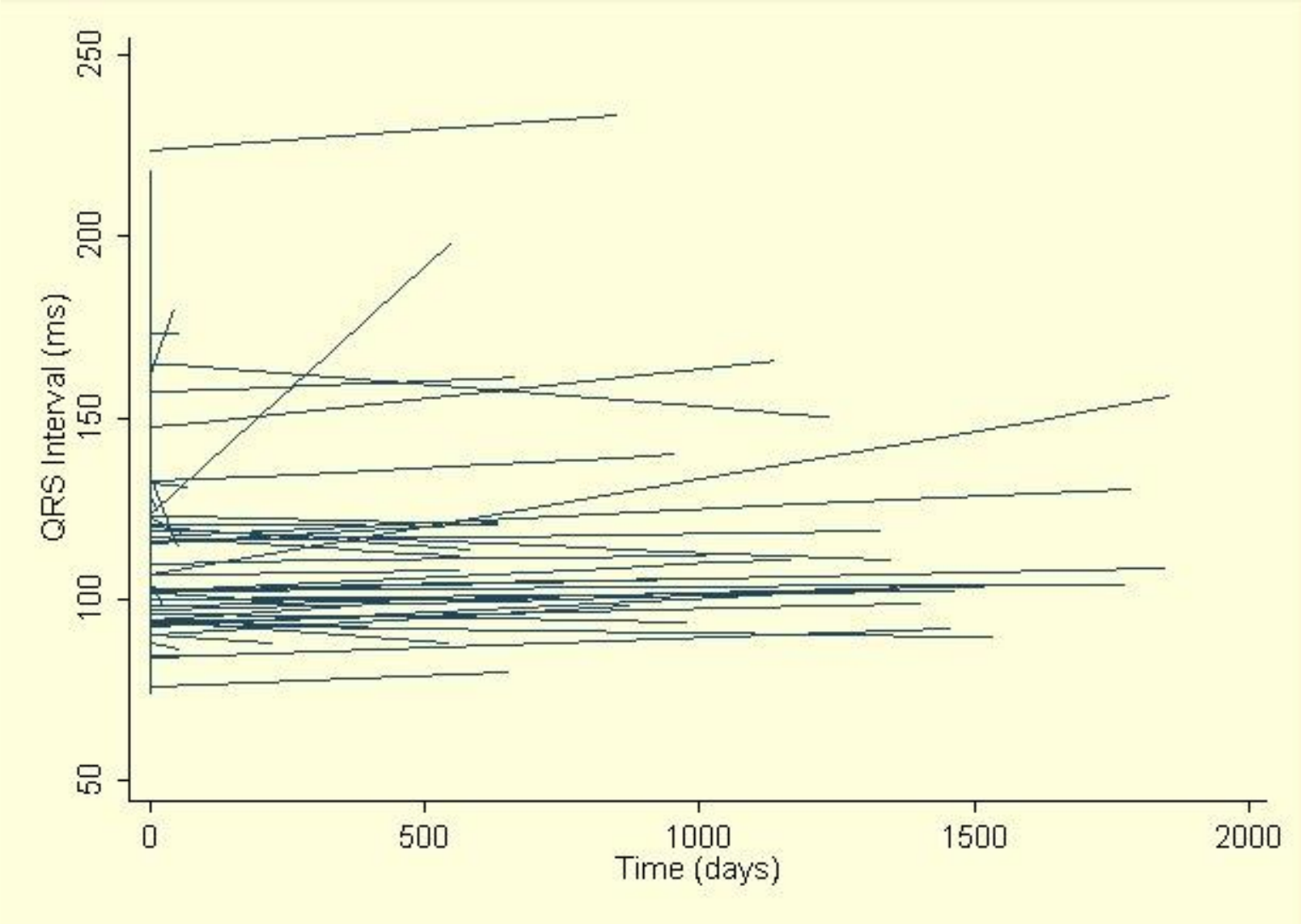
The mean PR interval increased from 185 ± 21 to 191 ± 26 msec (7% stable, 38% decrease, 55% increase).

Longitudinal Trends in QRS Interval

Sixty one percent of all patients exhibited a nonspecific intraventricular conduction delay. Of the remaining 39%, 6 (8%) patients had left bundle branch block, 2 (3%) had left anterior fascicular block, 1 (1%) had right bundle branch block, and the remaining had normal QRS duration. The mean QRS interval increased from 113 ± 27 to 116 ± 33 msec (12% stable, 41% decrease, 47% increase).



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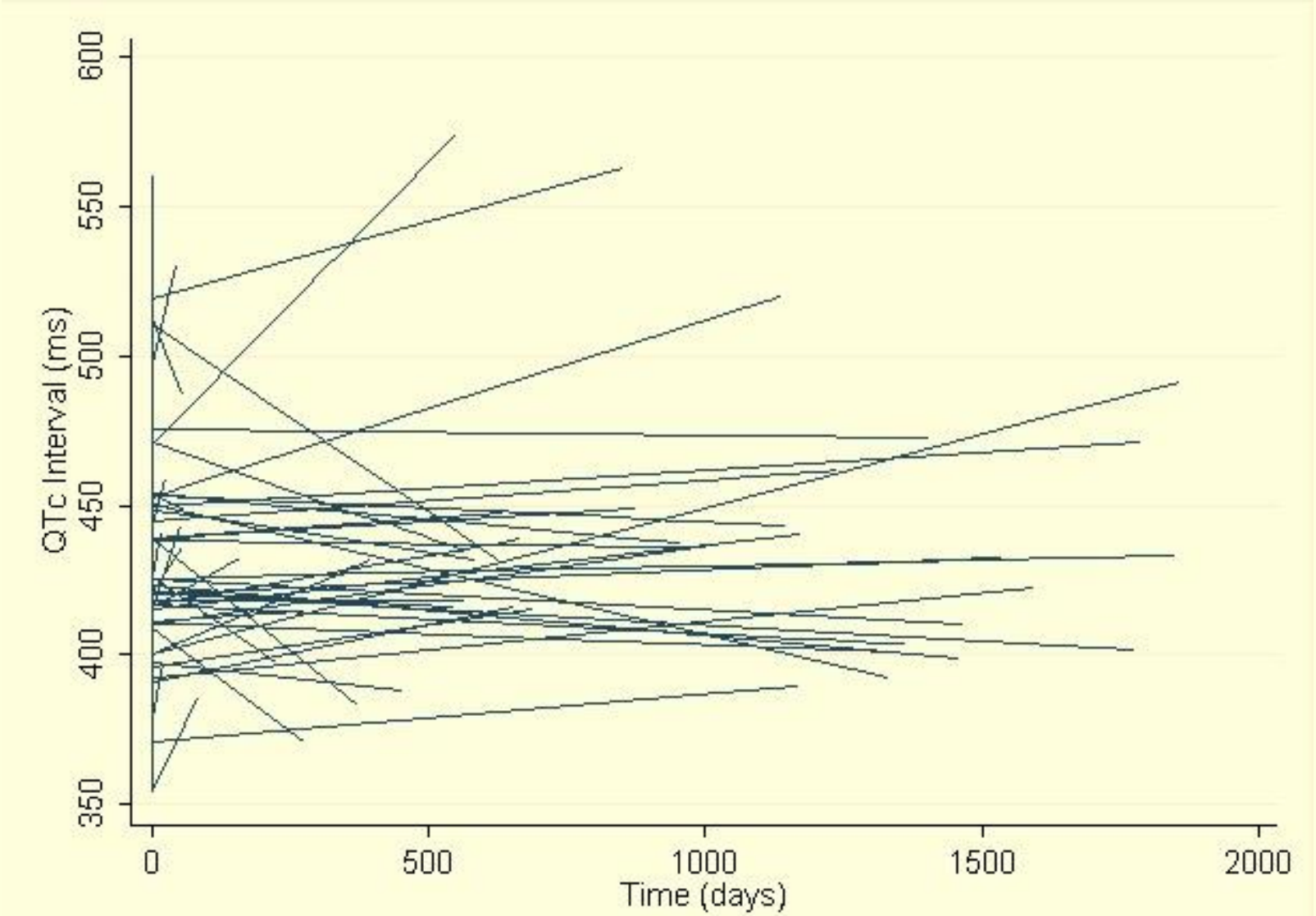
Longitudinal Trends in QTc Interval



