

An Update: Arrhythmogenic Right Ventricular Cardiomyopathy

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Cape Cod Veterinary Specialists



Overview

- Definition of ARVC
- (Patho)Physiology
- Genetics
- Patient information
- Diagnosis
- Treatment
- Prognosis

ARVC

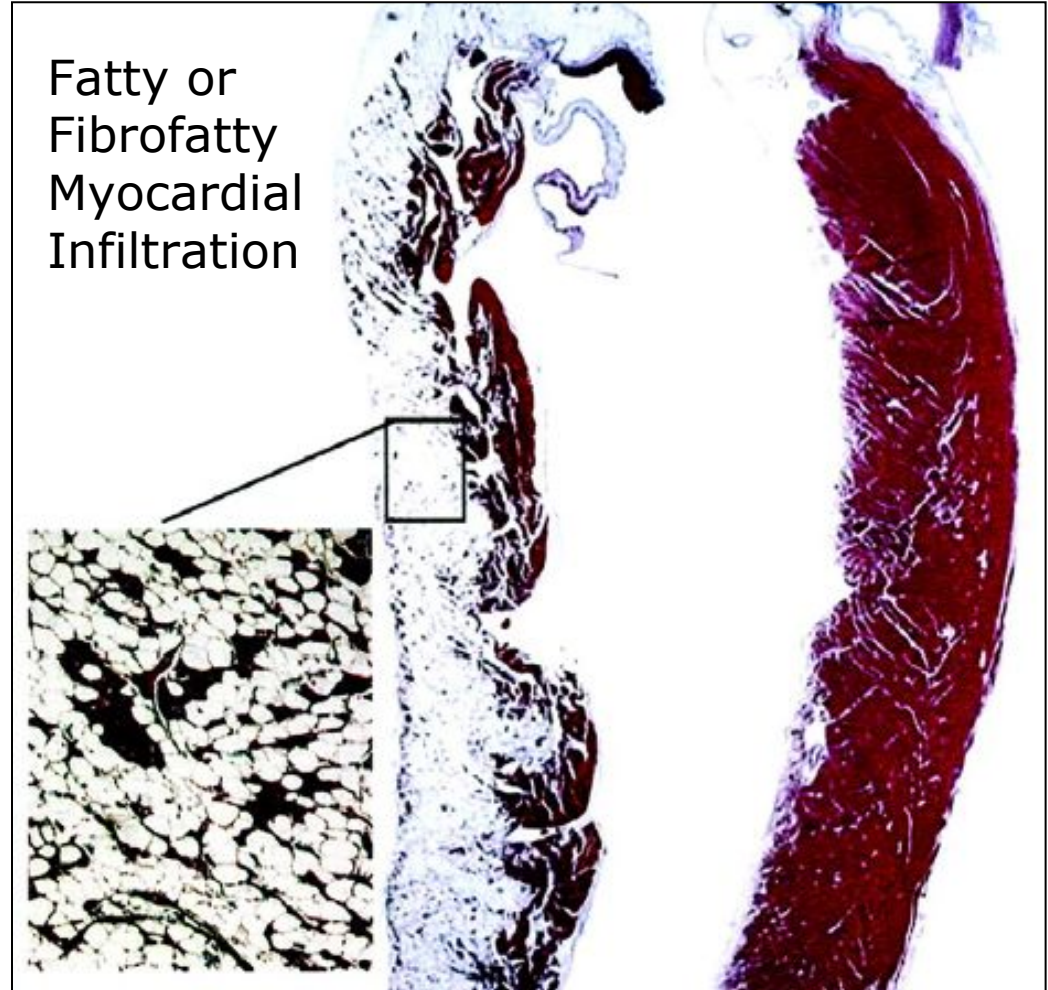
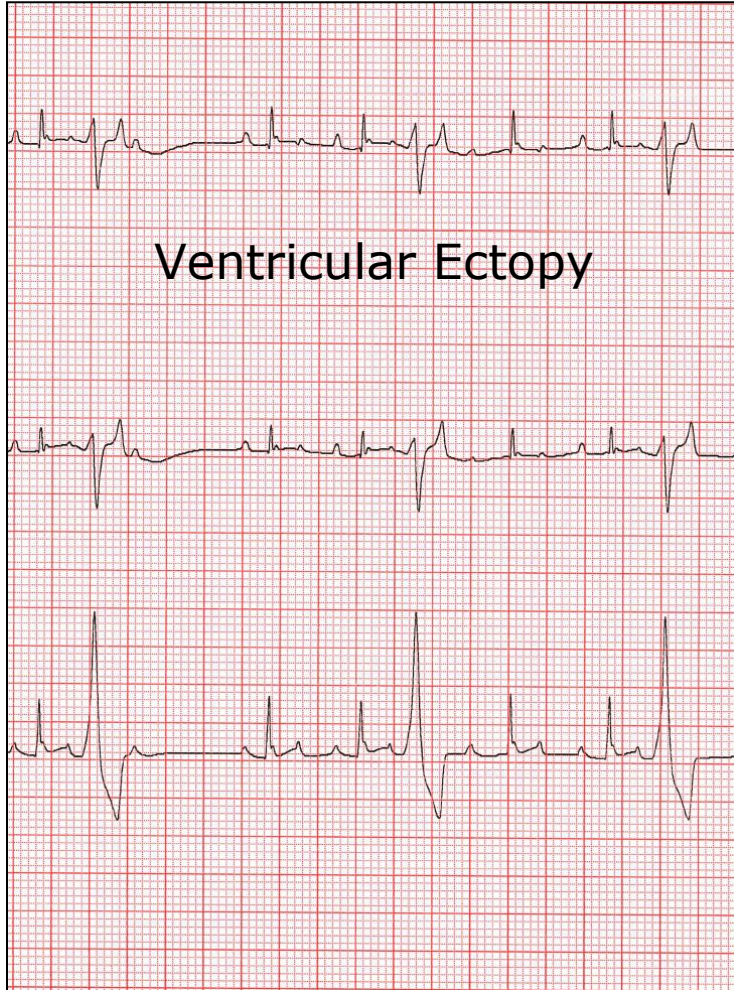
Definition



An inherited disease
resulting in
ventricular arrhythmias
and
unique myocardial changes

ARVC

Definition



ARVC

History of ARVC

- Boxer cardiomyopathy
 - Initially described in 1983
 - Ventricular ectopy
 - Syncope
 - Sudden death
- Reclassified in 2004
 - Arrhythmogenic right ventricular cardiomyopathy
 - Parallels to human disease

ARVC (Patho) Physiology

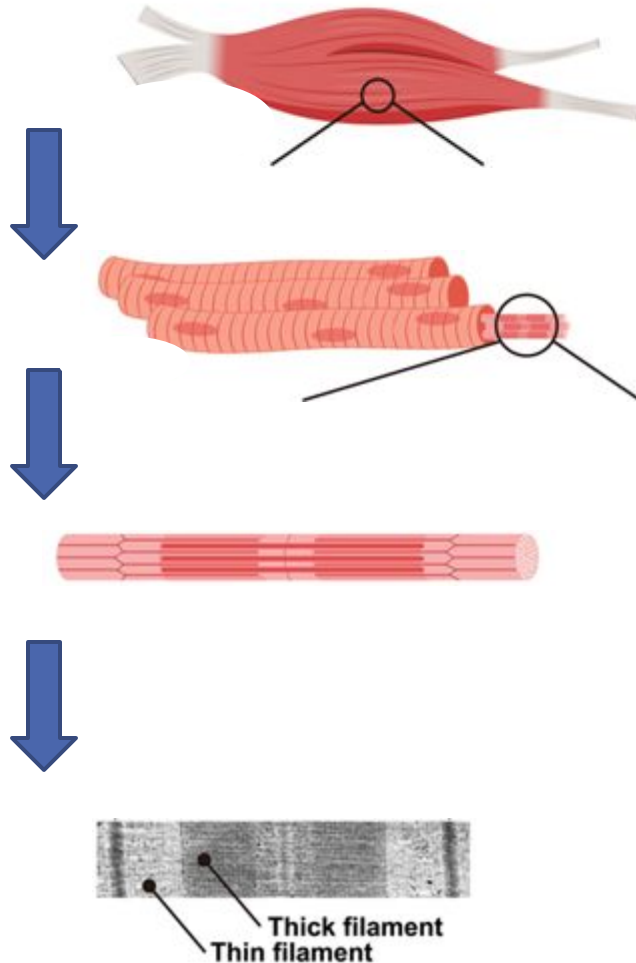
Cardiac Muscle

Cardiac muscle

Myofiber

Myofibrils

Sarcomere



ARVC (Patho)Physiology

The Sarcomere

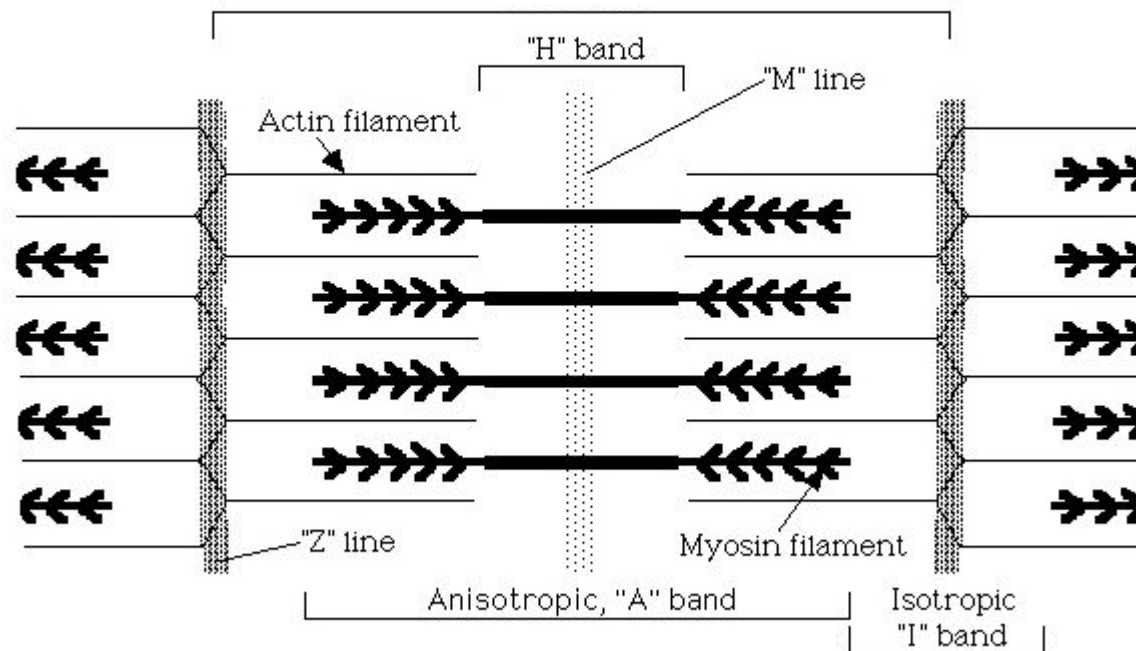
- Sarcomere major components
 - Actin, myosin, troponin complex, titin
- Other filaments & proteins
 - Maintain cell shape
 - Link sarcomere to cell surface
 - Cell-to-cell adhesions
 - Organize cellular contents
 - Intracellular transport
 - Strengthen nuclear membrane

ARVC (Patho) Physiology

The Sarcomere

H band = myosin filaments

M-line – myosin filament connections

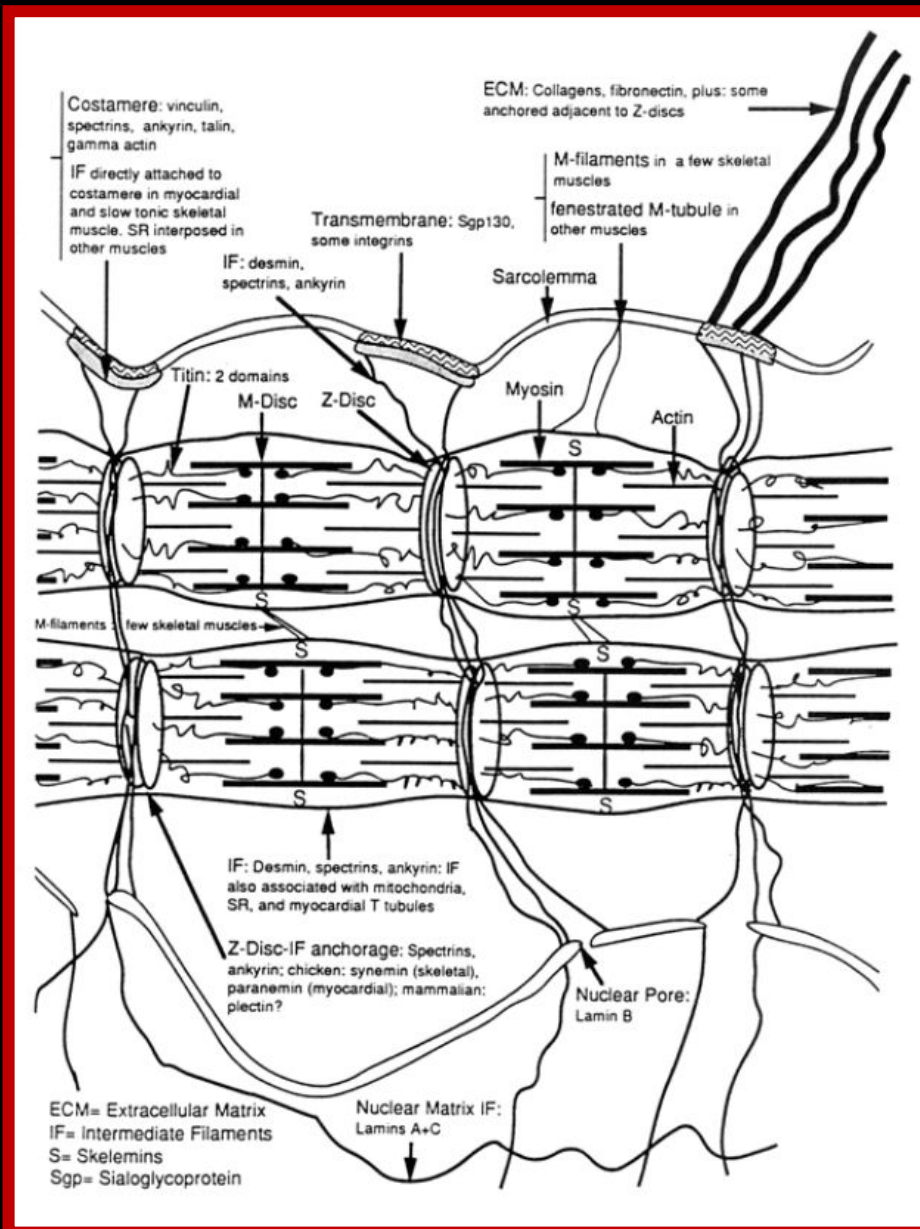


A band = overlapping acting and myosin

Z line = adjacent sarcomeres anchor via actin filaments

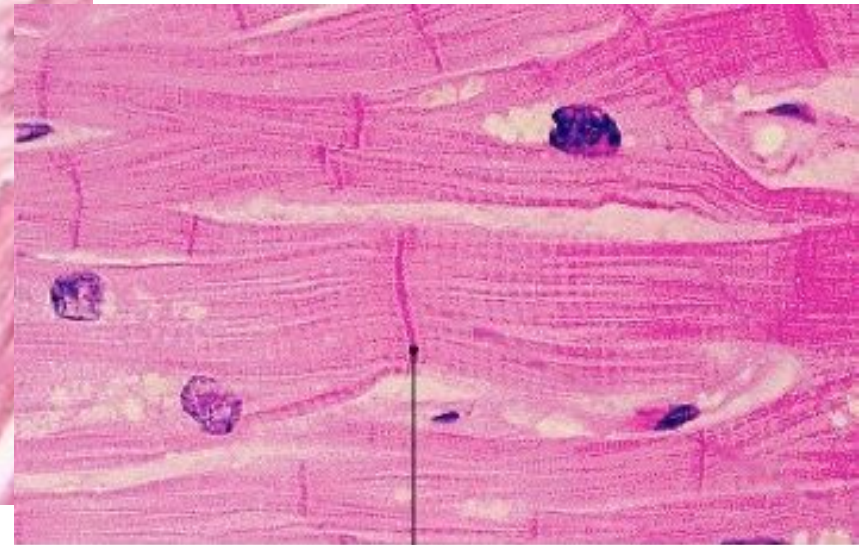
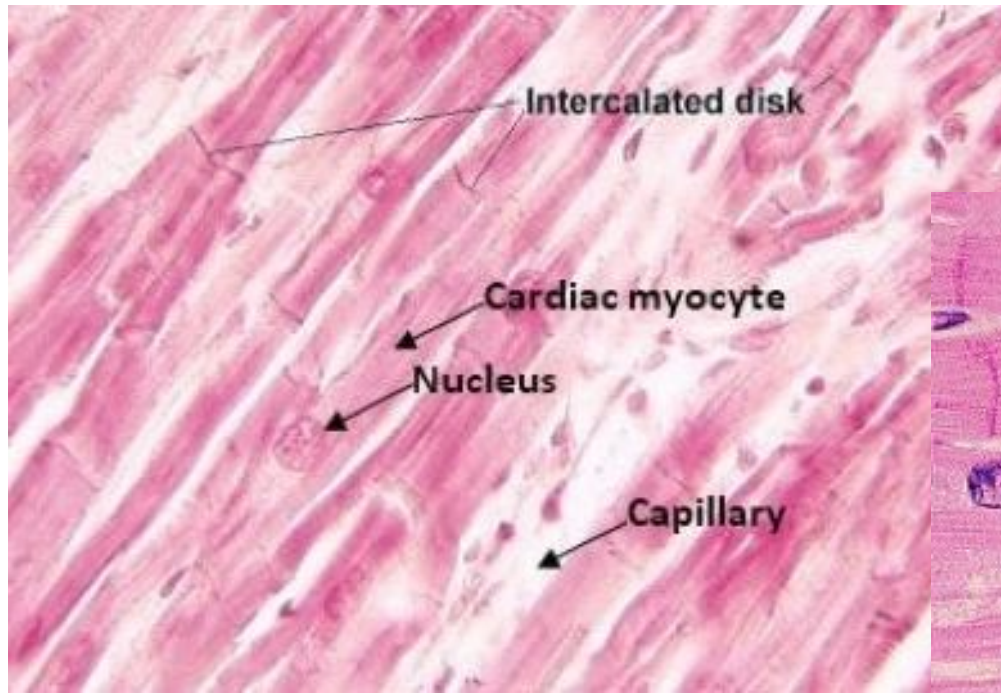
I band = thin filaments & the Z line

The Sarcomere



ARVC (Patho) Physiology

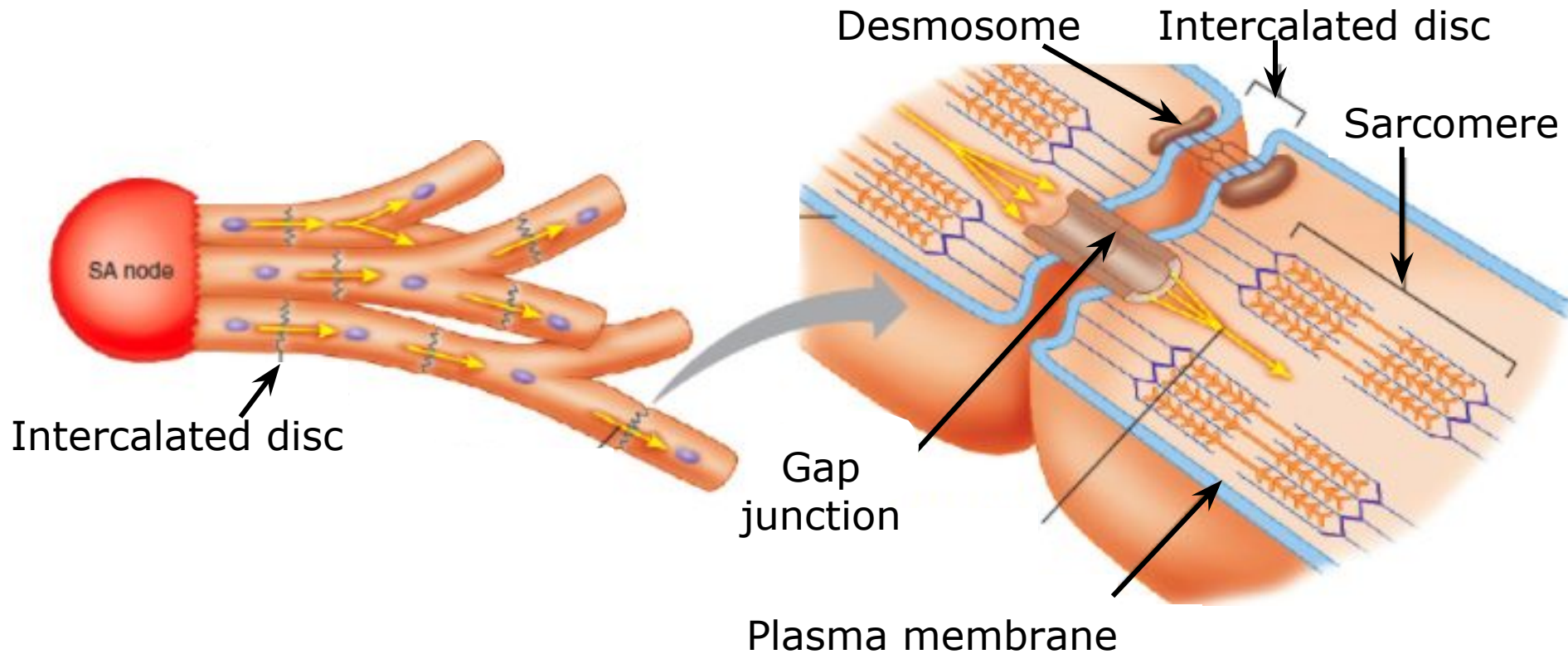
Intercalated Disc



Cardiac muscle cells connect at intercalated discs

ARVC (Patho) Physiology

Intercalated Disc



ARVC (Patho)Physiology

Intercalated discs

- Specialized complexes
 - Desmosomes (macula adherens)
 - Hold cells together
 - Necessary for signal transduction
 - Abnormalities □ weakened cell adhesions
 - Exacerbated by stress
 - Fascia adherens
 - Site of myofilament attachment to sarcolemma
 - Gap junctions
 - Allow ion transport & action potentials

ARVC (Patho)Physiology

The Wnt Pathway

- Wnt signaling
 - Controls normal development of the RV myocardium
 - Altered Wnt releases paracrine factors
 - Differentiation of fibrocytes and preadipocytes □
mature adipocytes □ □ □ fibrofatty replacement
- Abnormal Wnt in both people and Boxer ARVC

ARVC (Patho)Physiology

Striatin

- Cardiac protein
 - Found in intercalated discs
 - Co-localizes with desmosomes
 - Component of Wnt pathway
- Striatin mutation
 - Abnormal cell to cell adhesions
 - Mechanical instability

ARVC (Patho)Physiology

Abnormal Calcium Handling

- Decreased ryanodine receptor mRNA and protein levels
- Decreased calstabin 2 mRNA and protein levels
 - Abnormal calcium regulation
 - Calcium “leak” induced ventricular arrhythmias

ARVC

Genetics

- Boxers as model of disease
- Several genes evaluated
 - >16 genetic mutations identified in human ARVC
 - 50% people mutated desmosomal protein
 - Mutations associated with
 - Abnormal cell-to-cell adhesions
 - Myocardial instability
 - Abnormal cell signaling



ARVC

Genetics

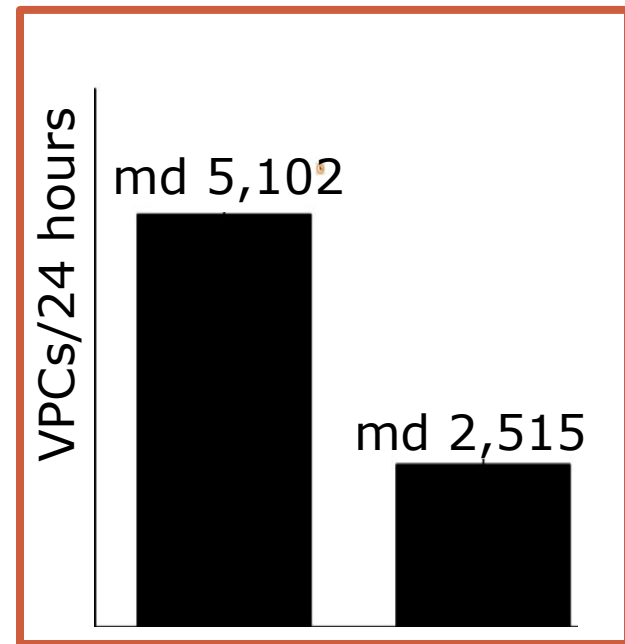
- Boxer striatin mutation
 - Only identified Boxer genetic mutation
 - Chromosome 17
 - Autosomal dominant
 - Incomplete penetrance
 - Variable expressivity
 - Inconsistent association with disease

9 – 16% of ARVC Boxers do not carry a striatin mutation

ARVC Genetics

Striatin

- Homozygous (HO) Boxers
 - ~100% disease penetrance
 - Younger age of onset
 - Higher number of VPCs/24 hrs
 - More severe ventricular arrhythmias
 - Myocardial disease
 - Worse outcome
- Heterozygous (HE) Boxers
 - 82% disease penetrance



ARVC Genetics

Striatin

- ARVC as a “spectrum”

	Homozygous	Heterozygous	Negative
Normal Boxers (n = 16)	0	5	11
ARVC Boxers Arrhythmia (n = 29)	6	23	0
Myocardial Boxers Arrhythmia + DCM (n = 33)	15	15	3

ARVC

Boxer Disease Features

- Adult onset
- Age-related penetrance
- 3 classifications
 - Concealed: Asymptomatic arrhythmias
 - Overt: Symptomatic ventricular arrhythmias*
+/- RV changes
 - DCM phenotype: Arrhythmias, LV dysfunction, CHF

***sudden death**

ARVC

Patient Signalment

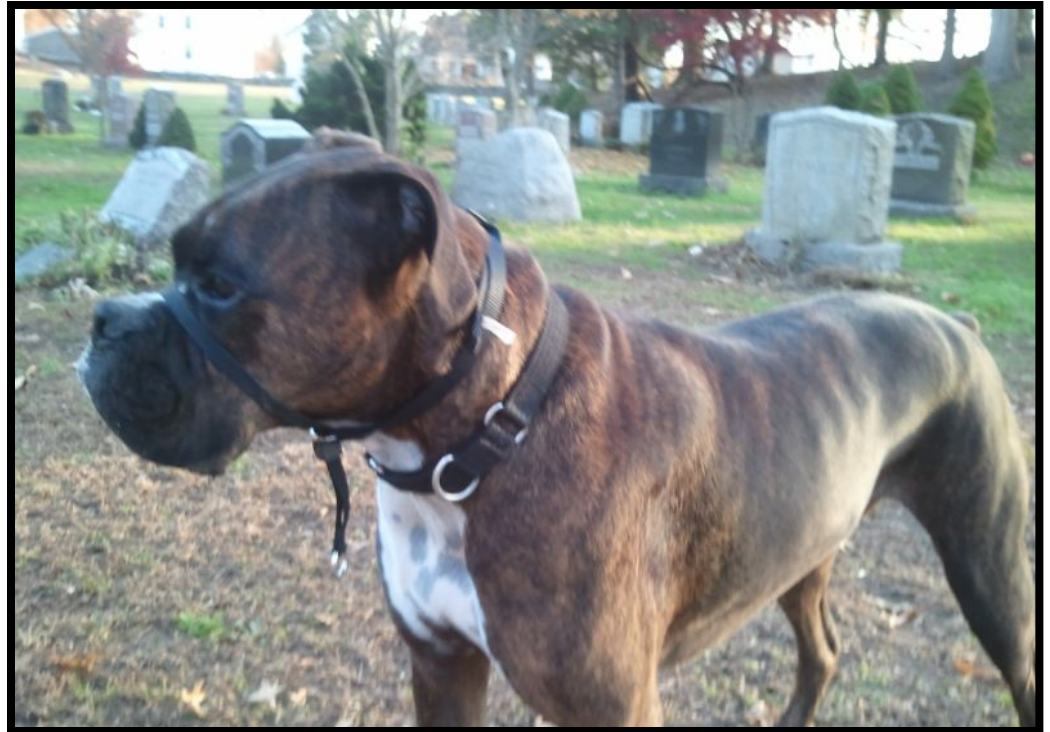
- Boxers and English Bulldogs
 - Bullmastiff, Dachshund, Labrador Retriever, Siberian Husky, Dalmation, Shetland sheepdog, Weimaraner
- Middle age
 - Range 1 – 11yr
 - Median 6yr
- Males overrepresented
- Occurs in cats and horses



ARVC

Patient Presentation

- Normal
- Weakness
- Syncope*
- "Seizures"
- Coughing
- Labored breathing
- Abdominal swelling



***1/3rd Boxers are syncopal**

ARVC

Patient Physical Exam

- Normal
- Arrhythmia on auscultation
- Pulse deficits
- Weak pulses
- Soft systolic apical murmur
- Exam findings consistent with CHF

ARVC Diagnosis

Cardiac Checklist



- Family history
- Clinical history
- Signalment
- ECG
- Echocardiogram
- 24 hour heart rate monitor

ARVC Diagnosis

Evaluate for Systemic Disease



- Lab work
 - CBC, chemistry panel, UA, endocrine testing
 - Infectious disease testing
- Abdominal ultrasound

Avoid tunnel vision

ARVC Diagnosis

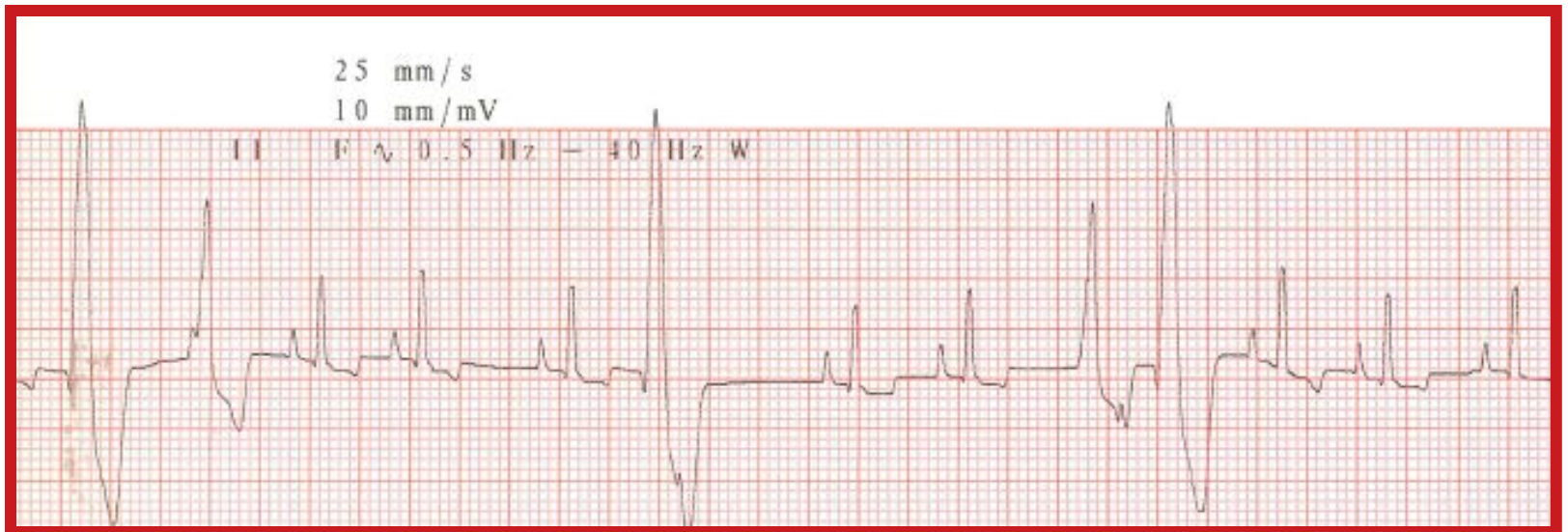
Cardiac Evaluation

- Blood pressure
- Thoracic radiographs
- Electrocardiogram

ARVC Diagnosis

ECG

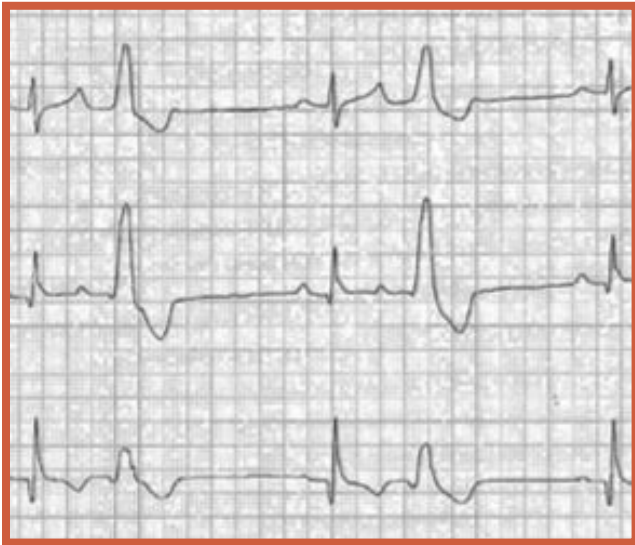
- Normal
- Ventricular ectopy
 - Upright VPCs
 - Often uniform, occasionally multiform



ARVC Diagnosis

ECG

- Isolated
- Patterns: bigeminy, trigeminy
- Pairs or couplets



ARVC Diagnosis

ECG

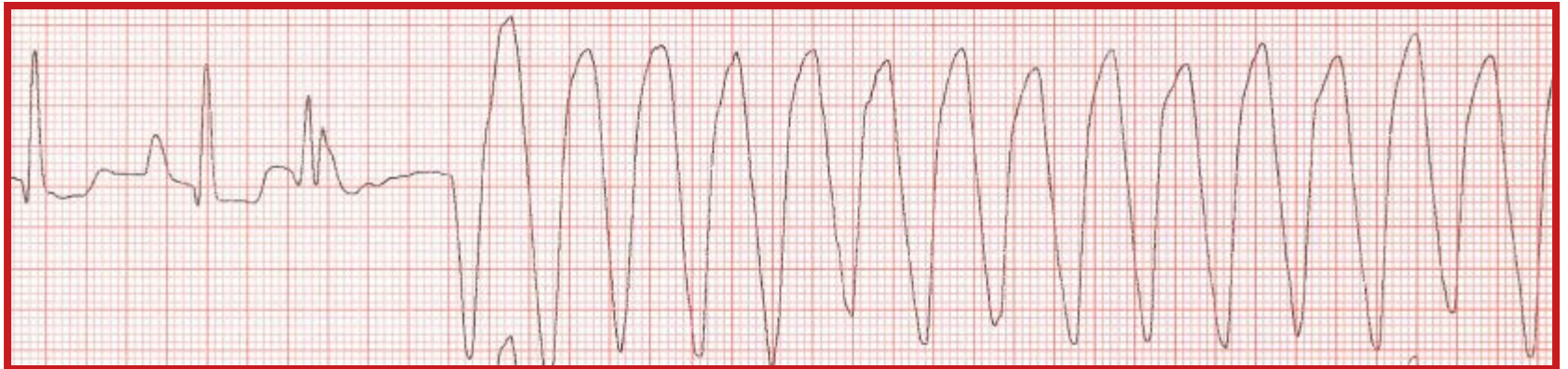
- Persistent ventricular tachycardia
 - Continuous series of VPCs
 - > 3 VPCs



ARVC Diagnosis

ECG

- R-on-T phenomenon
 - R wave occurs on the preceding T wave
 - Results in depolarization during the “vulnerable period”
 - May decompensate to ventricular fibrillation



ARVC Diagnosis

Holter Monitor

- First ambulatory ECG completed in 1961
 - Conducted by Norman J. Holter and W.R. Glasscock
 - The first system weighed 85lb
- First commercial device released in 1962



ARVC Diagnosis

Holter Monitor

- Benefits
 - Provides diagnostic, prognostic, and therapeutic information
 - 24 to 48 hour screening
 - Multiple leads assessed
 - Correlations between rhythm and activity
 - Annual screening
 - Pre-breeding screening

Navix Diagnostix. Inc.

100 Myles Standish Blvd

Taunton, MA 02780

800-543-7275

HOLTER REPORT

Patient: [REDACTED]

ID: 01562

DOB: NA

Age: NA

Sex: Male

Scan No.: 01562

Report Date: 12/15/2021, 1:14 PM

Test Date: 12/8/2021, 11:30 AM

Referring Physician: Quinn

Interpreting Physician: Quinn

Hook-Up:

Scanned By: HLC

Site ID: 300

Recorder SN: 49646

Indications:

Medications:

Navix Diagnostix. Inc.

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Taunton, MA 02780

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Hook-Up:

Scanned By: HLC

Site ID: 300

Recorder SN: 49646

[REDACTED] was monitored for 23:59 hours; 23:48 hours were analyzed. During this time his average heart rate (HR) was 88, with a min. HR of 18 at 2:17:03 AM(2) and a max. HR of 240 at 6:43:24 AM(2). He had 7438 pauses greater than 2.0 sec. The longest pause was 5.295 sec. at 3:34 AM(2). There were 93416 Total Beats.

Mr. [REDACTED] test showed 65 VPB's. He had 55 isolated VPB's, 2 VPB pairs, and 1 VPB run. 6 beats were in VPB runs. The longest/fastest run had 6 beats at 7:36:05 AM(2) and had a rate of 101 bpm.

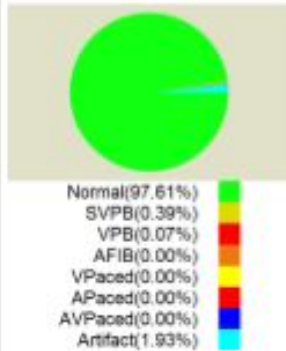
Mr. [REDACTED] test showed 365 SVPB's (100 % prematurity), 5 SVPB pairs, and 7 SVPB runs. The longest run had 41 beats at 11:26:22 AM(2) and had a rate of 199 bpm, the fastest run had 37 beats at a rate of 211 at 10:51:00 PM(1). There were 0 aberrant SVPB's.