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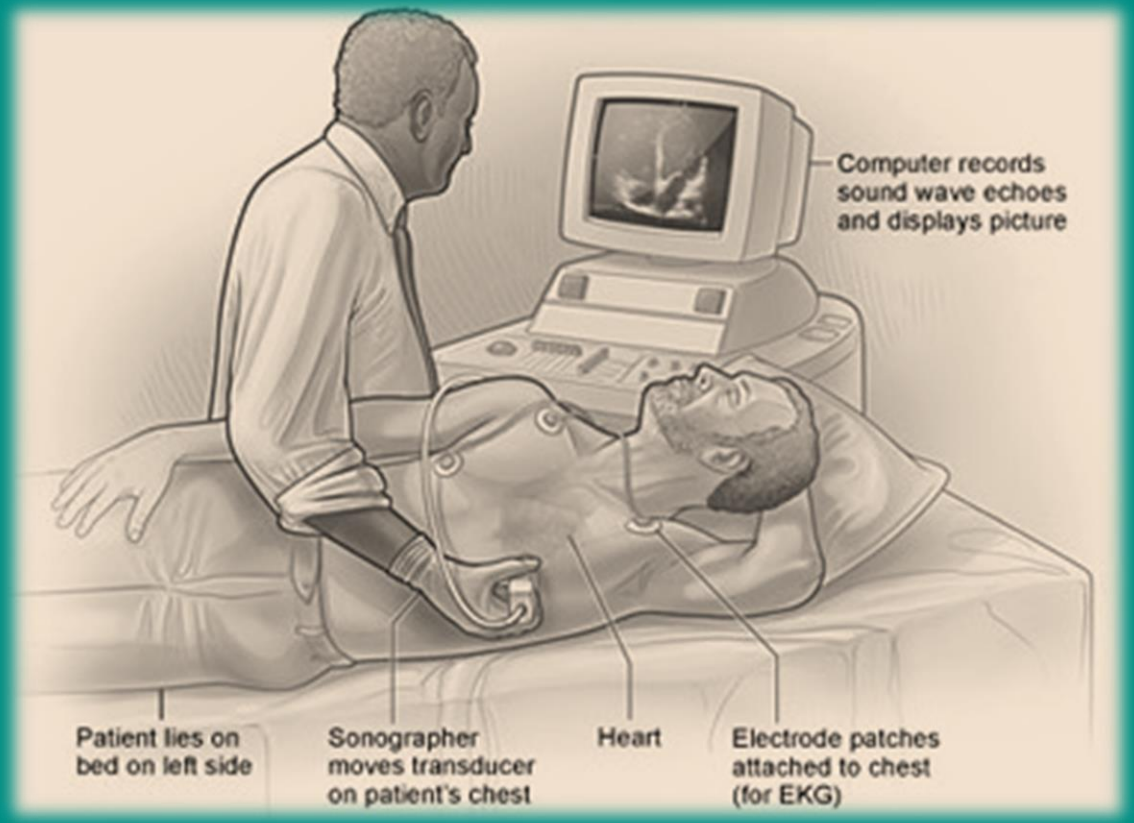
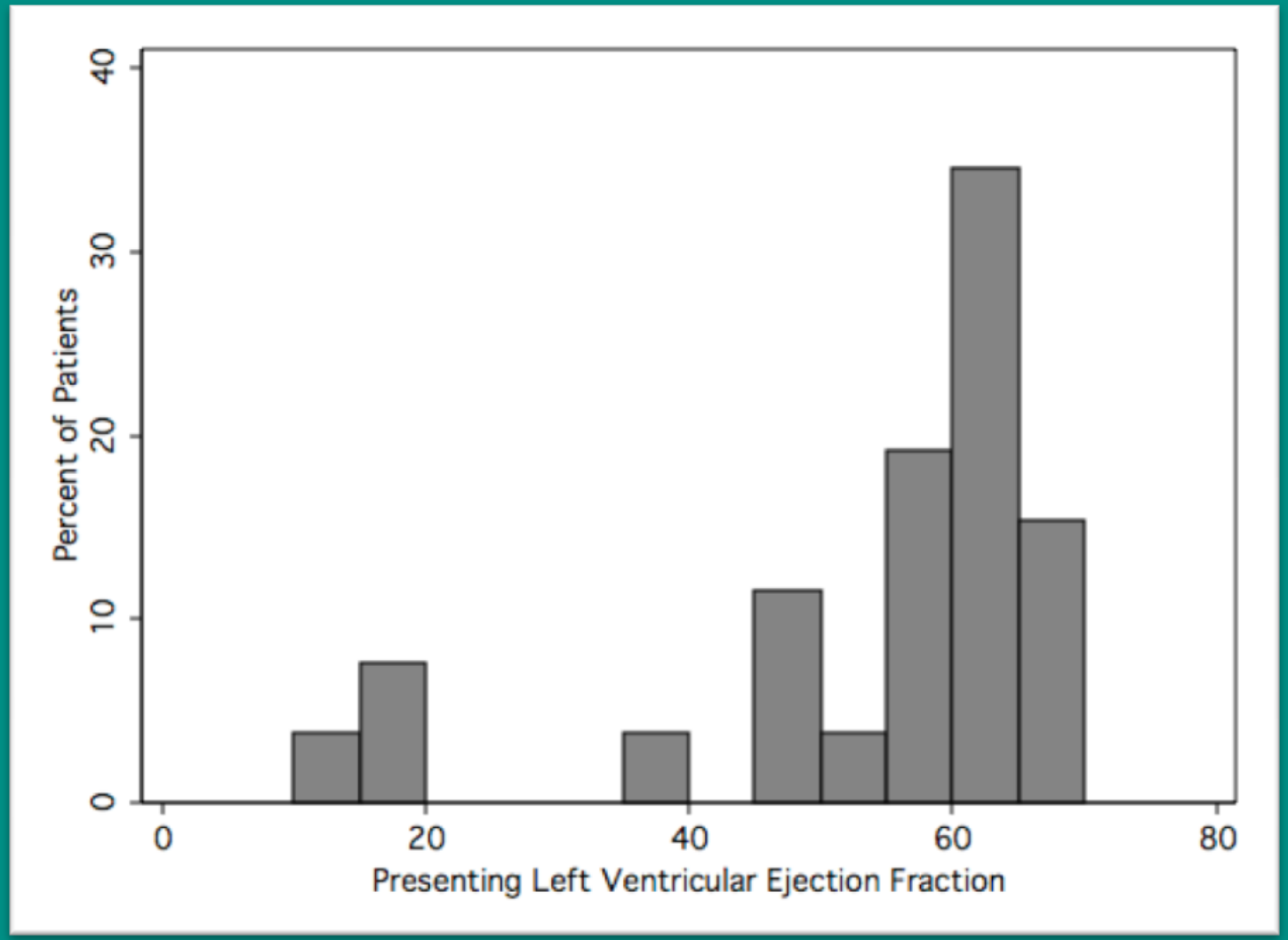
The QTc interval increased from 430 ± 34 to 436 ± 44 msec (2% stable, 37% decrease, 61% increase).