IMPRESSIONS: THE PREDOMINANT RHYTHM WAS SINUS WITH EPISODES OF SINUS ARRHYTHMIA. VEA WAS MULTIFORM. PATIENT WAS ASYMPTOMATIC. RECORDING QUALITY WAS GOOD. SCANNED BY HEIDI CERIANI

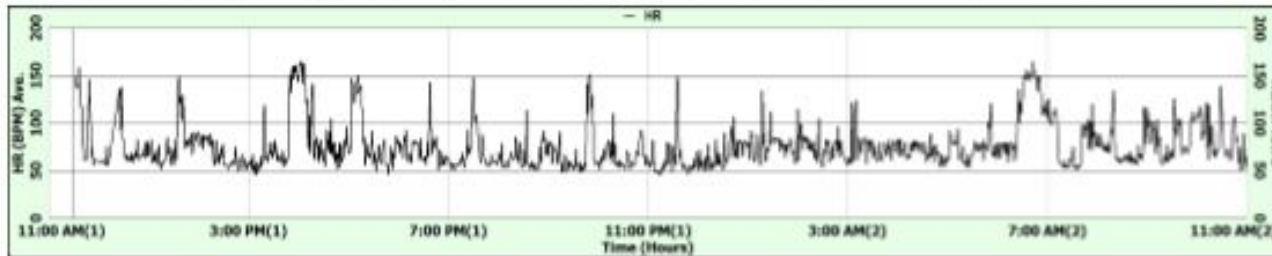
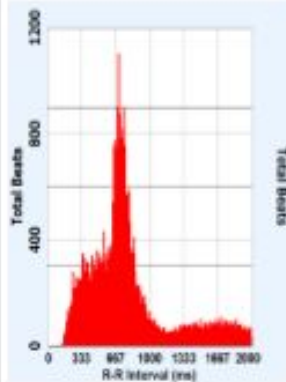
General Summary Report

Start	HR Min.	Avg.	Max.	Tot. Bts	VPB	V-Pair	V-Run	SVPB	SV-Pair	SV-Run	Pause	Analyzed	Rhythm
11:30 AM(1)	40	126	211	2720	1	0	0	0	0	0	64	29:05	
12:00 PM(1)	38	96	189	4012	2	0	0	3	0	0	214	59:58	
1:00 PM(1)	39	100	193	3934	3	0	0	9	1	1	313	59:25	
2:00 PM(1)	31	72	130	3107	1	0	0	0	0	0	387	1:00:00	
3:00 PM(1)	31	108	182	4348	0	0	0	0	0	0	329	55:58	
4:00 PM(1)	35	122	199	4193	2	0	0	5	1	0	478	56:48	
5:00 PM(1)	33	120	211	4058	1	0	0	6	0	0	444	59:15	
6:00 PM(1)	33	88	183	3182	5	0	0	57	1	0	492	59:57	
7:00 PM(1)	39	87	182	4036	0	0	0	11	0	0	87	1:00:00	
8:00 PM(1)	34	78	166	3416	2	0	0	5	0	0	254	1:00:00	
9:00 PM(1)	36	96	188	3741	0	0	0	1	0	0	294	59:43	
10:00 PM(1)	33	77	179	3481	4	0	0	56	0	3	249	1:00:00	
11:00 PM(1)	33	82	184	3213	1	0	0	4	0	0	423	59:57	
12:00 AM(2)	33	76	163	3315	5	0	0	5	0	0	333	1:00:00	
1:00 AM(2)	34	88	157	3224	5	0	0	4	0	0	516	1:00:00	
2:00 AM(2)	33	81	145	2939	4	0	0	0	0	0	535	1:00:00	
3:00 AM(2)	33	87	161	3363	0	0	0	43	1	1	426	59:58	
4:00 AM(2)	30	78	126	2626	5	0	0	29	0	0	601	1:00:00	
5:00 AM(2)	34	87	164	3169	2	0	0	20	0	0	498	59:59	
6:00 AM(2)	39	142	242	5992	2	1	0	2	0	0	250	58:31	
7:00 AM(2)	31	98	185	4573	9	0	1	36	0	0	90	1:00:00	
8:00 AM(2)	45	86	170	4385	2	0	0	3	0	0	7	1:00:00	
9:00 AM(2)	38	99	187	4994	5	0	0	3	0	0	6	59:59	
10:00 AM(2)	39	100	177	4859	3	1	0	7	0	0	68	59:57	
11:00 AM(2)	40	117	175	2529	1	0	0	56	1	2	80	29:59	
TOTALS	30	88	242	93416	65	2	1	365	5	7	7438	23:48:36	

Rhythm Breakdown



R-R Normals



Ventricular Summary Report

Start	Min. HR	Avg. HR	Max. HR	Total Beat	VPB	VPB Iso.	VPB Pair	Runs	Run Bt.	Run Long	Big.	Tri.	Quad.
11:30 AM(1)	40	126	211	2728	1	1	0	0	0	0	0	0	0
12:00 PM(1)	38	96	189	4012	2	2	0	0	0	0	0	0	0
1:00 PM(1)	39	100	193	3934	3	3	0	0	0	0	0	0	0
2:00 PM(1)	31	72	130	3107	1	1	0	0	0	0	0	0	0
3:00 PM(1)	31	108	182	4348	0	0	0	0	0	0	0	0	0
4:00 PM(1)	35	122	199	4193	2	2	0	0	0	0	0	0	0
5:00 PM(1)	33	120	211	4058	1	1	0	0	0	0	0	0	0
6:00 PM(1)	33	88	183	3182	5	5	0	0	0	0	0	0	0
7:00 PM(1)	39	87	182	4036	0	0	0	0	0	0	0	0	0
8:00 PM(1)	34	78	166	3416	2	2	0	0	0	0	0	0	0
9:00 PM(1)	36	96	188	3741	0	0	0	0	0	0	0	0	0
10:00 PM(1)	33	77	179	3481	4	4	0	0	0	0	0	0	0
11:00 PM(1)	33	82	184	3213	1	1	0	0	0	0	0	0	0
12:00 AM(2)	33	76	163	3315	5	5	0	0	0	0	0	0	0
1:00 AM(2)	34	88	157	3224	5	5	0	0	0	0	0	0	0
2:00 AM(2)	33	81	145	2939	4	4	0	0	0	0	0	0	0
3:00 AM(2)	33	87	161	3363	0	0	0	0	0	0	0	0	0
4:00 AM(2)	30	78	126	2625	5	5	0	0	0	0	0	0	0
5:00 AM(2)	34	87	164	3169	2	2	0	0	0	0	0	0	0
6:00 AM(2)	39	142	242	5992	2	0	1	0	0	0	0	0	0
7:00 AM(2)	31	98	185	4573	9	3	0	1	6	6	0	0	0
8:00 AM(2)	45	86	170	4385	2	2	0	0	0	0	0	0	0
9:00 AM(2)	38	99	187	4994	5	5	0	0	0	0	0	0	0
10:00 AM(2)	39	100	177	4859	3	1	1	0	0	0	0	0	0
11:00 AM(2)	40	117	175	2529	1	1	0	0	0	0	0	0	0
TOTALS	30	88	242	93416	65	55	2	1	6	6	0	0	0

Supraventricular Summary Report

Start	Min. HR	Avg. HR	Max. HR	Total Beat	SVPB	SVPB Iso.	SVE Pair	Runs	Run Bt.	Run Long	Abberant	Analyzed
11:30 AM(1)	40	126	211	2728	0	0	0	0	0	0	0	29:05
12:00 PM(1)	38	96	189	4012	3	3	0	0	0	0	0	59:58
1:00 PM(1)	39	100	193	3934	9	4	1	1	3	3	0	59:25
2:00 PM(1)	31	72	130	3107	0	0	0	0	0	0	0	1:00:00
3:00 PM(1)	31	108	182	4348	0	0	0	0	0	0	0	55:58
4:00 PM(1)	35	122	199	4193	5	3	1	0	0	0	0	56:48
5:00 PM(1)	33	120	211	4058	6	6	0	0	0	0	0	59:15
6:00 PM(1)	33	88	183	3182	57	55	1	0	0	0	0	59:57
7:00 PM(1)	39	87	182	4036	11	11	0	0	0	0	0	1:00:00
8:00 PM(1)	34	78	166	3416	5	5	0	0	0	0	0	1:00:00
9:00 PM(1)	36	96	188	3741	1	1	0	0	0	0	0	59:43
10:00 PM(1)	33	77	179	3481	56	7	0	3	49	37	0	1:00:00
11:00 PM(1)	33	82	184	3213	4	4	0	0	0	0	0	59:57
12:00 AM(2)	33	76	163	3315	5	5	0	0	0	0	0	1:00:00
1:00 AM(2)	34	88	157	3224	4	4	0	0	0	0	0	1:00:00
2:00 AM(2)	33	81	145	2939	0	0	0	0	0	0	0	1:00:00
3:00 AM(2)	33	87	161	3363	43	37	1	1	4	4	0	59:58
4:00 AM(2)	30	78	126	2625	29	29	0	0	0	0	0	1:00:00
5:00 AM(2)	34	87	164	3169	20	20	0	0	0	0	0	59:59
6:00 AM(2)	39	142	242	5992	2	2	0	0	0	0	0	58:31
7:00 AM(2)	31	98	185	4573	36	36	0	0	0	0	0	1:00:00
8:00 AM(2)	45	86	170	4385	3	3	0	0	0	0	0	1:00:00
9:00 AM(2)	38	99	187	4994	3	3	0	0	0	0	0	59:59
10:00 AM(2)	39	100	177	4859	7	7	0	0	0	0	0	59:57
11:00 AM(2)	40	117	175	2529	56	10	1	2	44	41	0	29:59
TOTALS	30	88	242	93416	365	255	5	7	100	41	0	23:48:36

List of Strips Attached

Time	Strip Detail	Strip Label
11:31:42 AM(1)	HR: 133	START OF RECORDING
1:12:48 PM(1)	HR: 64	VE SINGLE
1:59:40 PM(1)	HR: 56	PAUSE/VE SINGLE
2:46:41 PM(1)	HR: 53	VE SINGLE/PAUSE
3:42:48 PM(1)	HR: 54	PAUSES
4:21:21 PM(1)	HR: 65	SVE PAIR/PAUSE
4:38:56 PM(1)	HR: 36	PAUSES
5:07:07 PM(1)	HR: 89	SINUS RHYTHM
6:20:04 PM(1)	HR: 53	PAUSES/VE SINGLES
6:22:33 PM(1)	HR: 50	SVE SINGLES/PAUSE
7:09:50 PM(1)	HR: 50	PAUSES/SVE SINGLE
8:51:30 PM(1)	HR: 54	PAUSE/VE SINGLE
9:35:56 PM(1)	HR: 53	SVE SINGLE/PAUSE
10:13:39 PM(1)	HR: 48	PAUSES
10:51:00 PM(1)	HR: 121	SVT 37BTS @ 211 1 OF 2
10:51:08 PM(1)	HR: 92	SVT 37BTS @ 211 2 OF 2

10:53:00 PM(1)

100

105

105

139

82

VE SINGLES

109

111

144

93

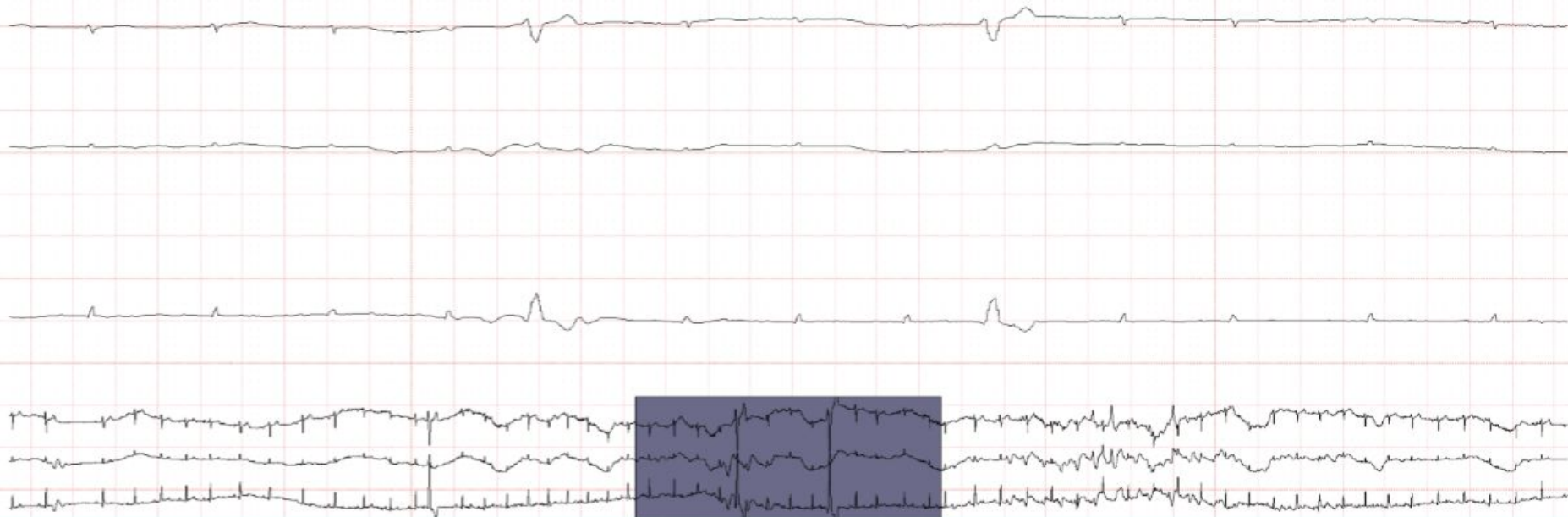
111

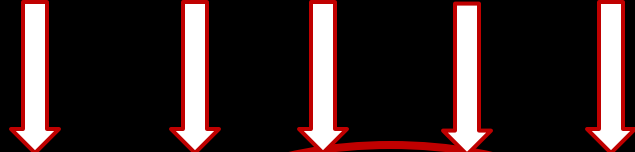
HR: 111

91

98

152





7:36:05 AM(2)

126

63

146

106

84

35

150

130

HR: 71
40

VTACH 6BTS @ 101/VE





██████████ was monitored for 23:59 hours; 23:59 hours were analyzed. During this time his average heart rate (HR) was 109, with a min. HR of 43 at 9:11:29 PM(1) and a max. HR of 202 at 3:01:43 PM(2). He had 15 pauses greater than 2.0 sec. The longest pause was 2.522 sec. at 5:01 AM(2). There were 132712 Total Beats.

Mr. ██████████ test showed 1416 VPB's. He had 1094 isolated VPB's, 80 VPB pairs, and 19 VPB runs. 111 beats were in VPB runs. ~~The longest run had 20 beats at 116 bpm at 5:02:14 PM(1) and the fastest run had 8bts with a rate of 280 bpm at 7:54 PM(1).~~ There were 3 bigeminy events with 10 bigeminy beats, 8 trigeminy events with 25 trigeminy beats, and 5 quadrigeminy events with 16 quadrigeminy beats.

Mr. ██████████ test showed 4 SVPB's (20 % prematurity), 0 SVPB pairs, and 0 SVPB runs. There were 0 aberrant SVPB's.

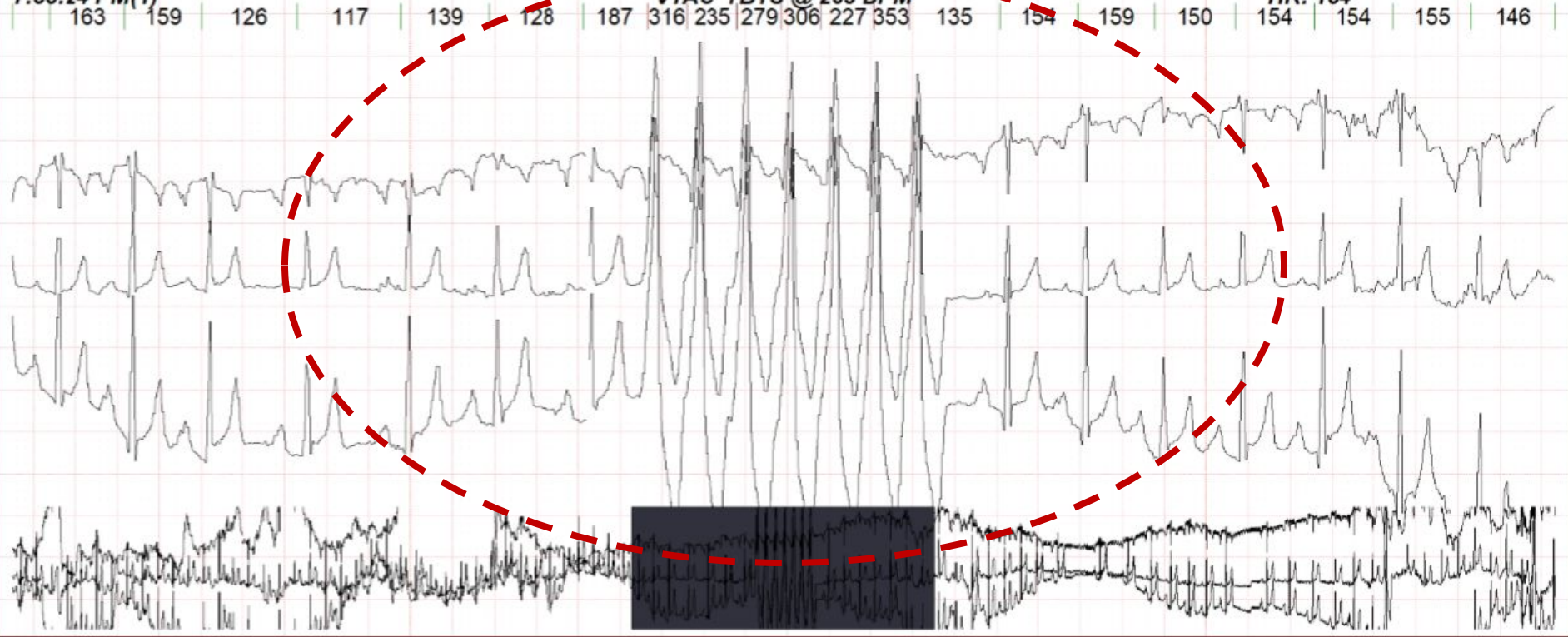
IMPRESSIONS: PREDOMINANT RHYTHM WAS SINUS. VEA WAS MULTIFORM. PT WAS ASYMPTOMATIC. RECORDING QUALITY WAS GOOD. SCANNED BY KMT



7:55:24 PM(1)

VTAC 7BTS @ 263 BPM

HR: 154



ARVC Diagnosis

24-Hr Holter Monitor Interpretation

- Normal: 0 – 20 isolated VPCs
- Possible ARVC: 50 – 100 isolated VPCs
- Suspicious ARVC :100 – 300 isolated VPCs
- Very likely ARVC: 300 – 1000 isolated VPCs
or
100 – 300 complex VPCs
- ARVC: > 1000 VPCs

ARVC Diagnosis

Holter Monitor Drawbacks

- High day-to-day variability
- Difficult to draw clinical conclusions
 - VPC number and complexity do not always determine if a patient is symptomatic
- Cost of Holter >\$500
- Test turn-around-time
- Company interpretation
- Patient comfort

ARVC Diagnosis

Home ECG Monitoring

- AliveCor or Kardia Device
- Cost to client \$100 - 250
- Allows client to intermittently record ECG
- Digital ECG transmission to cardiologist
- May overlook arrhythmia