Assessment of Heart Function



Prevalence of LV Dysfunction



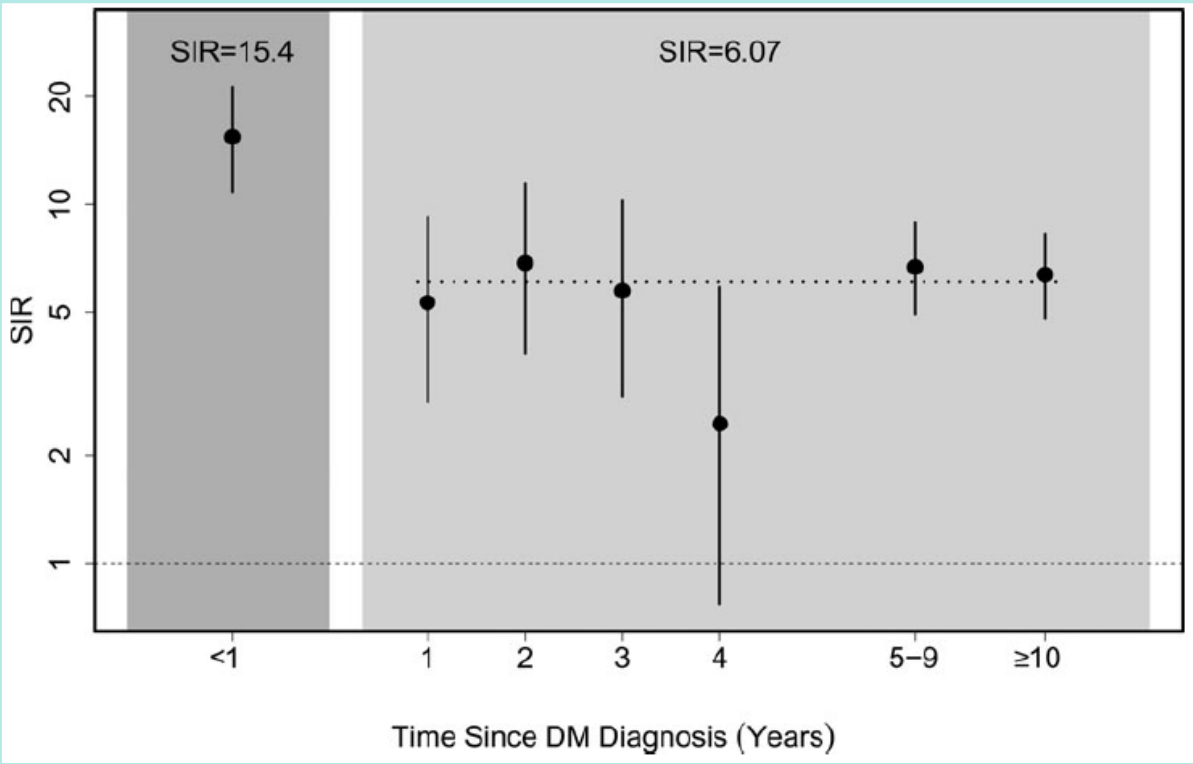
Danish National Experience

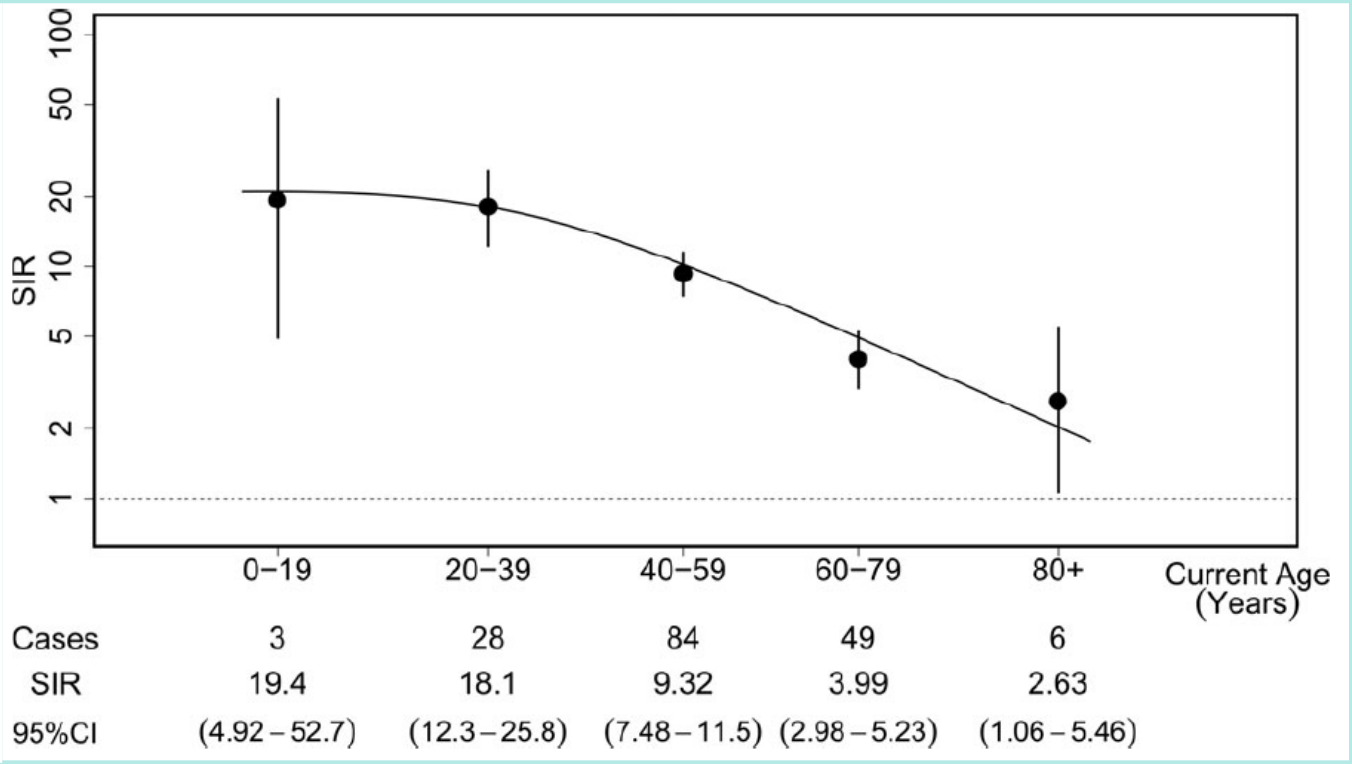
	Main DM cohort N = 1146		DM1 subcohort N = 485	
	n	%	*n*	%
Sex				
Male	609	53.1	236	48.7
Female	537	46.9	249	51.3
Age at diagnosis of myotonic dystrophy[a]				
0–14 years	124	10.8	51	10.5
15–29 years	214	18.7	107	22.1
30–44 years	321	28.0	145	29.9
45–59 years	340	29.7	132	27.2
60–74 years	130	11.3	46	9.5
75+ years	17	1.48	4	0.8
Calendar year at diagnosis of myotonic dystrophy				
1977–1978	53	4.62	0	0
1979–1982	113	9.86	7	1.4
1983–1986	76	6.63	3	0.6
1987–1990	70	6.11	8	1.6
1991–1994	102	8.90	24	4.9
1995–1998	93	8.12	34	7.0
1999–2002	203	17.7	108	22.3
2003–2006	178	15.5	118	24.3
2007–2011	258	22.5	183	37.7
Died during follow-up for *Any Cardiac Disease*[b]	224	[b]	44	[b]

Myotonic

Lund et al. **Eur Heart J** 35:2158-64, 2014.

Danish National Experience





Standard Incidence Ratio (SIR) compared to the background population for CM, CCD, arrhythmia, HF, CRM device

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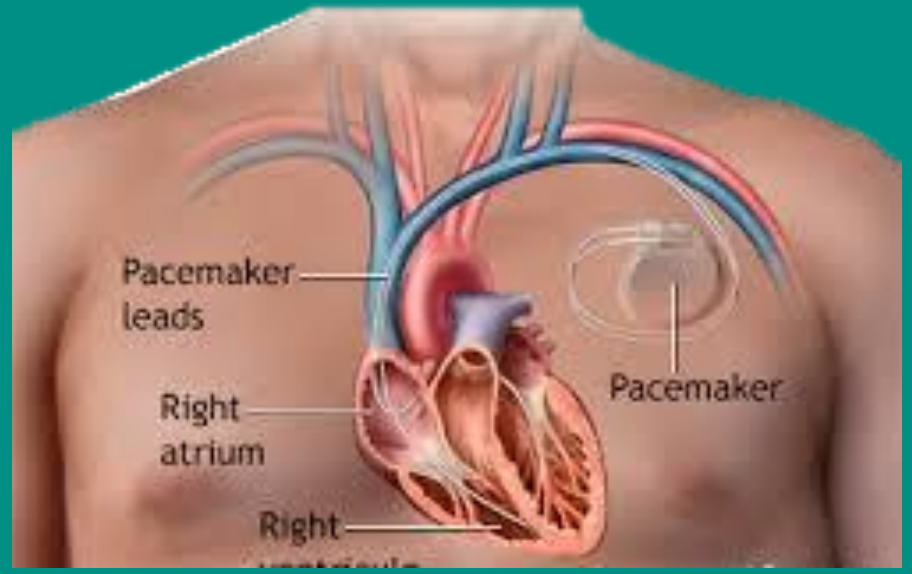
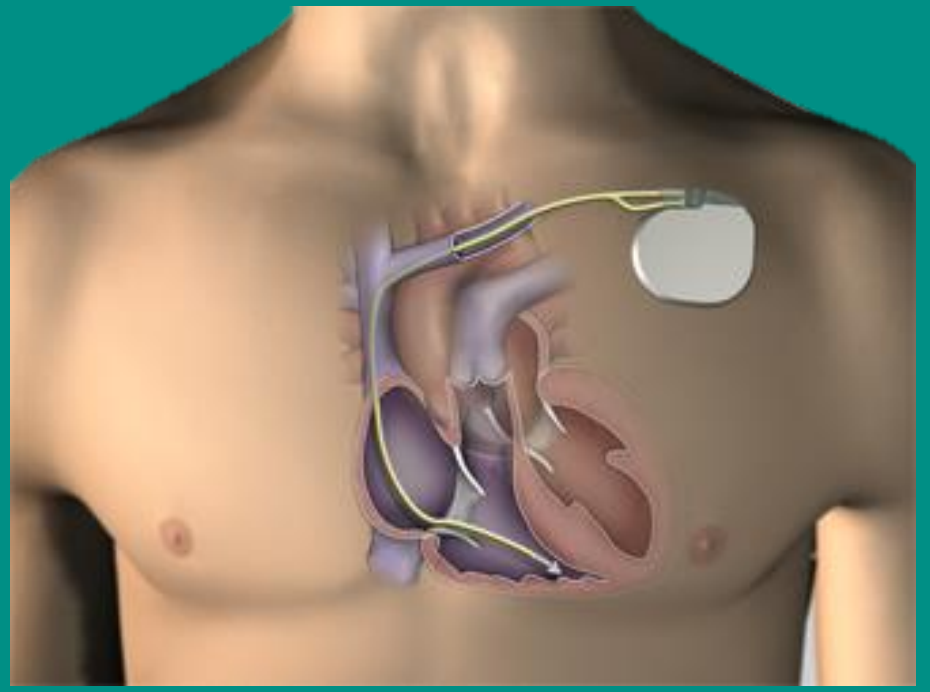
Lund et al. **Eur Heart J** 35:2158-64, 2014.

Sudden Death

- Mostly due to “heart block”
- Implantation of a pacemaker protects against this risk



- Rarely sudden death may be due to VT/VF
- Implantation of a defibrillator protects against this risk



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Myotonic Dystrophy – our experience

Variables	(N=168)
Age at diagnosis	37.6 ± 16.9
Duration of follow up (years)	5.2 ± 4.9
Male gender	77 (45.8%)
Type of DM	
Type I	136 (81.0)
Type II	28 (16.7)
Family History of Sudden Cardiac Death	31 (18.5)
CTG (MD type 1, N=80)	476 (196-795)
Medications	
Mexiletine	22 (13.1)
ASA	39 (23.2)
Betablocker	22 (13.1)
Statin	37 (22.0)

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Myotonic Dystrophy – our experience

Variables	(N=168)
Echocardiogram	
Ejection fraction	52.9 ± 12.2
LVEDD	4.5 ± 0.6
LV dysfunction during follow up (EF <50%)	20 (11.9)
Electrocardiogram on the initial visit	
HR	68.7 ± 15.1
PR	179.5± 29.2
QRS	109.0 ± 28.8
QT	434.6 ± 35.1
QRS axis	9.31 ± 48.5

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Predictors of Cardiac Dysfunction – our Experience

Variables	Adjusted Odds Ratio (95% CI)	P value
Age at diagnosis (Year)	-0.03 (-0.34 - 0.28)	0.86
MMD type II	-19.00 (-35.30 - (-2.71))	0.02
Gender	-2.39 (-11.73 - 6.9)	0.62
Heart rate (bpm)	-0.05 (-0.35 - 0.25)	0.74
PR (ms)	-0.01 (-0.10 - 0.07)	0.81
QRS interval (per 10 ms)	-3.45 (-4.87 - (-2.03))	<0.01
QT (ms)	0.03 (-0.08 - 0.15)	0.57
QRS axis (degree)	-0.01 (-0.08 - 0.10)	0.17

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- After ~5 years follow up
- LV dysfunction 11.9%

Predictors of Longitudinal PR, QRS, and QTc Interval Changes (After Adjusting for Heart Rate) in the Multivariate Random Effects Model

	PR Interval		QRS Interval		QTc Interval	
Variable (unit)	**Regression Coefficient**	**P**	**Regression Coefficient**	**P**	**Regression Coefficient**	**P**
Time	+8.7 msec / 1000 days	0.009	+3.3 msec / 1000 days	NS	+5.6 msec / 1000 days	NS
Age	+6.8 msec / 10 years	0.001	+9.3 msec / 10 years	<0.001	+10.4 msec / 10 years	<0.001
Female	-16.5 msec	0.047	+4.8 msec	NS	+26.3msec	0.009
Number of CTG repeats	+3.3 msec / 100 repeats	0.021	+4.7 msec / 100 repeats	<0.001	+1.9 msec / 100 repeats	NS
Family History of Sudden Death	-13.6 msec	NS	+18.1 msec	0.006	+16.5 msec	NS
NYHA Class	-13.6 msec	NS	-2.0 msec	NS	+12.4 msec	NS
Paroxysmal atrial fibrillation or flutter	+44.8 msec	<0.001	+14.9 msec	0.027	+ 12.6 msec	NS
Left Ventricular Ejection Fraction	+0.7 msec / 10% increase	NS	-16.6 msec / 10% increase	<0.001	-13.1 msec / 10% increase	0.002

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Results for a given variable simultaneously and reciprocally adjusted for all other variables in the table.