ARVC Diagnosis

Home ECG Monitoring

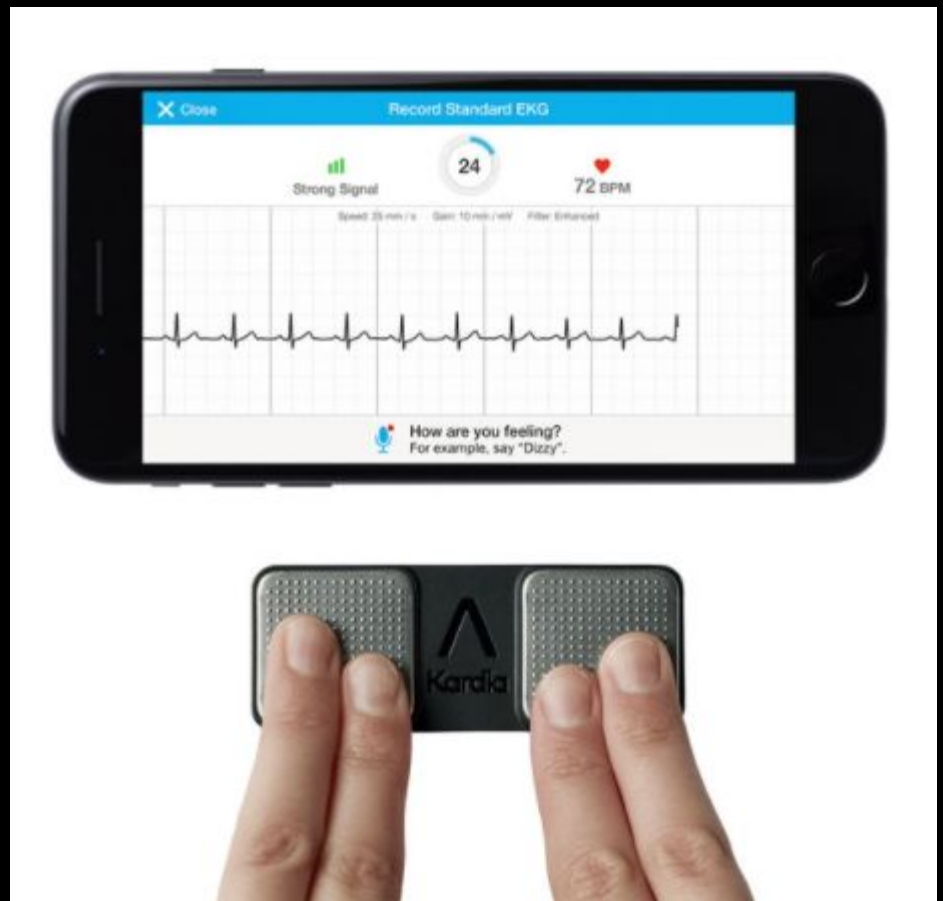
□ AliveCor or Kardia Device

Pros

- Cost to client \$150
- Allows client to intermittently record ECG
- Digital ECG transmission to cardiologist

Cons

- May overlook arrhythmia
- Requires active client participation
- Single lead
- Technology savvy



Patient:
Recorded:
Heart Rate:
Duration:

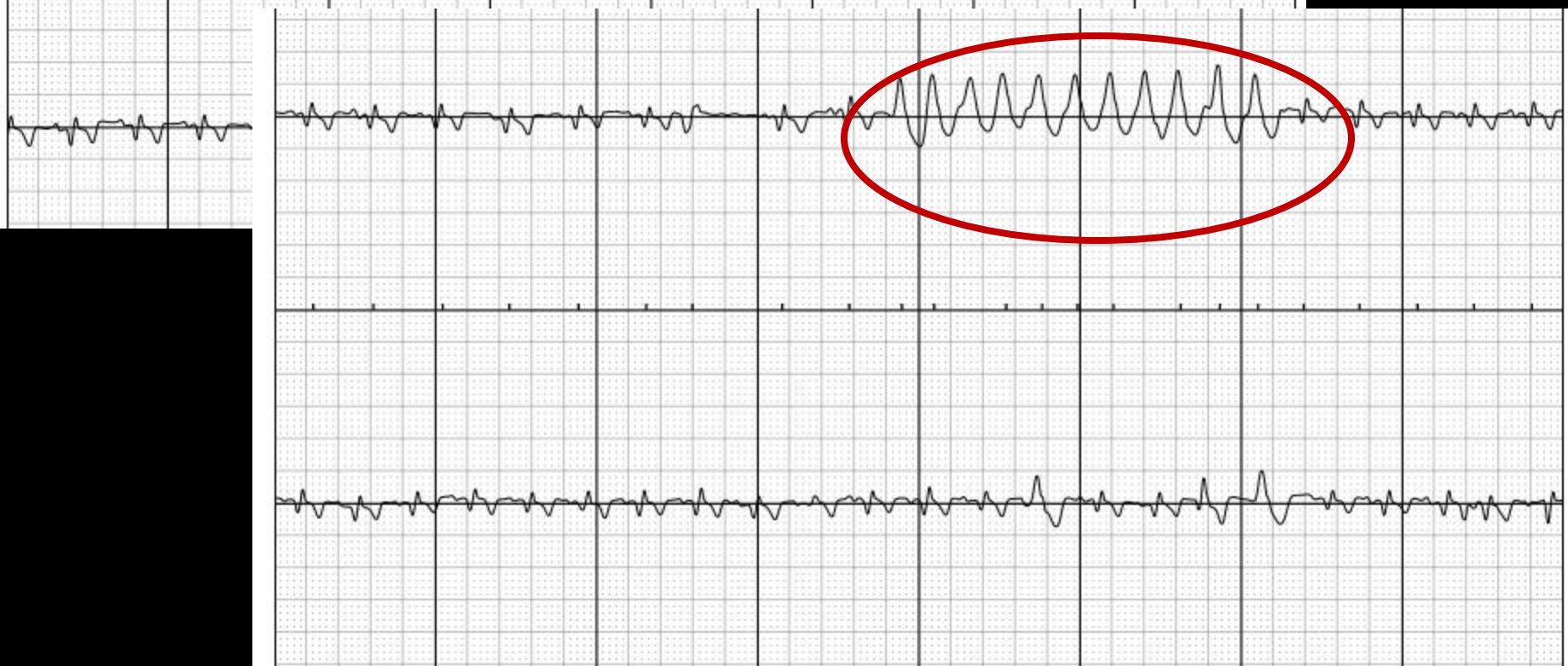
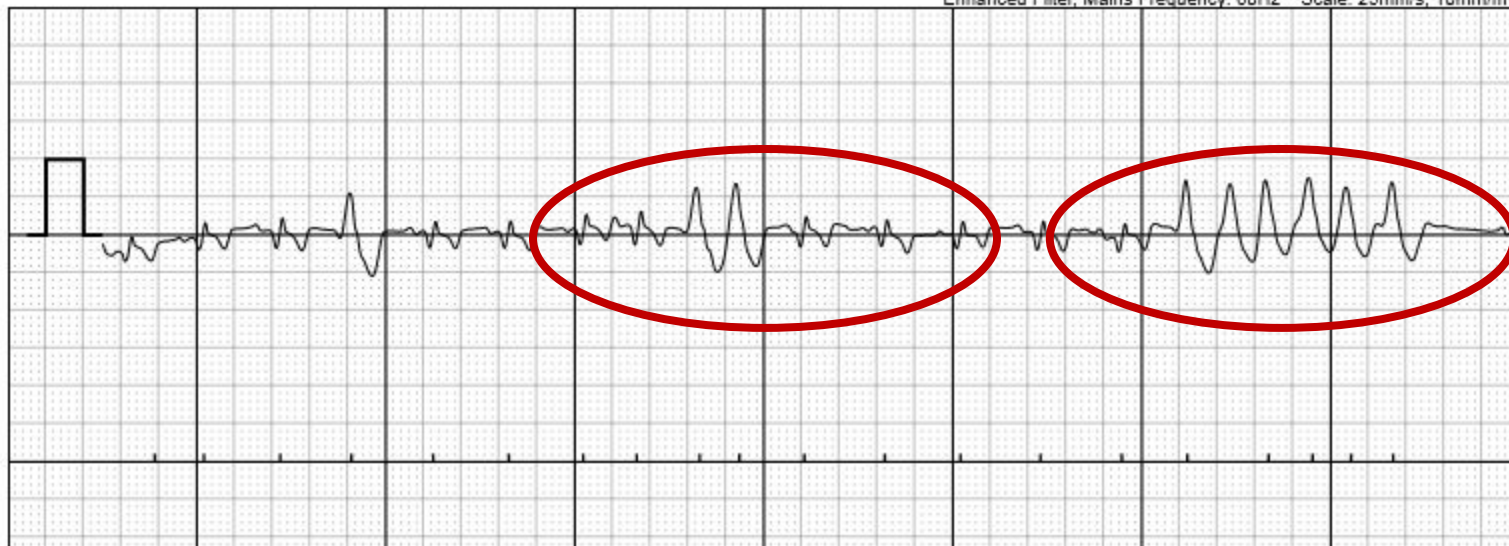
Instant Analysis:

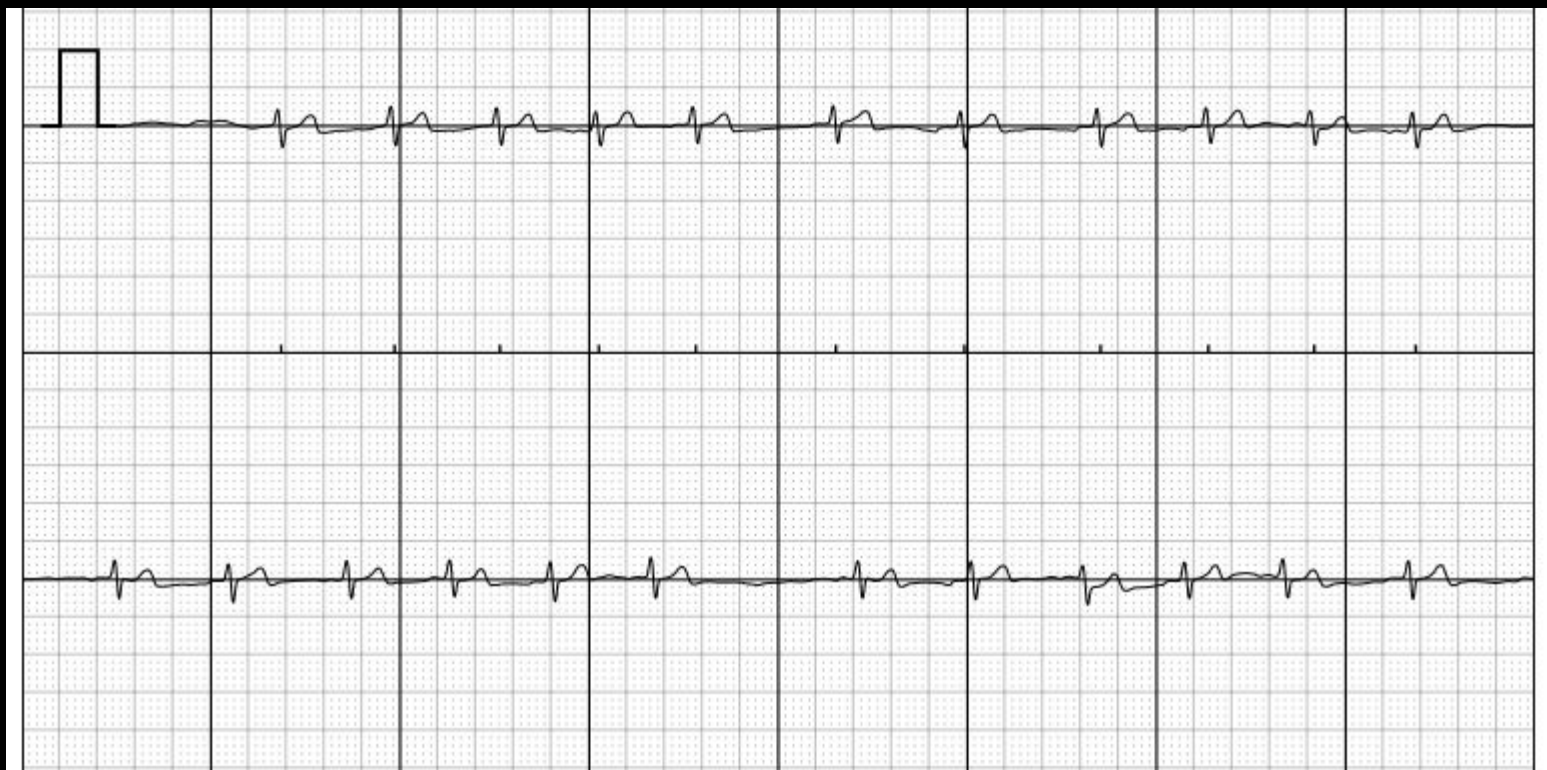
Unclassified

Kardia

Enhanced Filter, Main Frequency: 60Hz Scale: 25mm/s, 10mm/mV







ARVC Diagnosis

Extended ECG Monitoring

- Event monitors
 - 30 day monitor
 - Records only when activated
 - >\$500 - 700
- Implantable loop recorders
 - Minimally invasive (SQ)
 - Avoid problems with leads, discomfort
 - Requires sedation
 - >\$500 - 800



Sanders *et al.* JAAHA 2012;48(4): 269 – 272

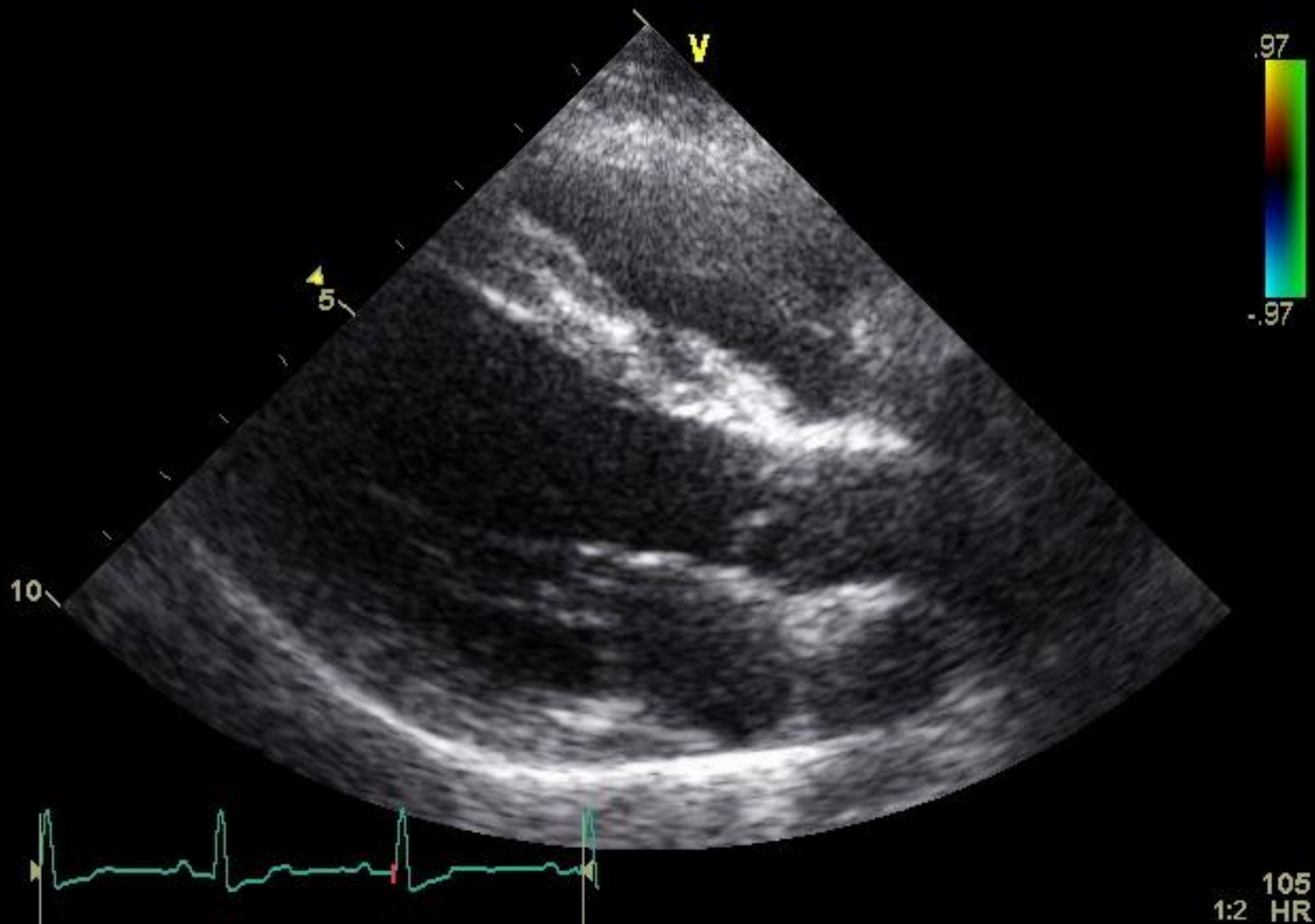
Mackie *et al.* JVC 2010;12:25-22

ARVC Diagnosis

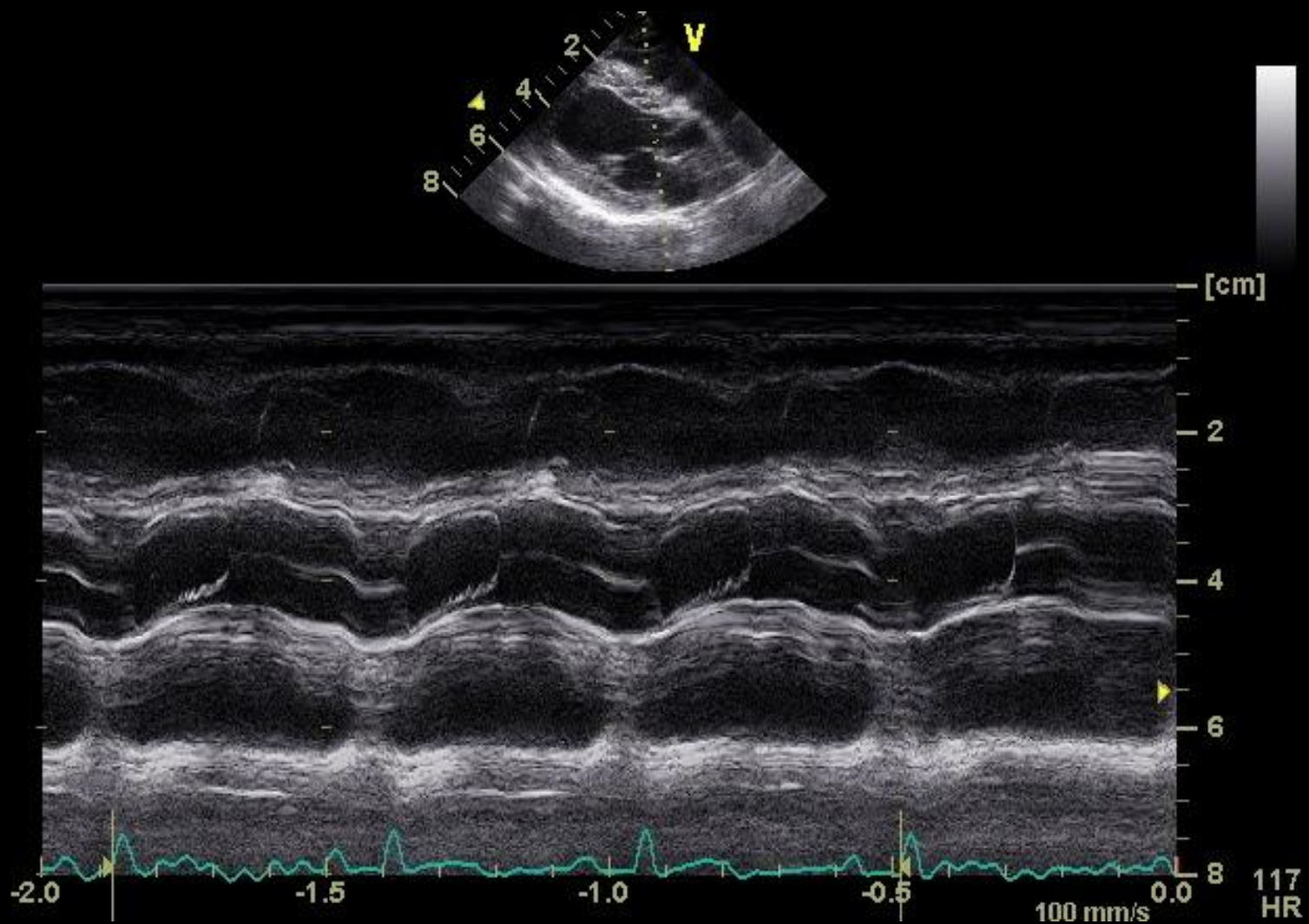
Cardiac Evaluation

- Echocardiogram
 - Often normal
 - Myocardial performance not affected in Boxers with concealed or arrhythmogenic disease
 - Right ventricular enlargement and dysfunction
 - Left ventricular enlargement and dysfunction
 - DCM