Multicenter Data – 406 Patients with DM1

Characteristic	Sudden Death	
	Relative Risk (95% CI)	P Value
Age†	1.16 (0.76–1.75)	0.50
Muscular-impairment score‡		
1 or 2		
3		
4		
5		
Heart failure		
Atrial tachyarrhythmia	5.18 (2.28–11.77)	<0.001
Pacemaker	1.35 (0.51–3.56)	0.54
Ventricular tachyarrhythmia		
Severe ECG abnormality§	3.30 (1.24–8.78)	0.02

- *PR > 240 ms*
- *QRS > 120*
- *2nd or 3rd degree AV block*

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NEJM 2008 Jun 19;358(25):2688-97

Atrial Fibrillation

- Possibly due to regions of atrial fibrosis
- Likely exacerbated by Sleep Apnea
- Risk factors
  - Age
  - Male gender

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Atrial Fibrillation

- Symptoms
  - Palpitations
  - Fatigue
- Thrombus formation
  - Stroke

In DM – Most important as predictor of future risk

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Other Tools for Cardiac Risk Stratification

- Longer Duration of ECG monitoring
  - Holter – 24hr, 48hr, 7 days
  - Implantable loop monitors

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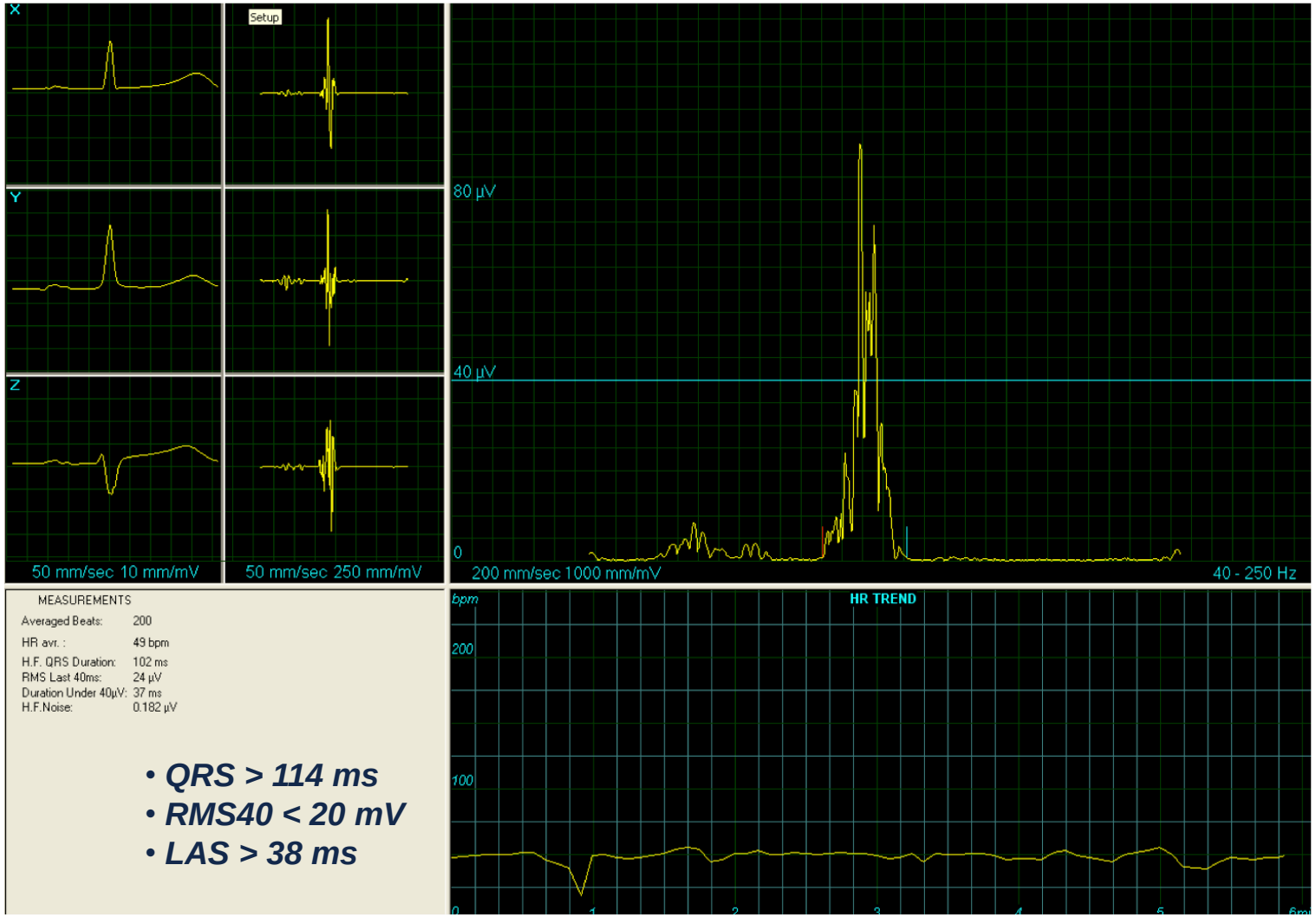
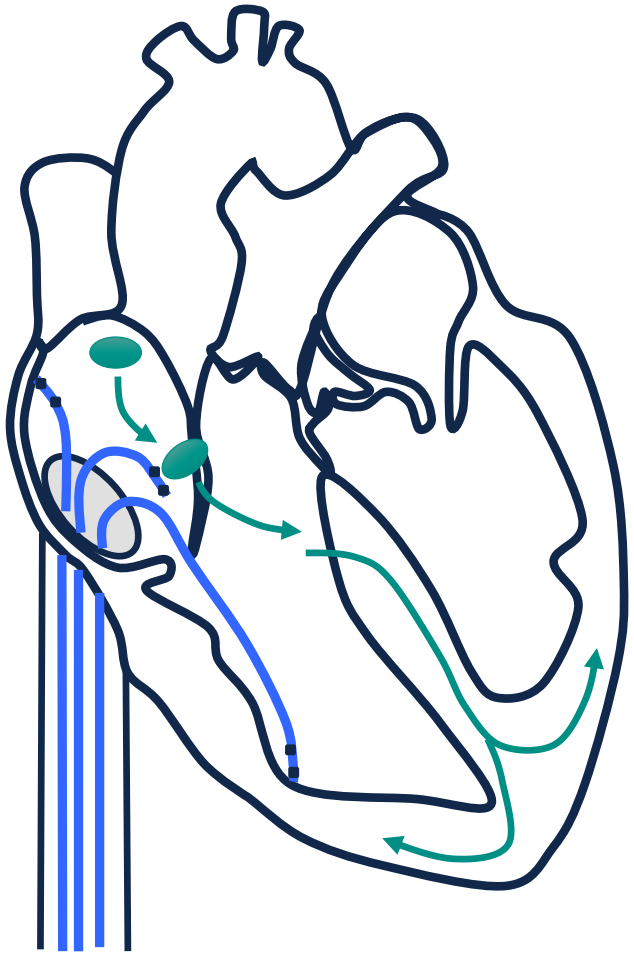
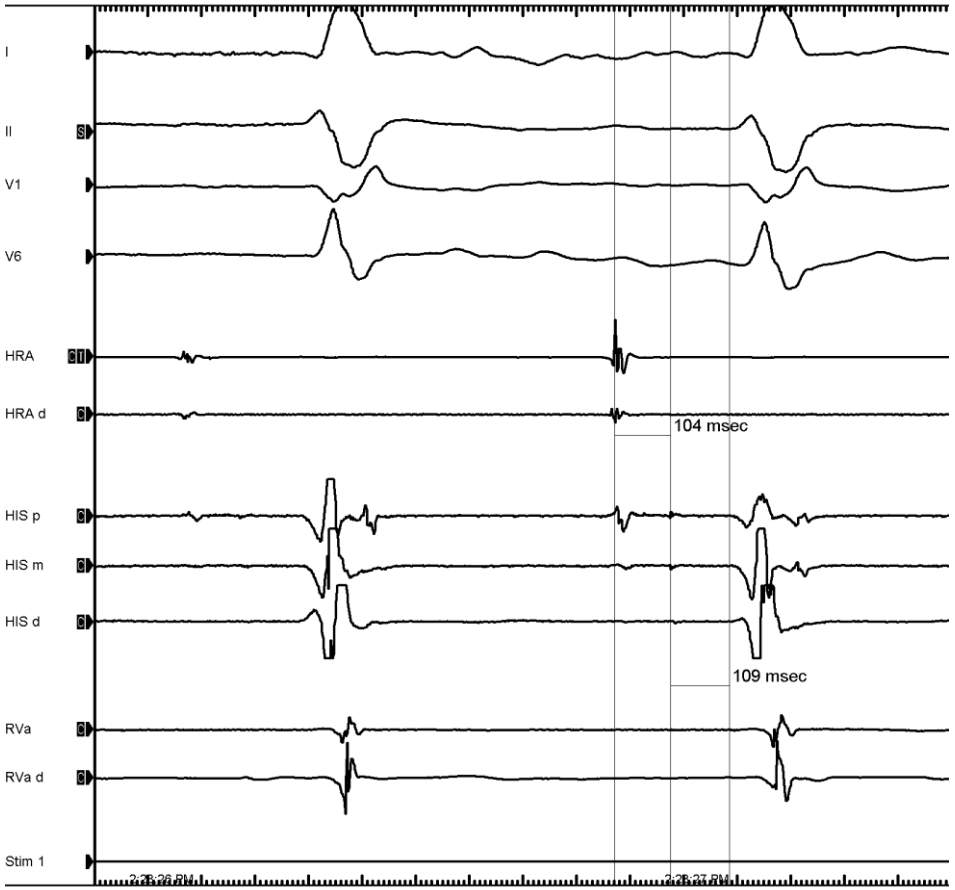
Signal Averaged ECG