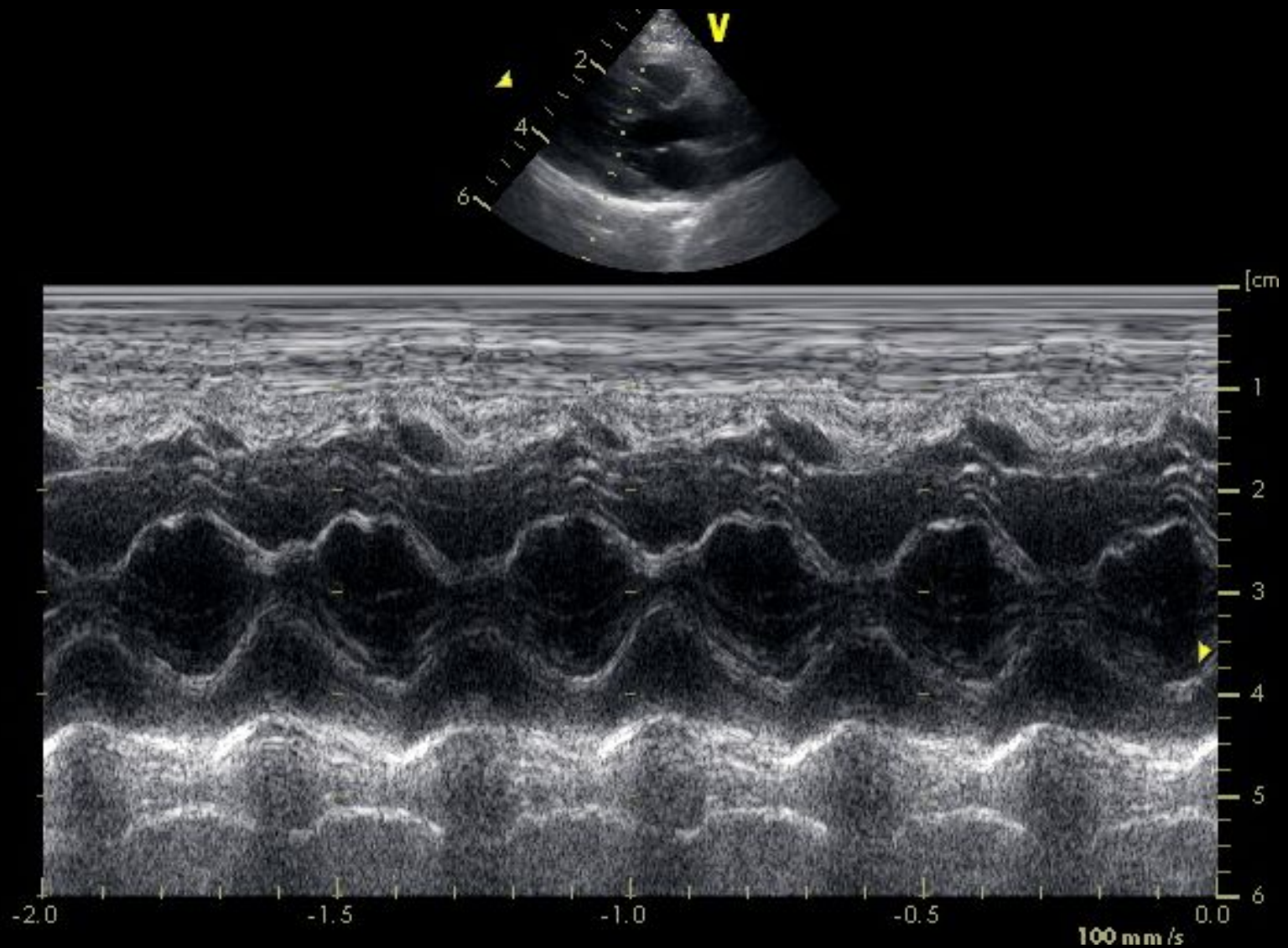
ARVC – Structurally Normal



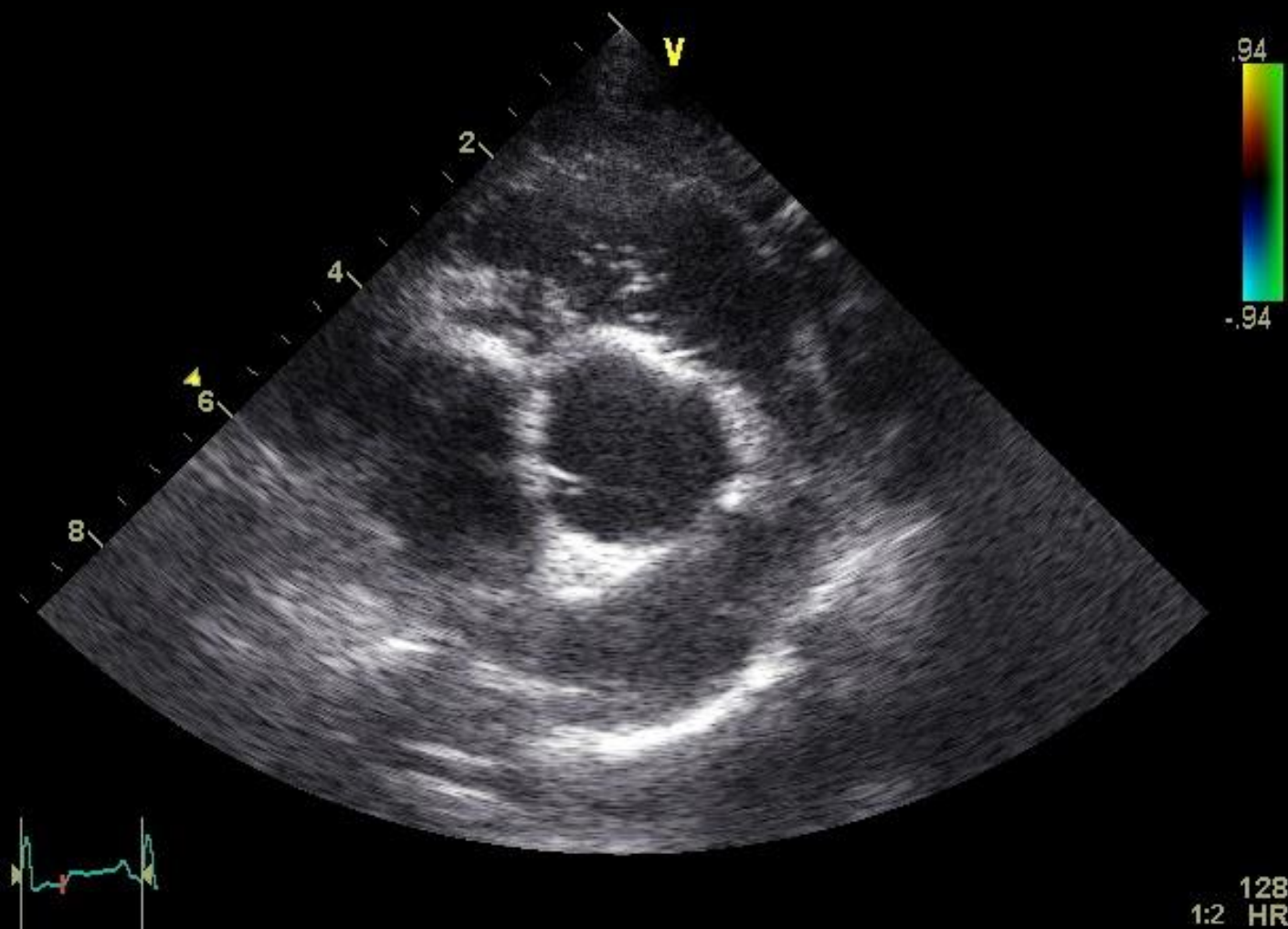
ARVC – Structurally Normal



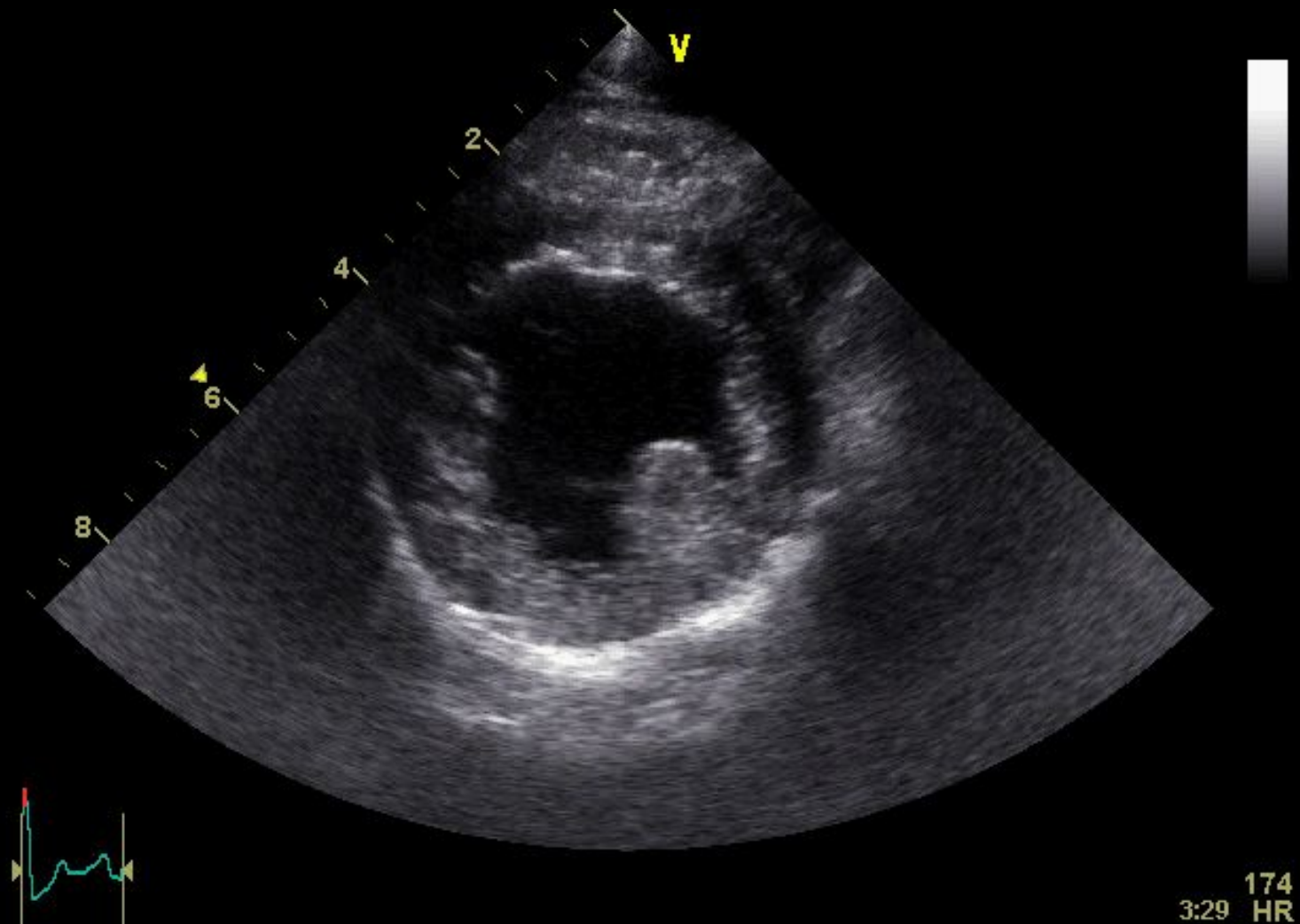
ARVC – Structurally Normal



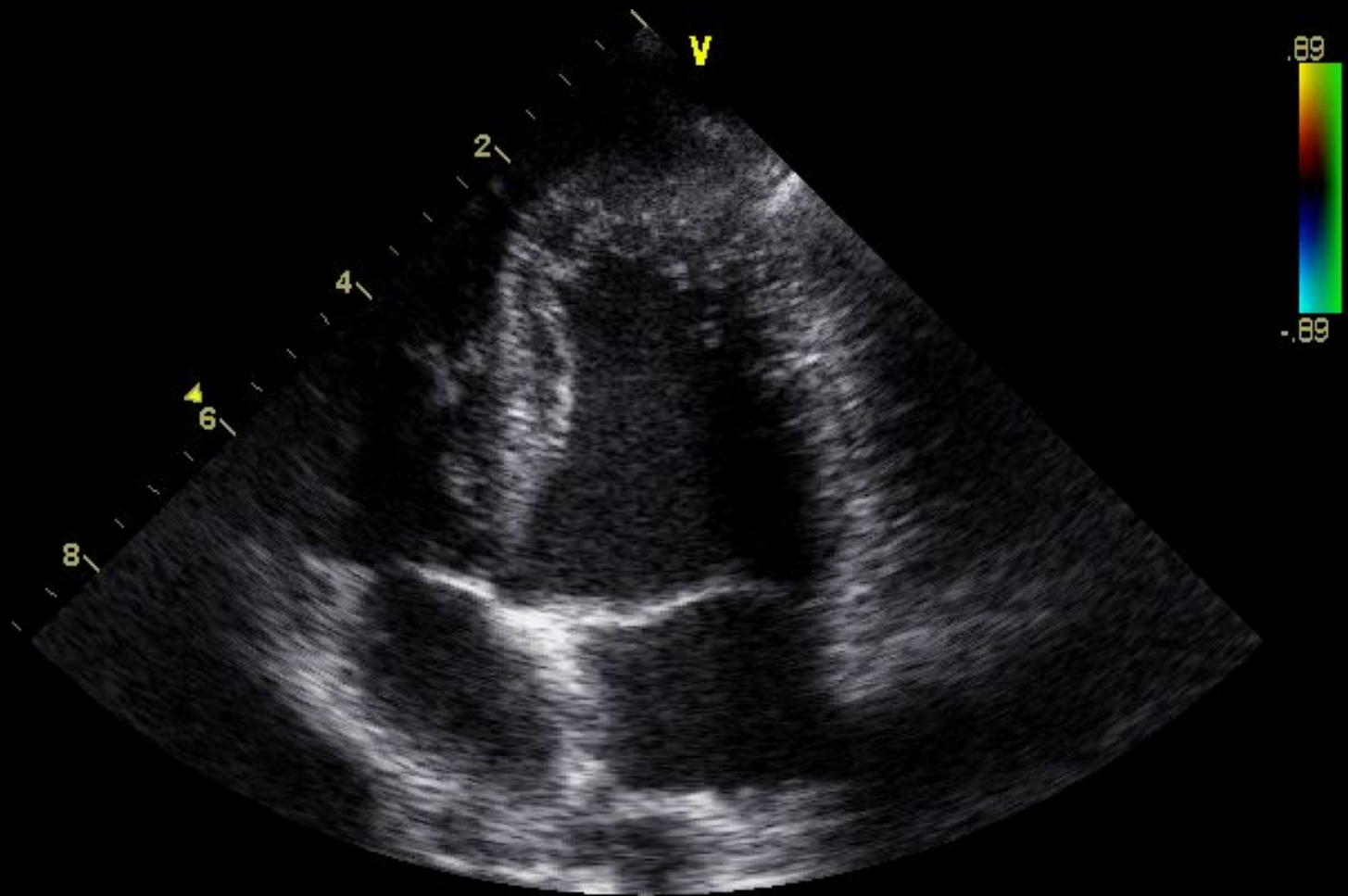
ARVC – Structurally Normal



ARVC – Structurally Normal

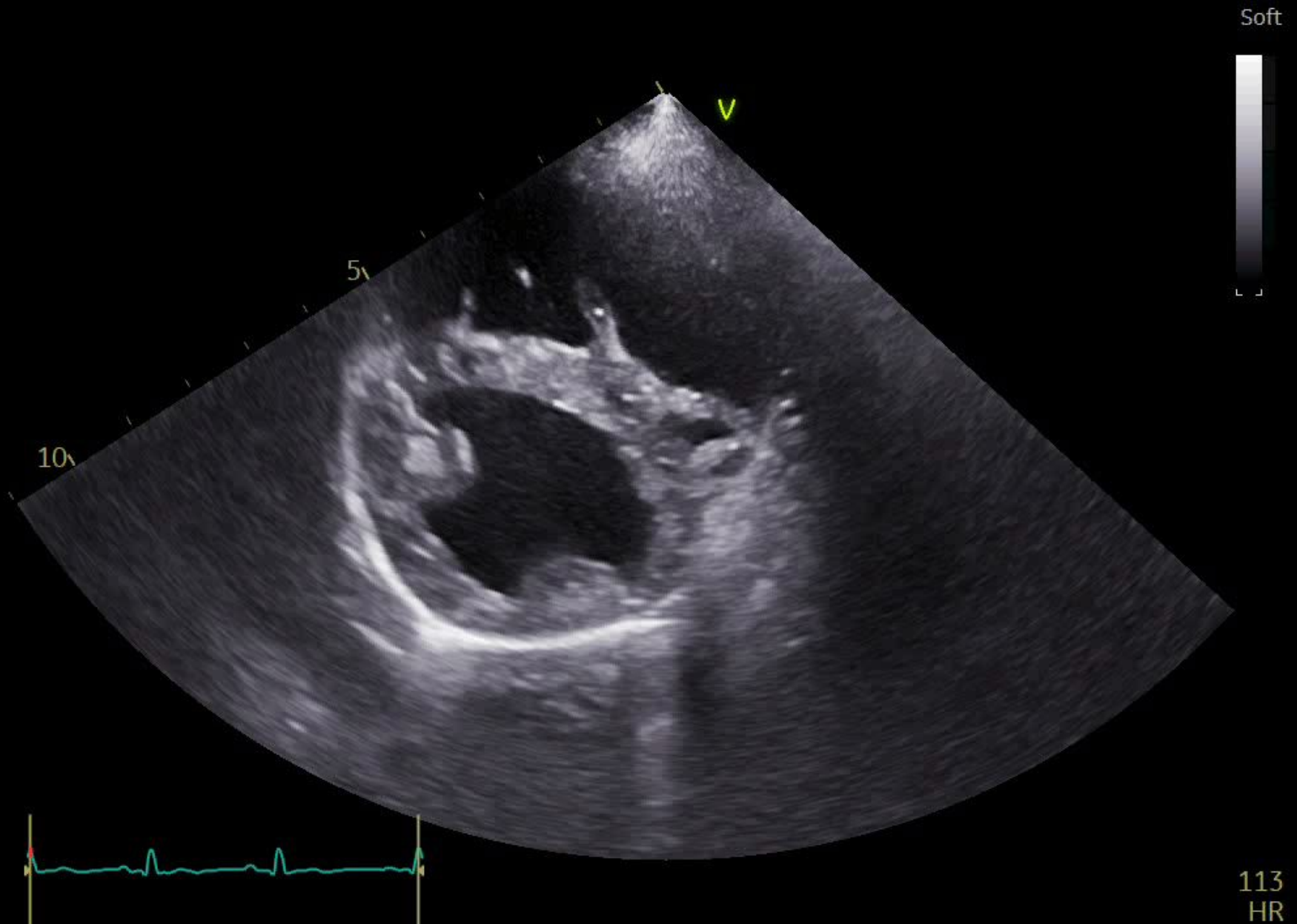


ARVC – Structurally Normal

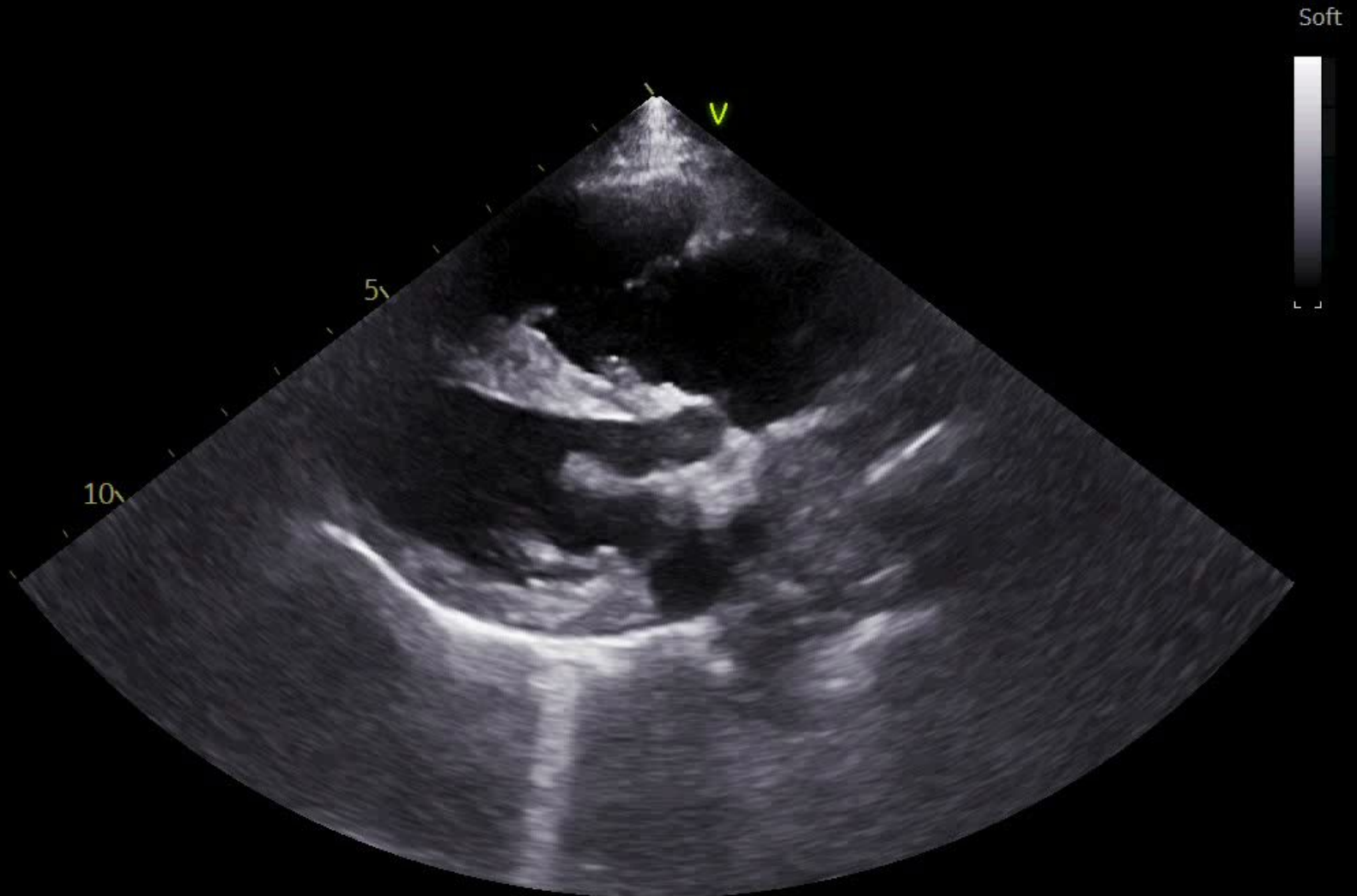


2:64

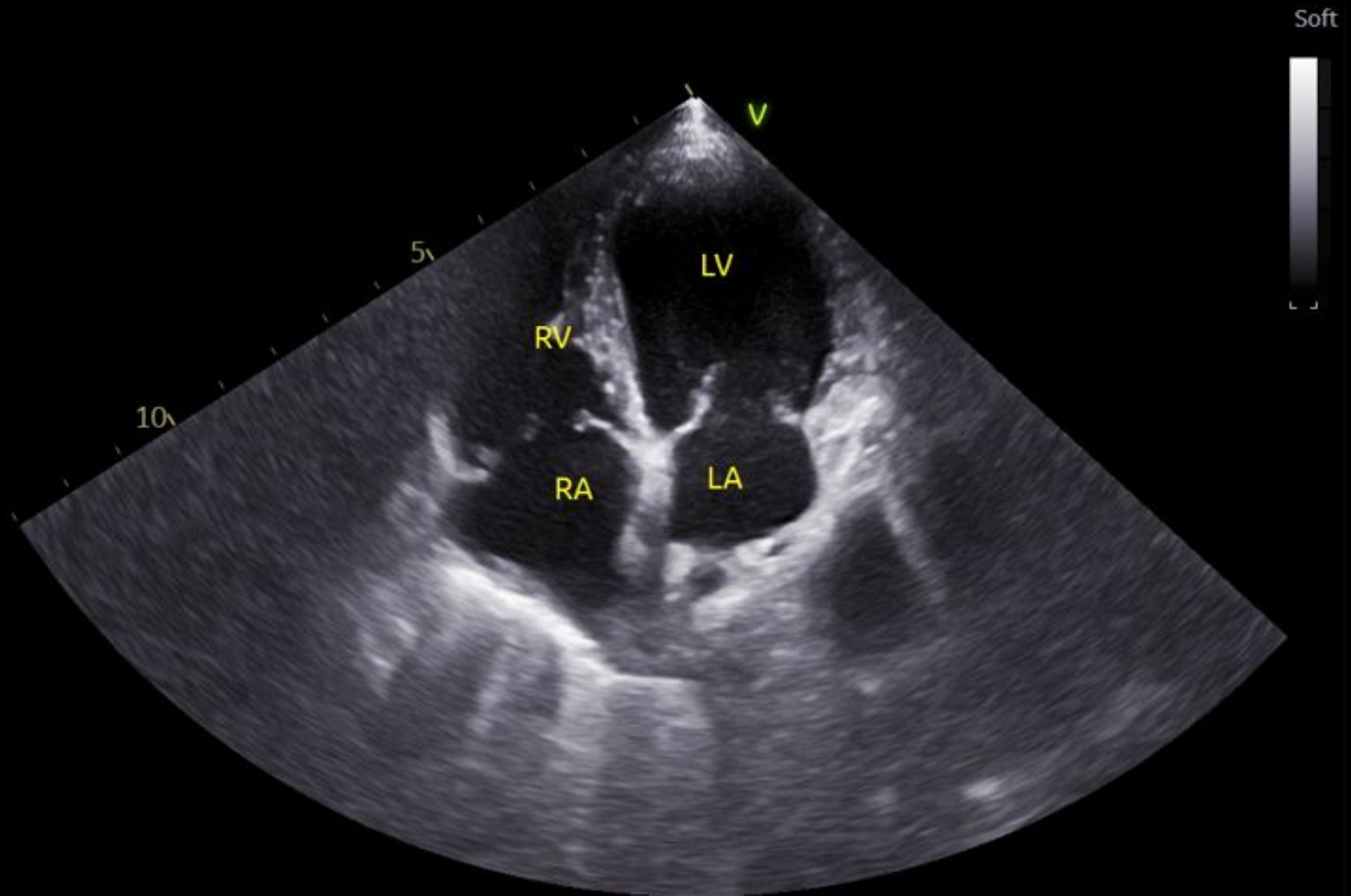
ARVC – RV Phenotype



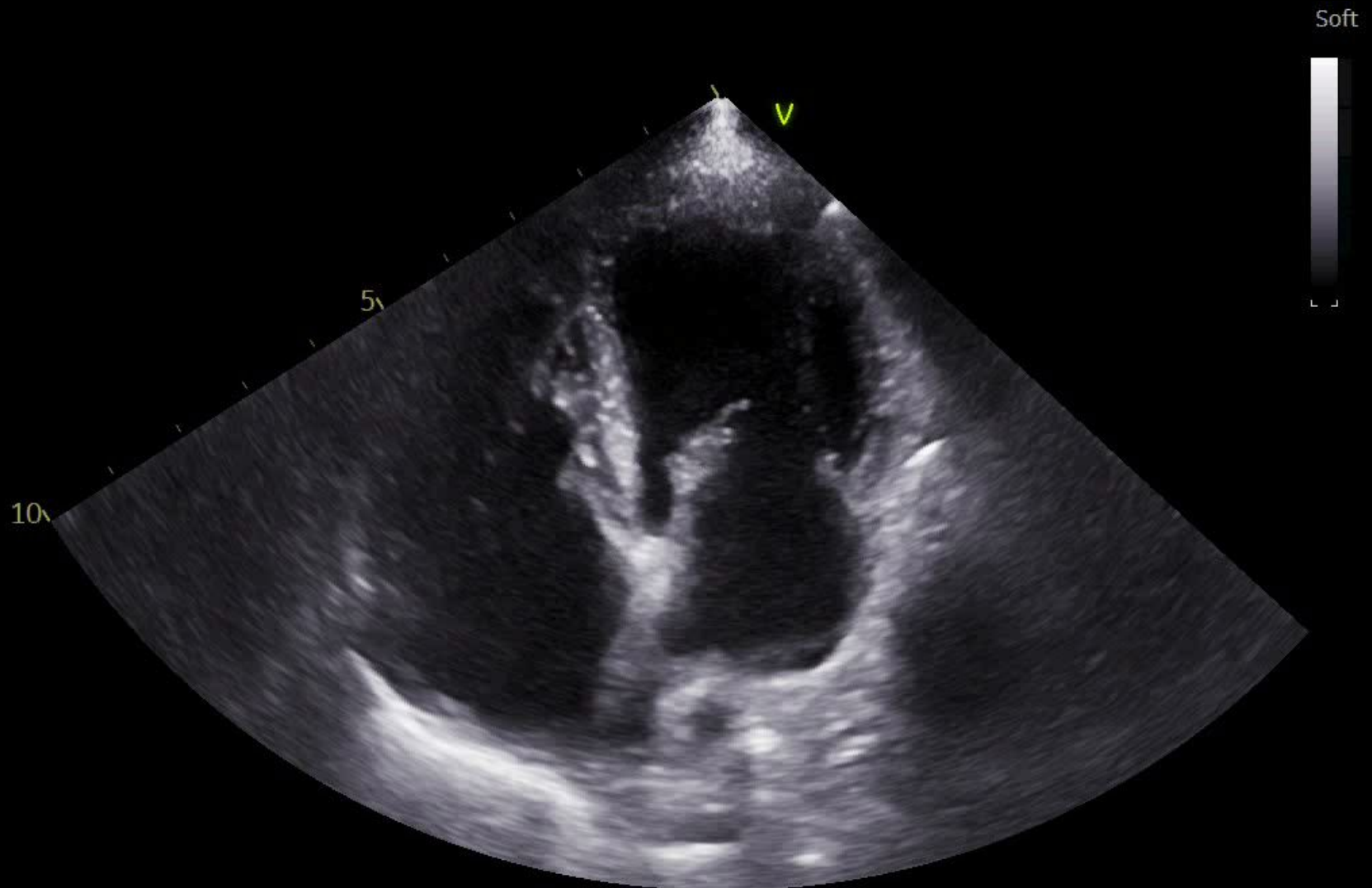
ARVC – RV Phenotype



ARVC – RV Phenotype



ARVC – RV Phenotype



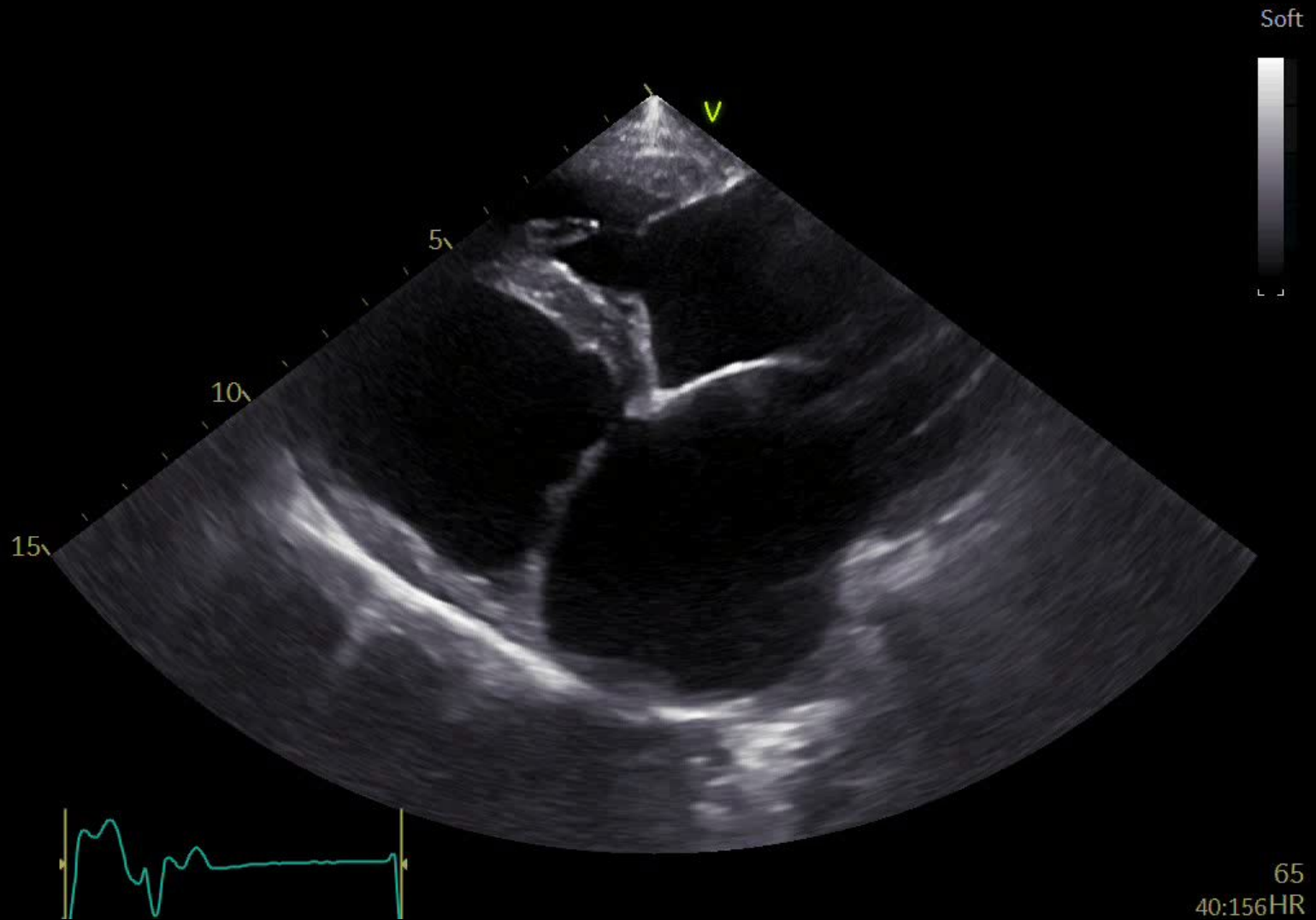
ARVC – RV Phenotype



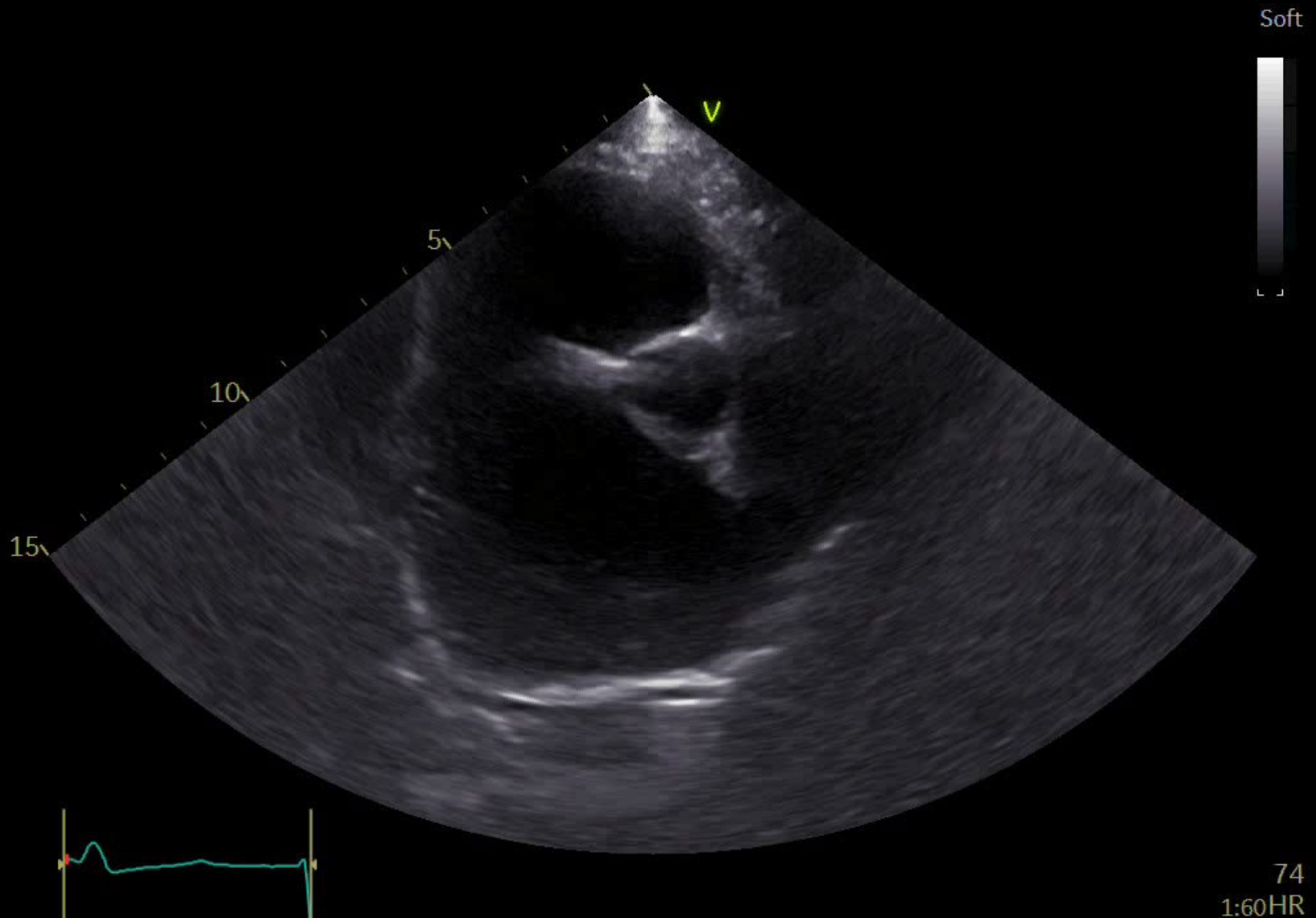
ARVC – RV Phenotype



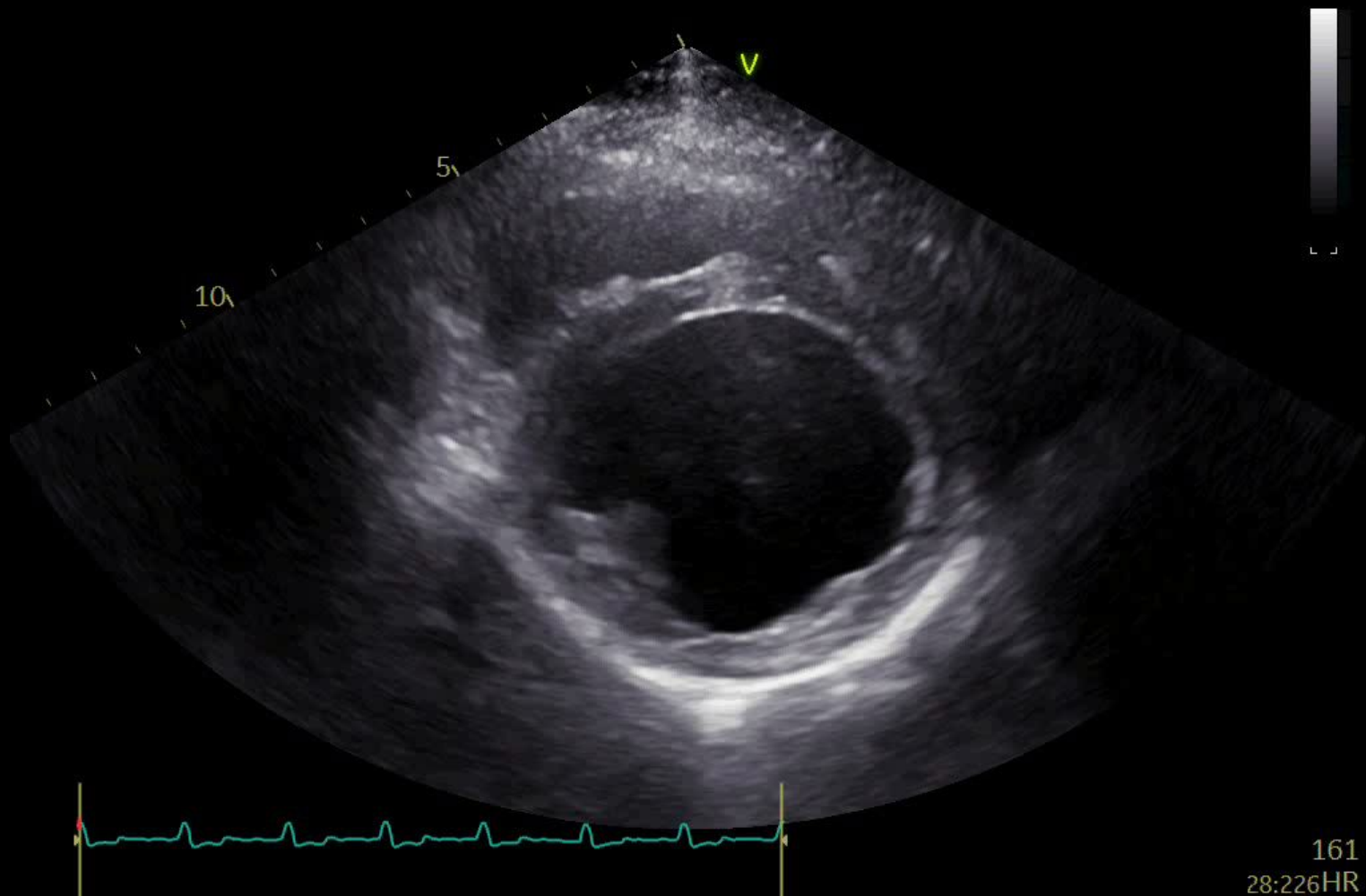
ARVC – Biventricular Phenotype



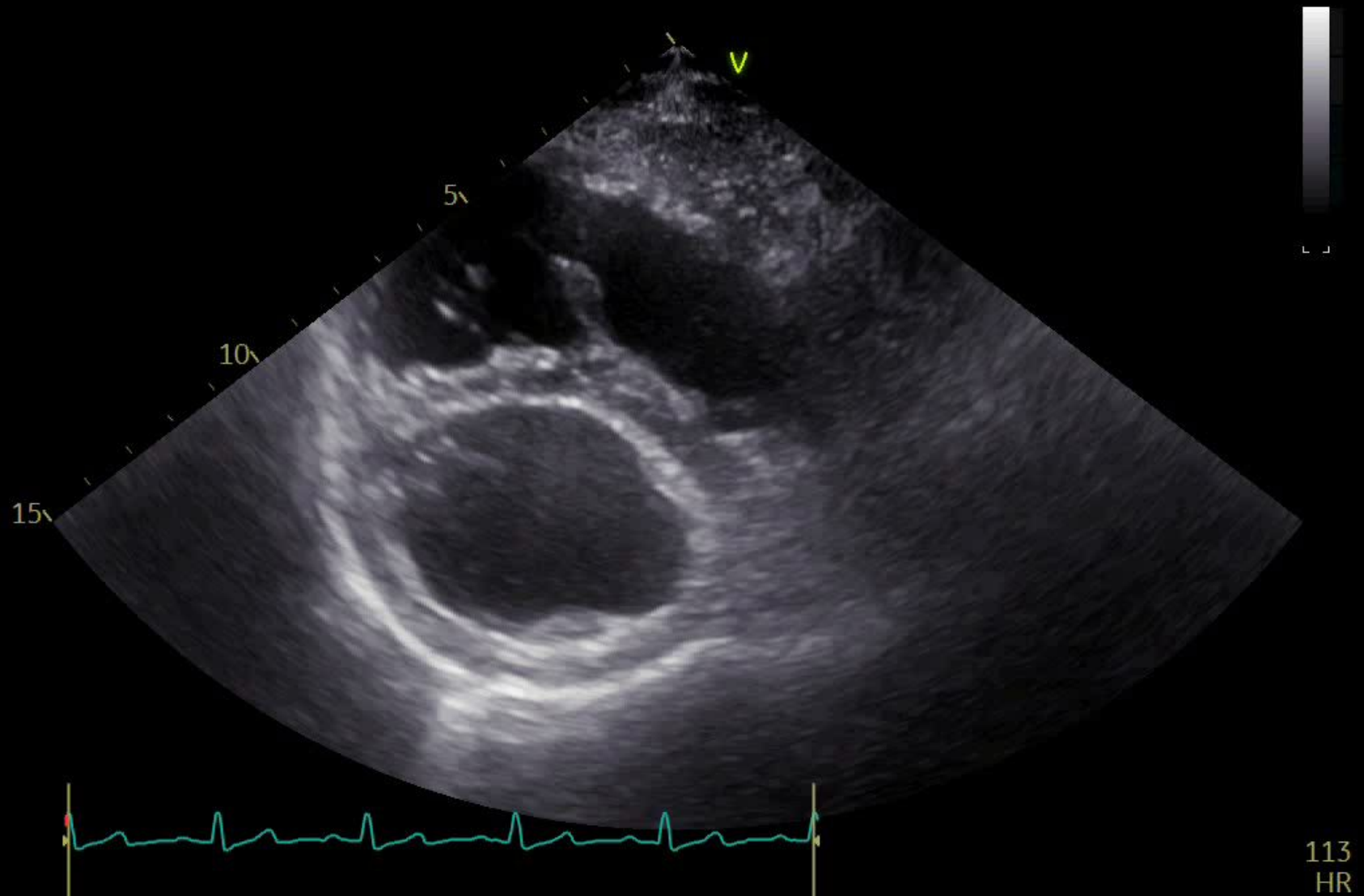
ARVC – Biventricular Phenotype



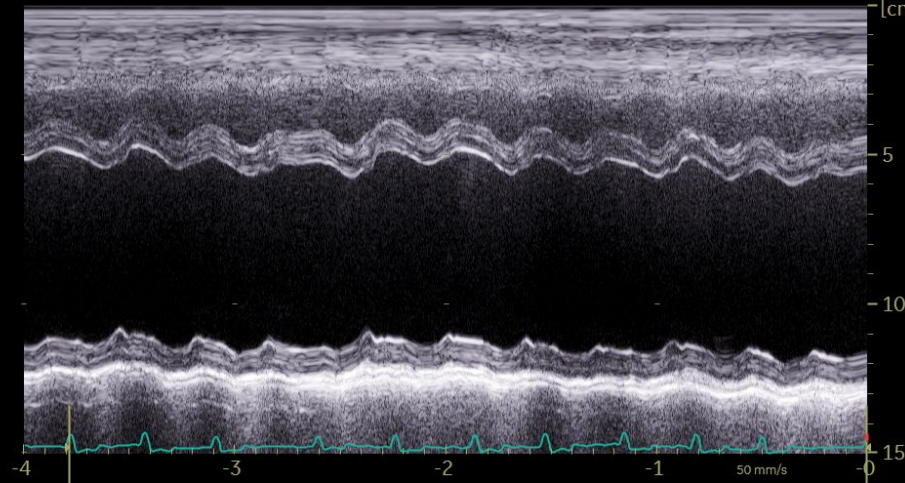
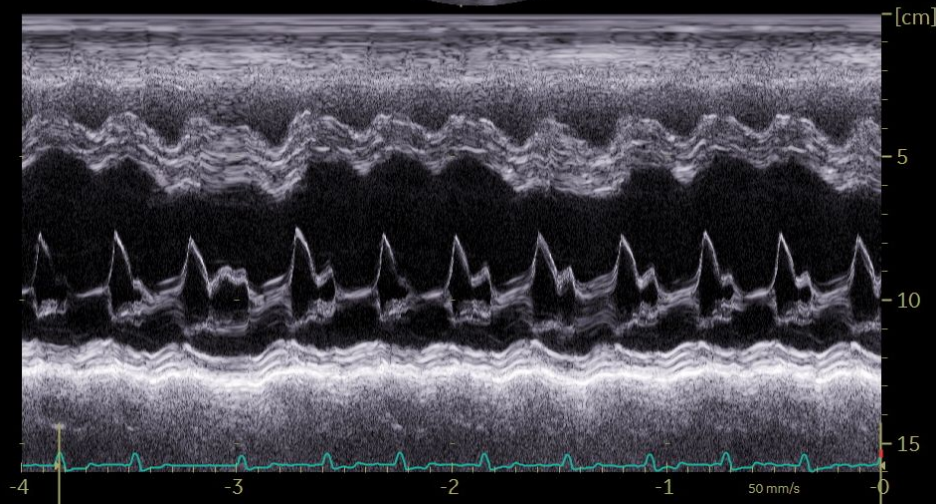
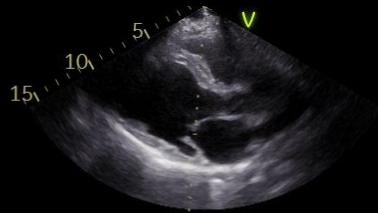