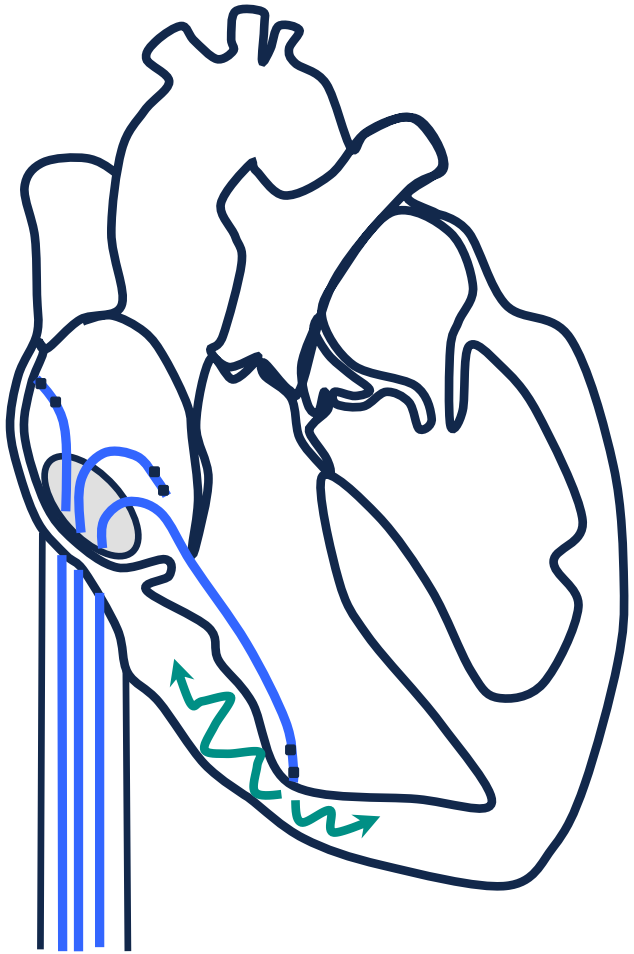
Not particularly useful if QRS prolongation present

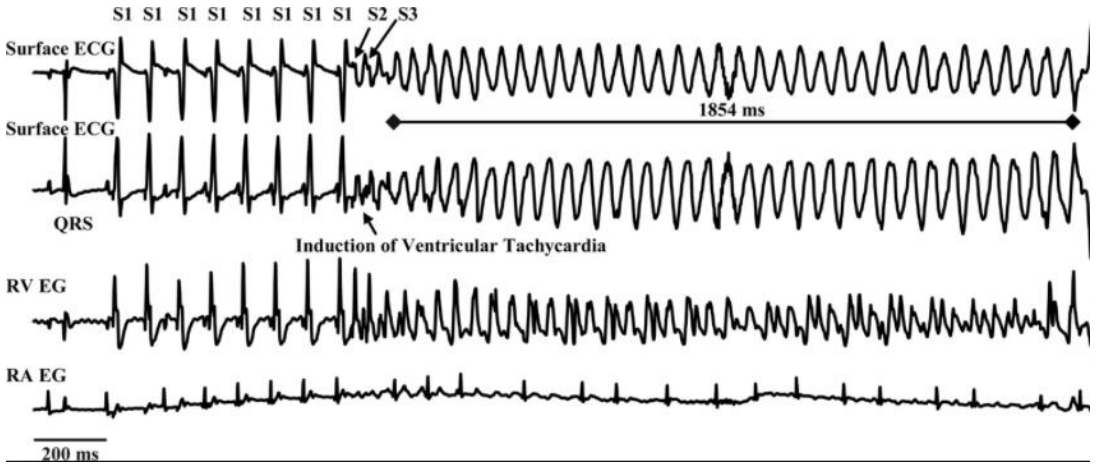
Electrophysiology Study



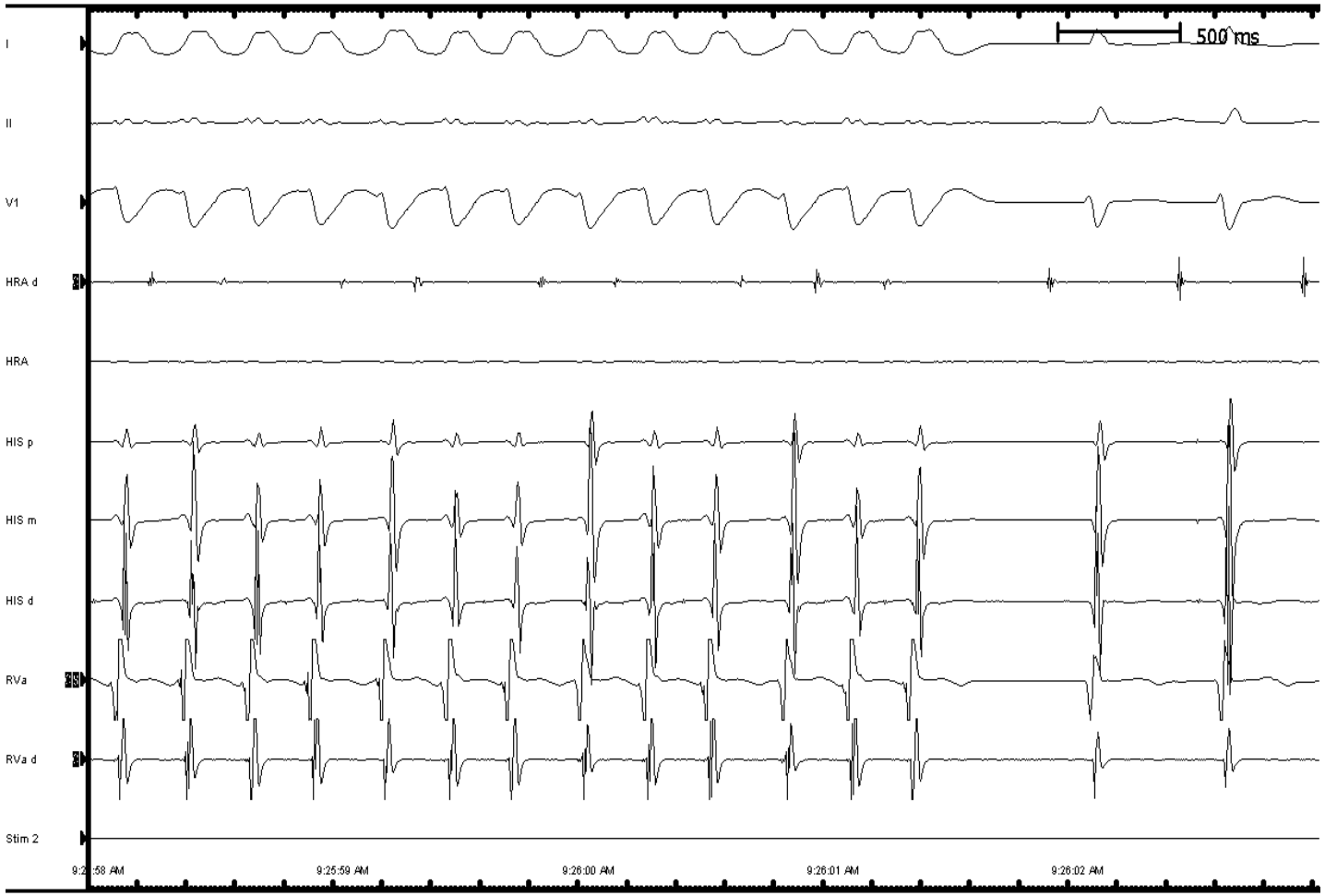


Electrophysiology Study





Ventricular Tachycardia



Is EP Testing Useful?

- Does EP study and prophylactic pacing improve survival compared to non-invasive management
  - Retrospective study: 2000-2009
  - Single tertiary center in Paris
    - >18 yrs
    - Genetically confirmed DM1

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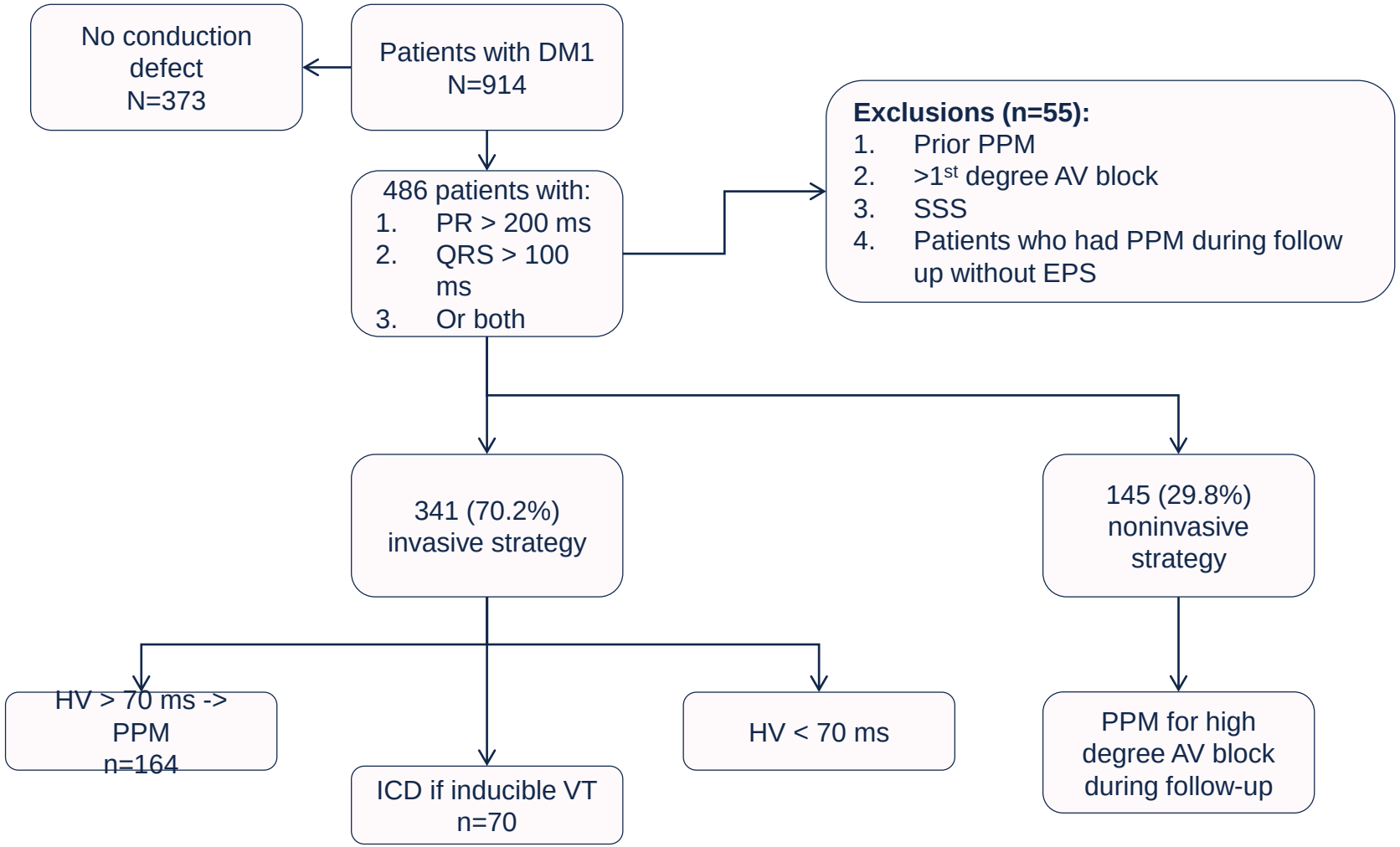
JAMA. 2012;307(12):1292-1301

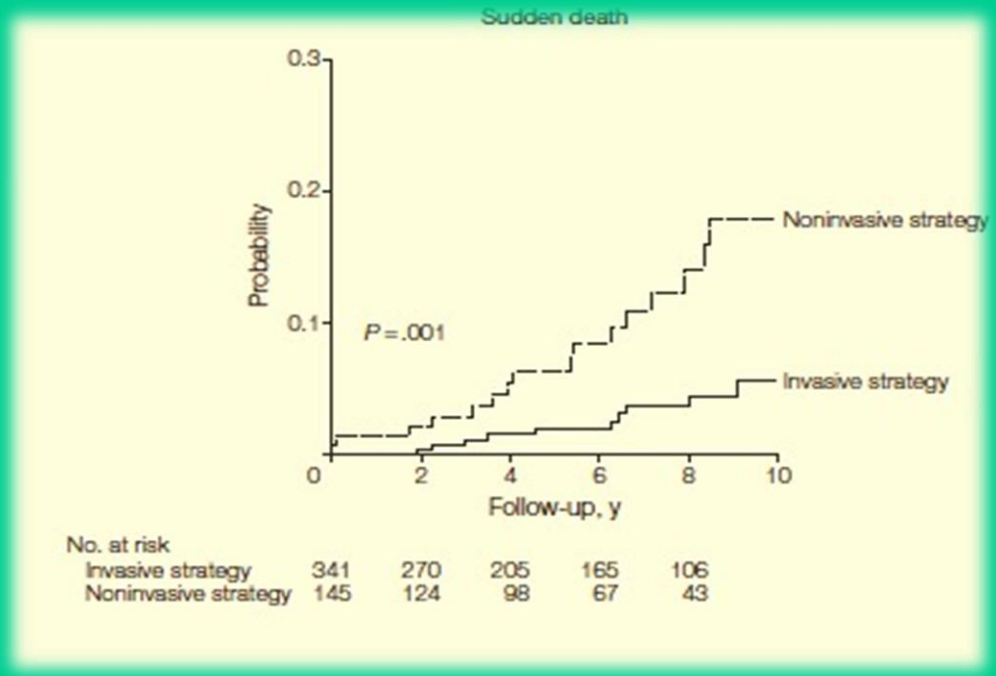
Is EP Testing Useful?



JAMA. 2012;307(12):1292-1301

Is EP Testing Useful?

- 150 pacemakers and 14 ICDs implanted
- No appropriate shocks



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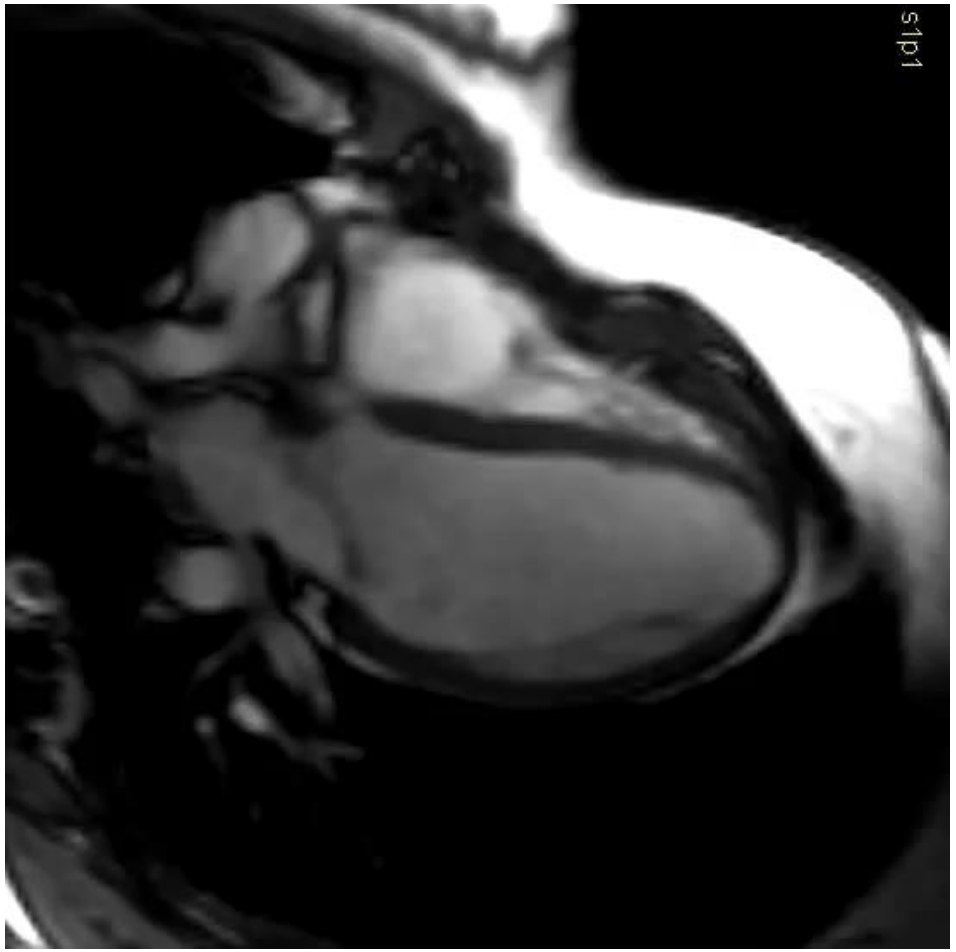
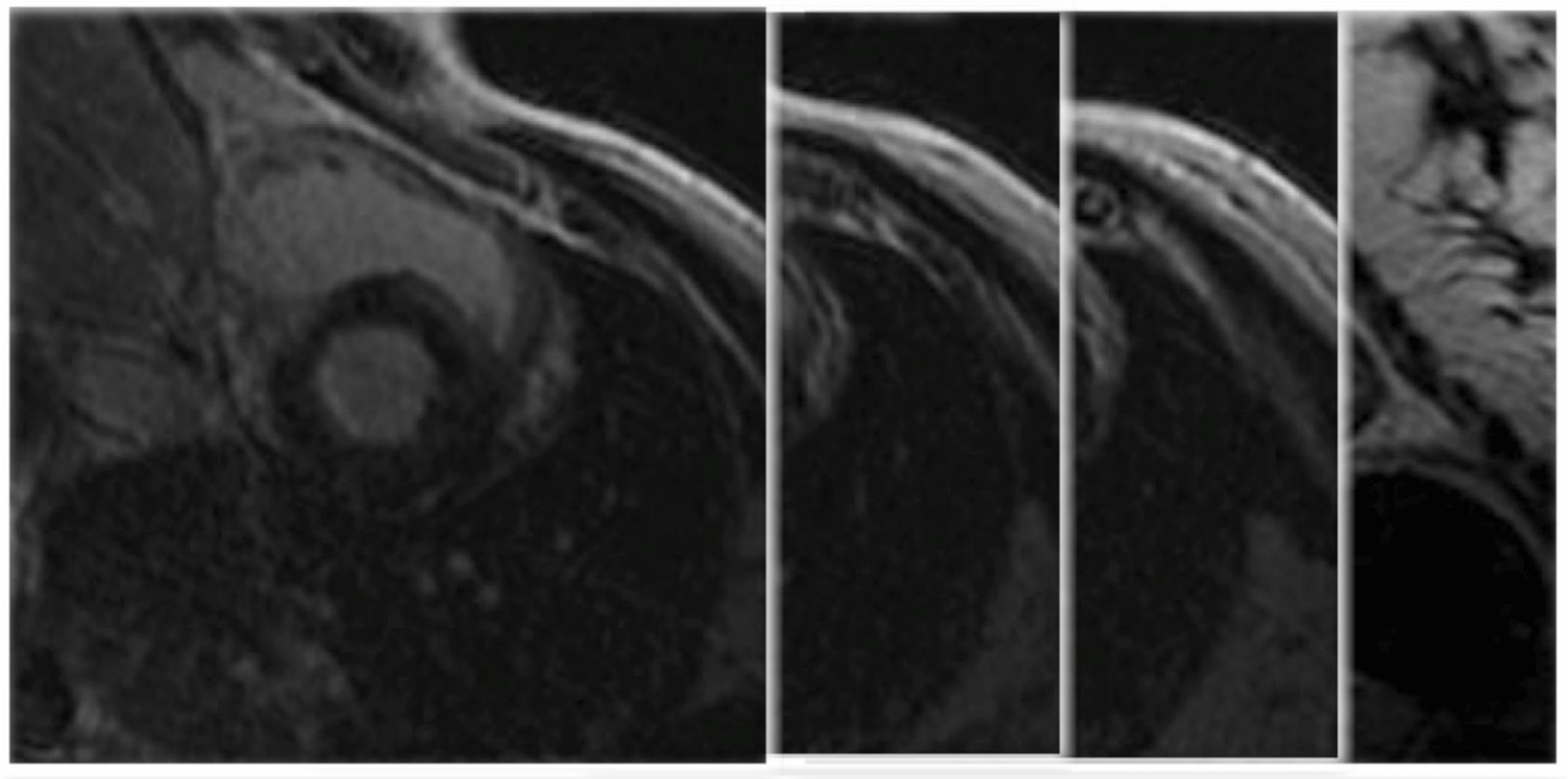
JAMA. 2012;307(12):1292-1301