ARVC – Biventricular Phenotype



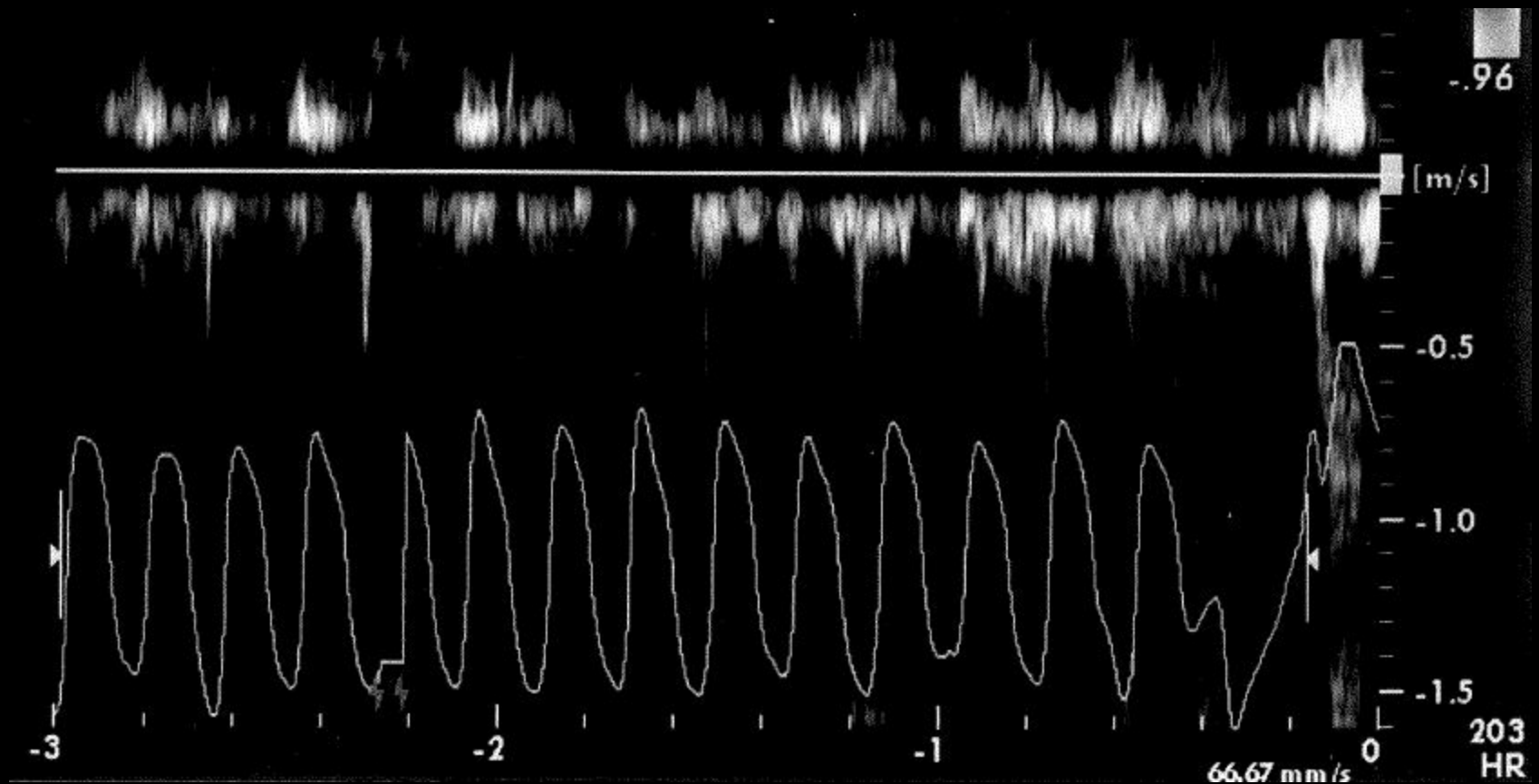
ARVC – Biventricular Phenotype



ARVC – Biventricular Phenotype



ARVC – Left Outflow at Vtach



ARVC Diagnosis

Cardiac Evaluation

- MRI (1.5T)
- Evaluate multiple cardiac parameters
 - Ejection fraction (EF%)
 - RV aneurysms & RV wall motion abnormalities
 - RV fibrofatty replacement
- Marginally helpful
 - ARVC Boxers have decreased RV EF%
 - Aneurysms are rare
 - Unable to identify fibrofatty replacement

ARVC Diagnosis

Genetic Testing

- Two tests available through NCSU
- EDTA blood sample or buccal swab
- \$48 for one test, \$70 for both
- Drawbacks
 - Second test is new
 - Not all positive Boxers develop symptoms
 - Some negative Boxers develop symptoms

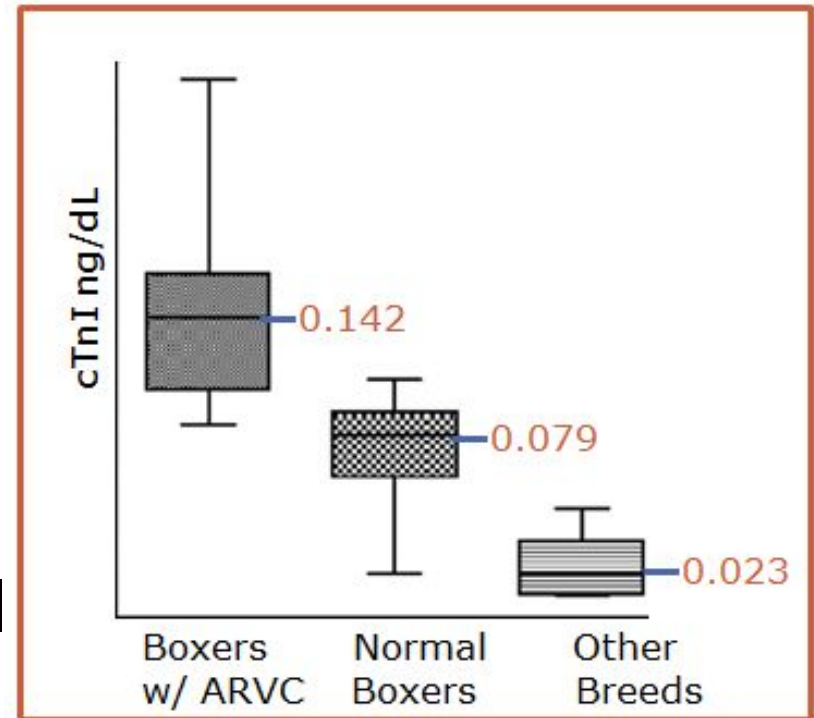
Boxer Arrhythmogenic Right Ventricular Cardiomyopathy
<http://www.cvm.ncsu.edu>



ARVC Diagnosis

Biomarkers

- cTnI
 - Single study
 - ARVC Boxers > Boxers > other breeds
 - Large inter-individual variability
 - Overlap between normal and abnormal Boxers



ARVC Diagnosis

Biomarkers

- NTproBNP
 - No publications
 - Increases with severe myocardial disease
- C-terminal BNP
 - Single study
 - No difference between ARVC Boxers, normal Boxers, and other breeds

ARVC Diagnosis

Biomarkers

- Antidesmosomal antibodies
 - Present in clinical ARVC Boxers
 - Absent in clinically normal Boxers
 - Study currently in progress
- Antiheart proteins
 - Noted in human ARVC patients
 - Component of inflammation is present
 - No veterinary studies to date

ARVC Diagnosis

Gross Pathology

- RV chamber dilation in $\sim 35\%$
- +/- RV thickening
- Rare myocardial aneurysms
- No change noted
 - Heart weight
 - RV wall thickness
 - LV wall thickness

Canine ARVC Gross Pathology



ARVC Diagnosis

Histopathology

- Fatty form
 - 2/3 of Boxers
 - Adipocytes replace normal RV myocardium
 - Diffuse
- Fibrofatty form
 - Multifocal or diffuse fatty infiltration
 - Extensive areas of fibrosis
 - Subepicardial and midmyocardial