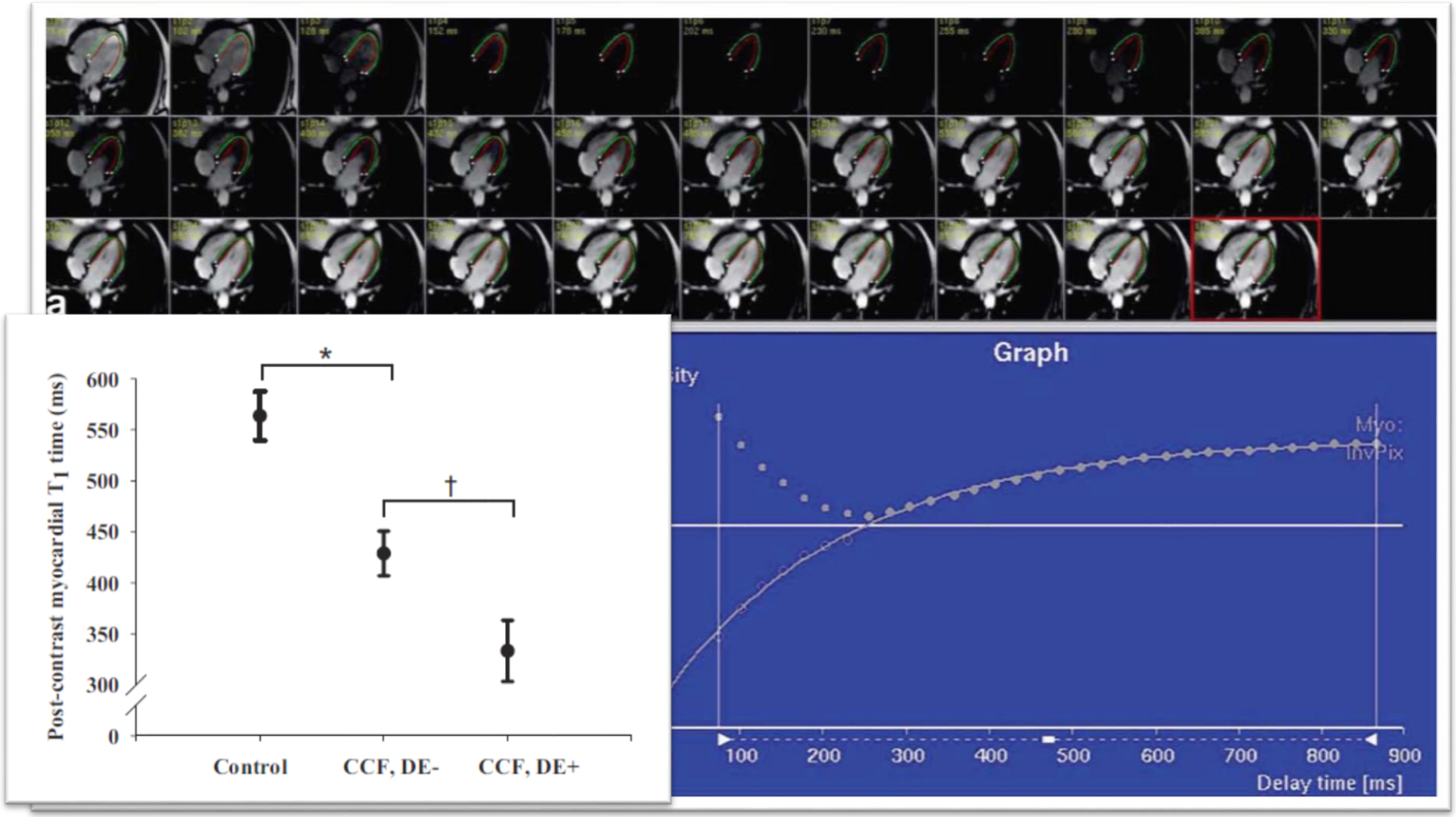
MRI – LV Function



MRI – Scar



MRI – Diffuse Scar



- *Accumulation of gadolinium in fibrotic tissue attenuates the T_1 relaxation time proportional to the extent of fibrosis*

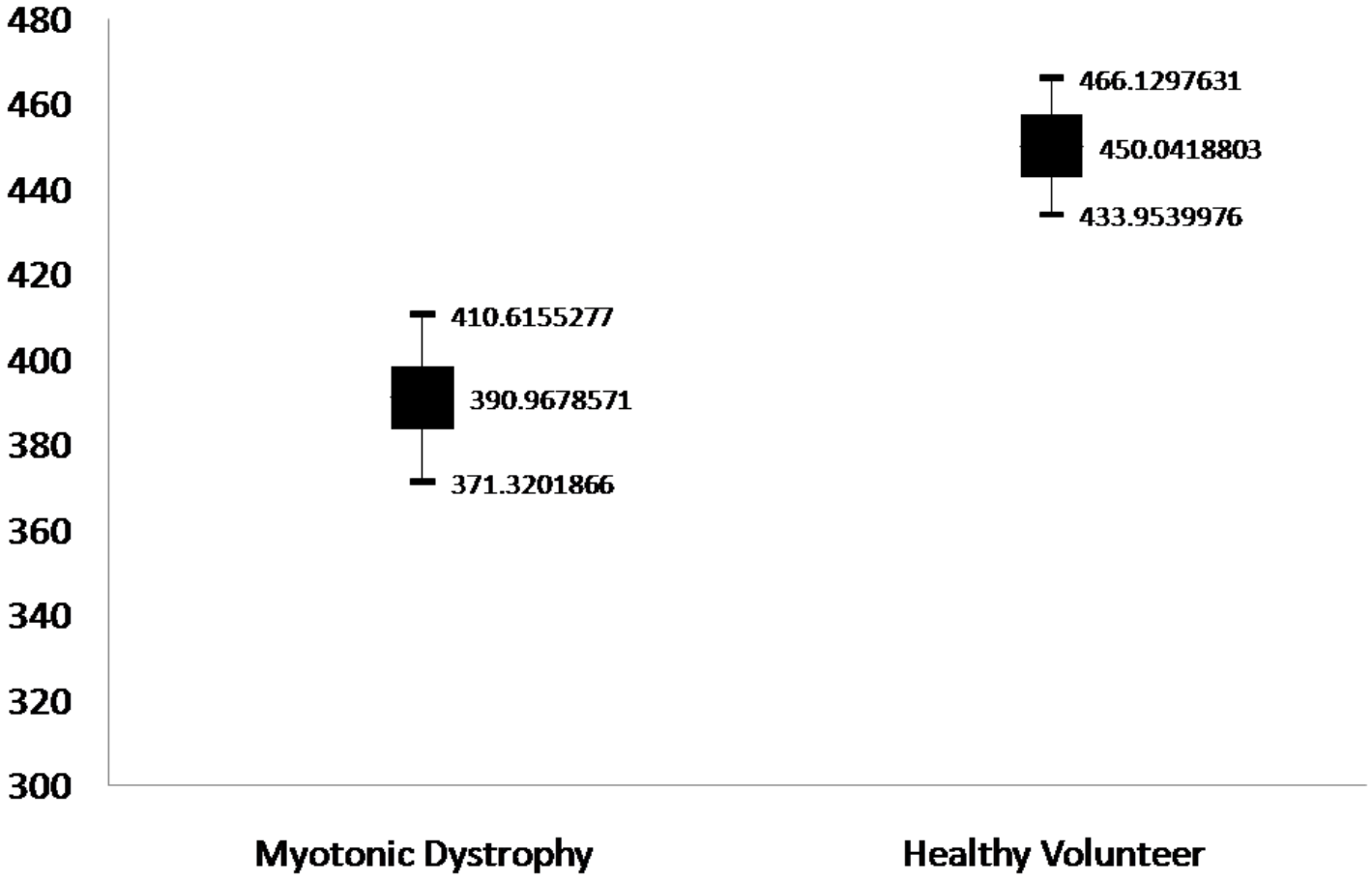
Magn Reson Med. 2011 May;65(5):1407-15

Differences in Cardiac Function & Volumes

	MMD-1 N=24 Mean±SD or % (n)	MMD-2 N=9 Mean±SD or % (n)	All MMD Patients N=33* Mean±SD or % (n)	Healthy Volunteers N=13 Mean±SD or % (n)
Left Ventricular Parameters				
LV mass index (g/m^2)	56.8 ± 12.8	62.7 ± 12.9	58.6 ± 12.9	58.9 ± 5.4
LV end-diastolic volume index (ml/m^2)	**58.1 ± 17.8** §	65.7 ± 16.6	**60.3 ± 17.6** δ	68.9 ± 9.7
LV end-systolic volume index (ml/m^2)	23.9 ± 11.9	26.0 ± 11.5	24.5 ± 11.7	25.7 ± 5.9
Mass/Volume Ratio	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.87 ± 0.2
Stroke volume index (ml/m^2)	**34.2 ± 8.9** §	39.7 ± 6.1	**35.8 ± 8.4** δ	43.2 ± 5.2
Cardiac index (L/min/m^2)	**2.2 ± 0.6** ¶ §	2.6 ± 0.3	**2.33 ± 0.6** δ	2.7 ± 0.3
Ejection Fraction (%)	59.6 ± 8.4	61.7 ± 6.6	60.2 ± 7.9	63.0 ± 5.1
Ejection Fraction <55% (yes)	**31.8 (7)** §	11.1 (1)	**25.8 (8)** δ	0 (0)
Right Ventricular Parameters				
RV end-diastolic volume index (ml/m^2)	**62.9 ± 12.9** §	72.8 ± 14.9	65.8 ±14.0	72.0±9.7
RV end-systolic volume index (ml/m^2)	28.7 ± 7.3	33.0 ± 10.8	29.9 ± 8.5	30.6 ± 4.6
RV Stroke volume index (ml/m^2)	**34.2 ±8.6** §	39.8 ±6.4	**35.8 ± 8.3** δ	41.4 ±5.9
RV Ejection Fraction (%)	54.3 ±7.3	55.4 ±5.8	54.6 ± 6.8	57.5 ± 3.0
Atrial Volumes				
Left atrial volume index (ml/m^2)	29.9 ± 6.7	38.1 ± 13.2	32.3 ± 9.6	34.1 ± 4.9
Right atrial volume index (ml/m^2)	**23.4 ± 6.5**§	32.9 ± 11.5	**26.0 ± 9.1** δ	34.9 ± 7.5

¶ P<0.05 MMD-1 vs. MMD2; § P<0.05 MMD-1 vs. healthy volunteers; ǂ P<0.05 MMD-2 vs. healthy volunteers; δ P<0.05 total MMD patients vs. healthy volunteers

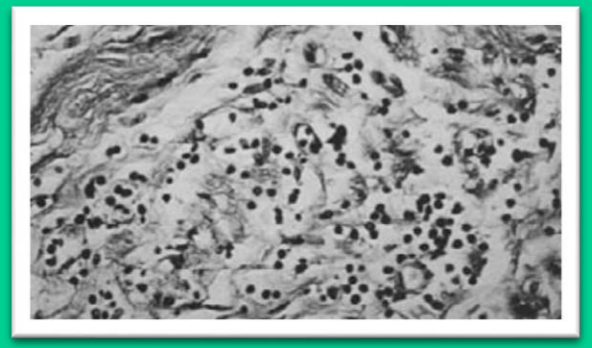
T1 Time in MMD Patients & Controls



The mean myocardial T1 time of MMD patients was significantly shorter than control subjects (394.5 ± 57.6 ms vs. 441.4 ± 32.0 ms, respectively; p<0.0001)

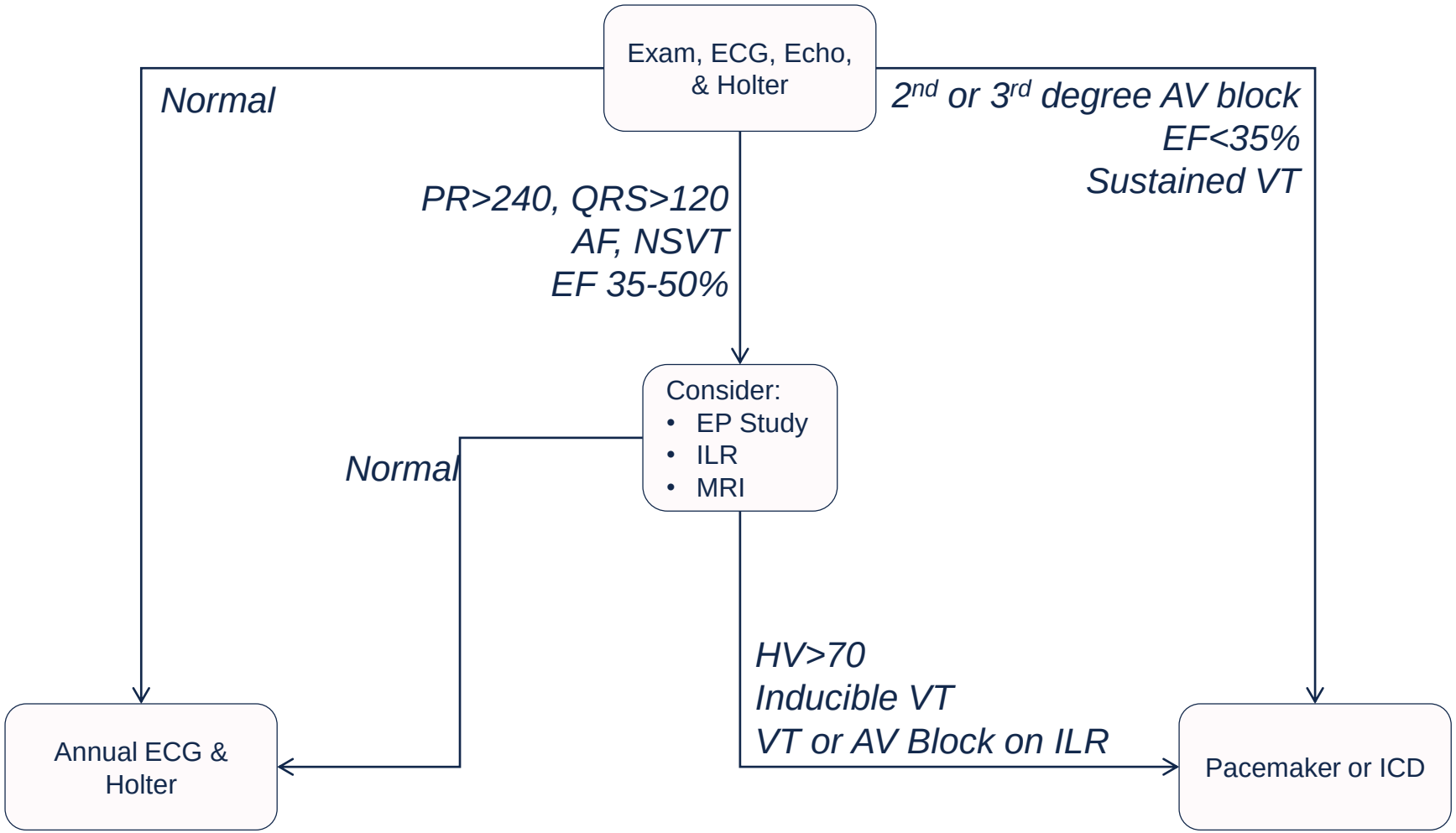
MRI Results

- Parameters that are lower in DM compared to controls
  - LV end-diastolic volume index
  - Stroke volume and cardiac index
  - Myocardial T1 relaxation time
- Among MMD patients, those with severe conduction disease had longer myocardial T1 times
- These findings suggest
  1. The early presence of diffuse myocardial fibrosis in patients with MMD
  2. Greater edema, fat, and/or inflammatory infiltration in advanced disease states



Myotonic

Current Evaluation of the Asymptomatic DM Patient



Adapted from: IJC 184 (2015) 600–608

Summary

- Myotonic dystrophy
  - 1/3 of deaths are sudden
  - Related in most cases to AV block
- Patients with AF and severe ECG abnormalities are at higher risk of progression to AV block
- EPS +/- PPM implant appears warranted in patients with syncope or evidence of conduction disease
- Role for ICDs is unclear

Myotonic

Thank you!