ARVC Diagnosis

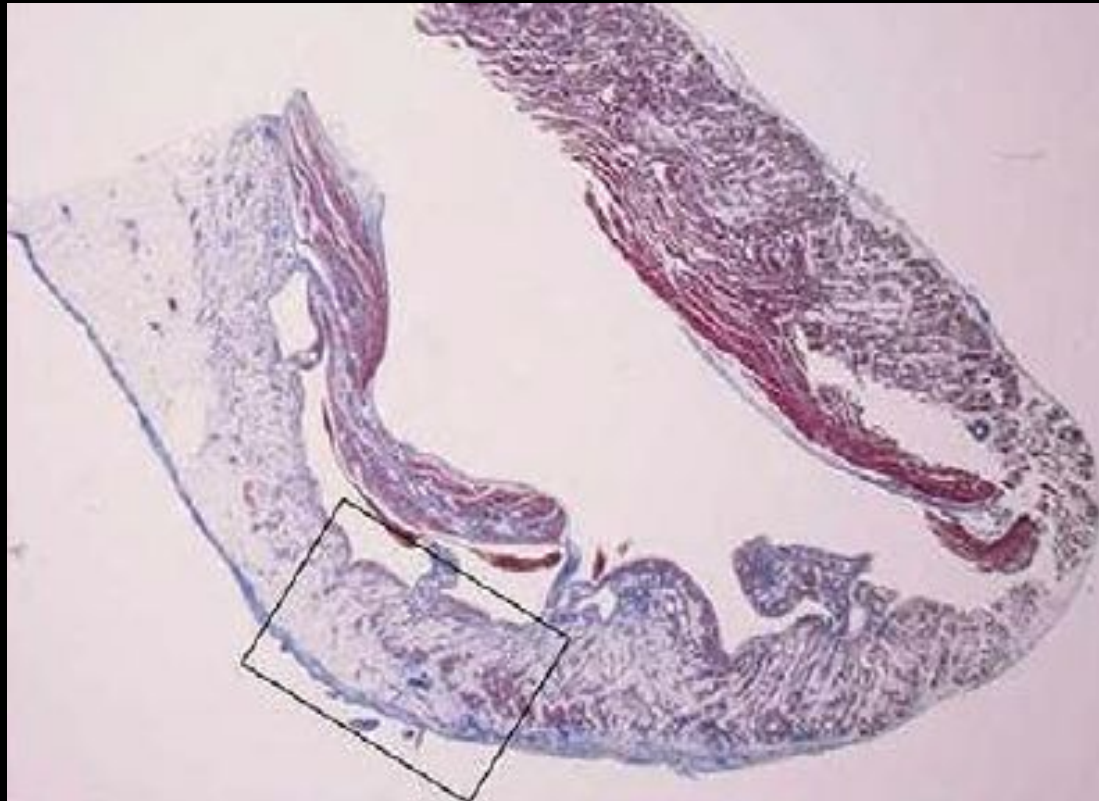
Histopathology

- Infiltration RV > LV > atrial myocardium > IVS*
- Myocyte atrophy
- Myocarditis
- Myocyte death

Replacement of normal cardiomyocytes sets the stage for ventricular arrhythmias

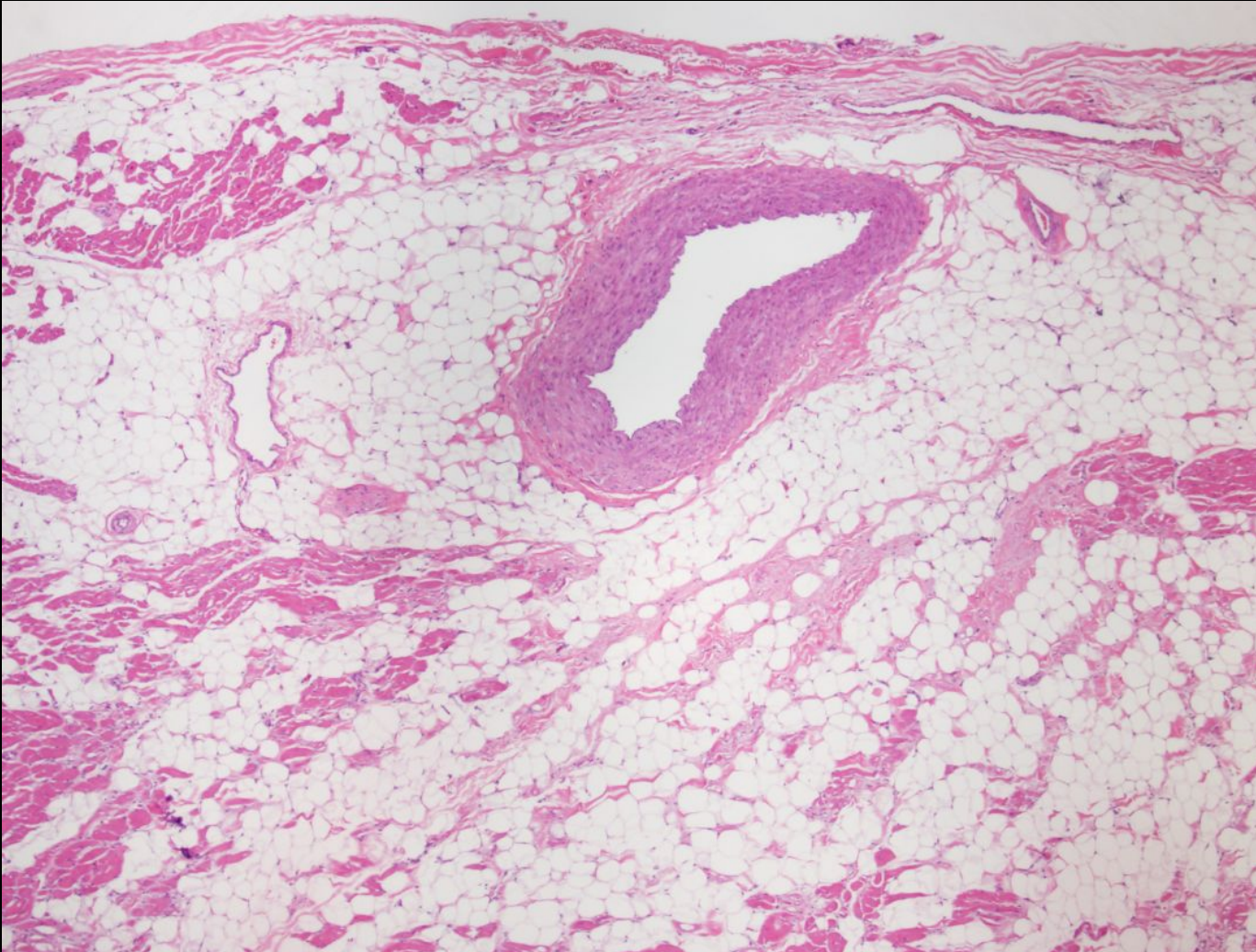
Canine ARVC

Histologic Section of RV



Canine ARVC

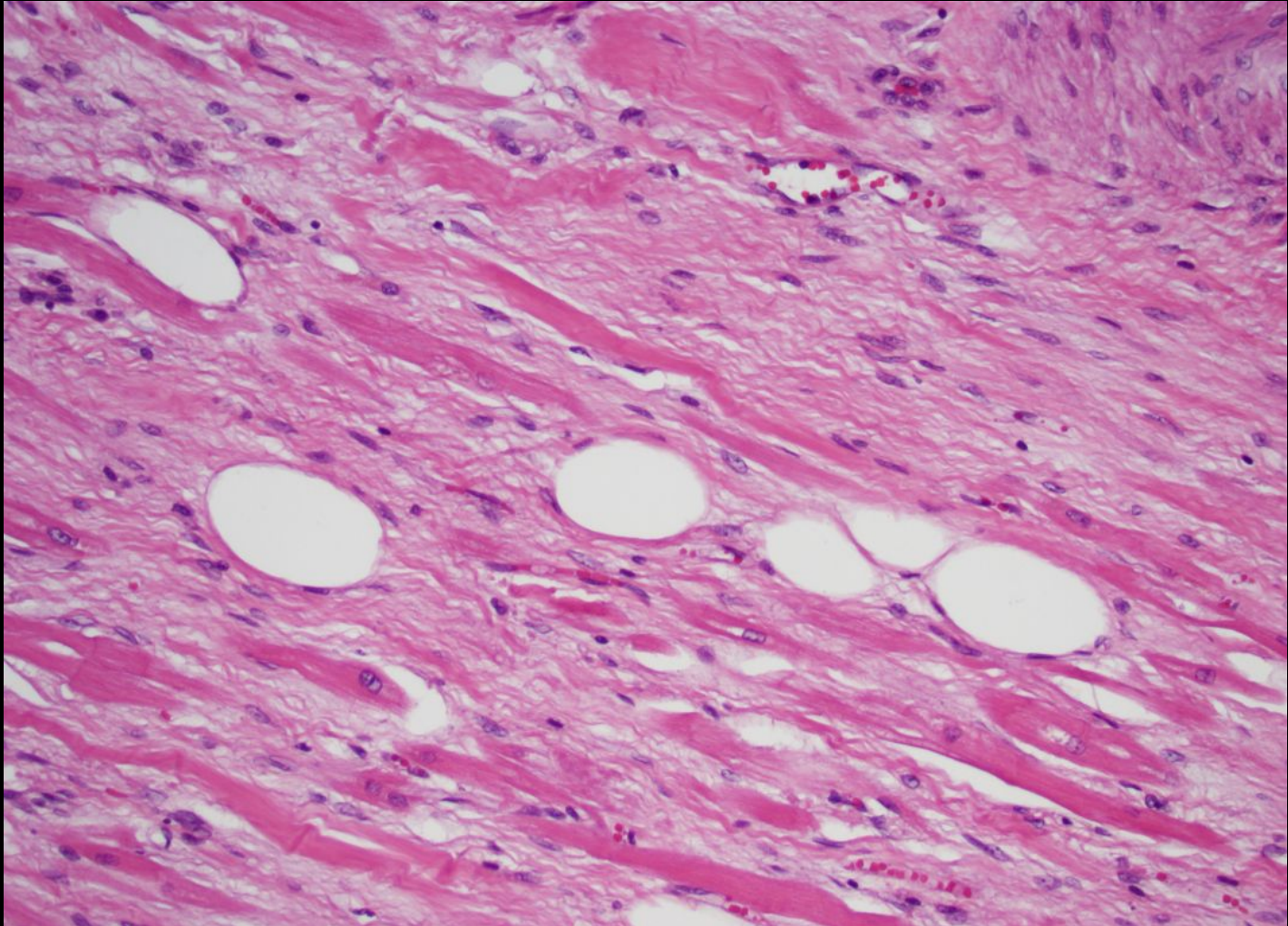
RV Adipocyte Infiltration



Courtesy of Dr. P. Mouser

Canine ARVC

LV Fibrous Changes



Courtesy of Dr. P. Mouser

ARVC Diagnosis

Ultrastructure Studies

- Remodeled intercalated discs
- Abnormal desmosomes
- Decreased desmosomes
- Abnormal gap junctions
- Abnormal fascia adherens
- Altered sarcomeres

ARVC Treatment

Antiarrhythmic Goals

- Palliative
- Decrease severity of arrhythmia
 - >80% reduction in VPCs
- Decrease clinical signs and syncope



ARVC Treatment

Antiarrhythmic Goals

- Antiarrhythmics do not decrease risk of sudden death
- Antiarrhythmics do not prolong survival



ARVC Treatment

When to Treat Arrhythmias

- Asymptomatic patients
 - Number of VPCs?
 - Complex VPCs
 - Bigeminy or trigeminy
 - Couplets or triplets
 - Sustained ventricular tachycardia
 - R-on-T
 - Multiformal
- Symptomatic patients
 - Weakness/pre-syncopal events
 - Syncope

ARVC Treatment

Antiarrhythmics

- Multiple options
 - **S**: Sotalol
 - **P**: Procainamide
 - **A**: Amiodarone
 - **M**: Mexiletine or lidocaine



ARVC Treatment

Antiarrhythmics

- Sotalol
 - Class 3 antiarrhythmic
 - Potassium channel blocker
 - Some beta-blocker effects
 - Dosing
 - Start 1.5 – 2.0 mg/kg PO BID
 - Uptitrate to 3.0 mg/kg PO BID
 - Contraindications
 - Negative inotrope
 - Caution with myocardial dysfunction or CHF

ARVC Treatment

Antiarrhythmics

- Mexiletine
 - Class 1b antiarrhythmic
 - Sodium channel blocker
 - Similar action to lidocaine
 - Dosing
 - Use alone or combine with sotalol if needed
 - Start 5 mg/kg PO TID
 - Uptitrate to 7 - 9 mg/kg PO BID
 - Contraindications
 - GI or neurologic disease

ARVC Treatment

Antiarrhythmics

- Amiodarone
 - Class 3 antiarrhythmic
 - “Broad spectrum”
 - Effects on Na⁺ channel, B-receptors, K⁺channels
 - Dosing
 - Loading required
 - 7 – 15 mg/kg PO BID x 1 week
 - 5 – 7 mg/kg PO BID x 2 – 3 weeks
 - 5 – 7 mg/kg PO SID long term

ARVC Treatment

Antiarrhythmics

- Amiodarone
 - Contraindications
 - Severe acute arrhythmia
 - Several long term side effects
 - Thyrotoxicity, hepatotoxicity, pulmonary toxicity, etc.
 - Requires baseline lab work and long term monitoring

ARVC Treatment

Antiarrhythmics

- Emergency interventions
 - Lidocaine: 2 mg/kg IV bolus (up to 4 doses)
50 – 80 ug/kg/min IV CRI
 - Procainamide: 10 mg/kg IV bolus (OK to repeat)
20 – 40 ug/kg/min IV CRI
 - Mg Sulfate: 0.2 – 0.3 mEq/kg/ IV slow bolus

ARVC Treatment

Antiarrhythmics

- Emergency interventions
 - Sotalol: 2 mg/kg PO BID*
 - Nexterone
 - Avoid amiodarone IV
 - Use nexterone cautiously
 - Starting bolus 0.5 -1 mg/kg IV
 - CRI 0.5 – 3 mg/kg/hour
 - Start oral amiodarone therapy during CRI taper

ARVC Treatment

Antiarrhythmics

- Not shown to decrease sudden death
- Side effects are common
 - May worsen arrhythmia
 - Weakness/hypotension
 - Negative inotropic effects
 - Systemic side effects
 - GI
 - Neurological
 - Endocrine
 - Hepatic

ARVC Treatment

Cardioversion

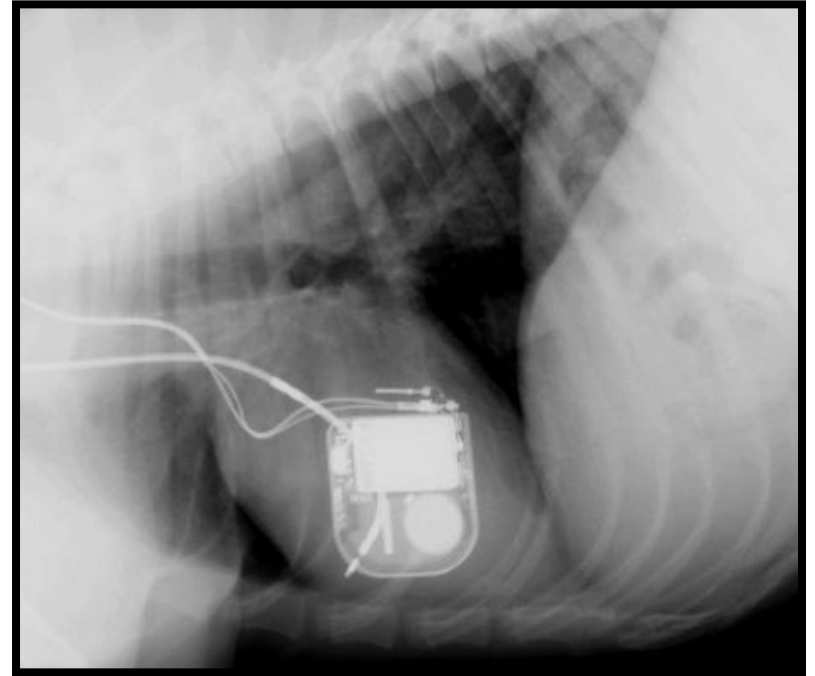
- ARVC Boxers who fail medical therapy may benefit from cardioversion
- Procedure
 - General anesthesia
 - Bi-phasic defibrillator with ECG synchronization
- Oral therapies may still be warranted



ARVC Treatment

Cardioverter Defibrillator

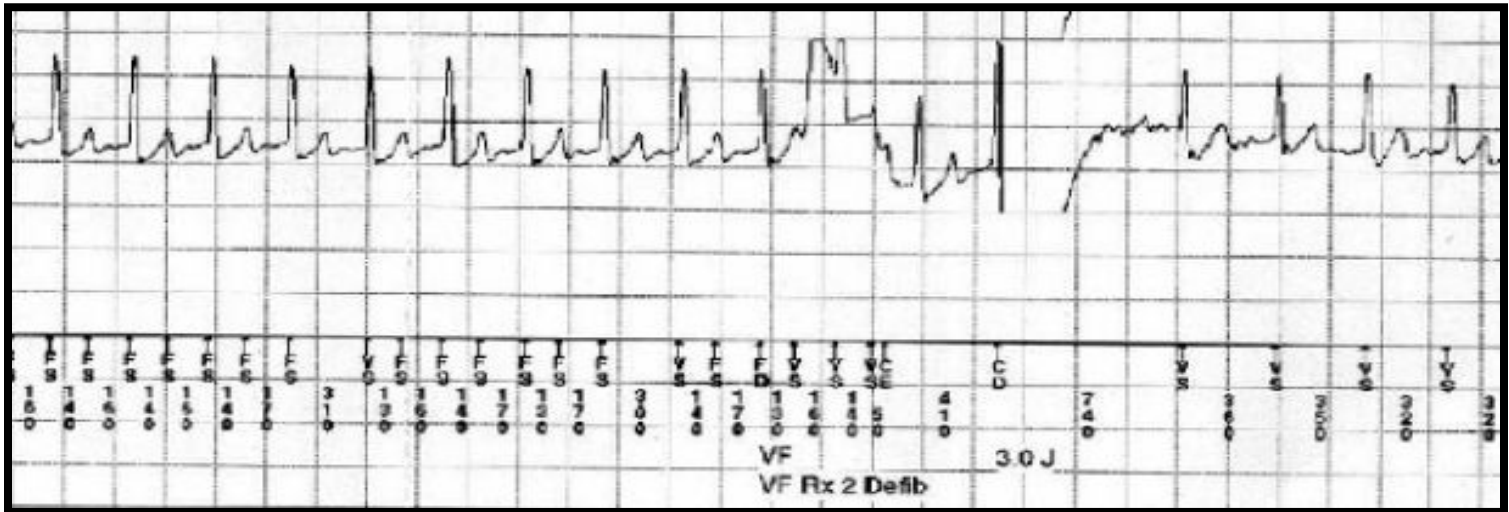
- Rare case reports
- Equipment
 - Pulse generator
 - High-voltage conducting lead
- Sense heart rhythm & sends shock when tachyarrhythmia is detected



Cardioverter Defibrillator

□ Drawbacks

- Cost
- General anesthesia
- Difficult to set for veterinary patients
- Inappropriate defibrillations



ARVC Treatment

Address CHF

- O2 supplementation
- Abdomino- or thoracocentesis
- Furosemide 2 mg/kg PO BID
- Pimobendan 0.2 – 0.3 mg/kg PO BID
- +/- enalapril
- +/- spironolactone

ARVC Treatment

Address Lifestyle

- Exercise
 - May precipitate arrhythmias
 - May potentiate myocyte damage
 - Concerns regarding exercise associated disease progression

ARVC Treatment

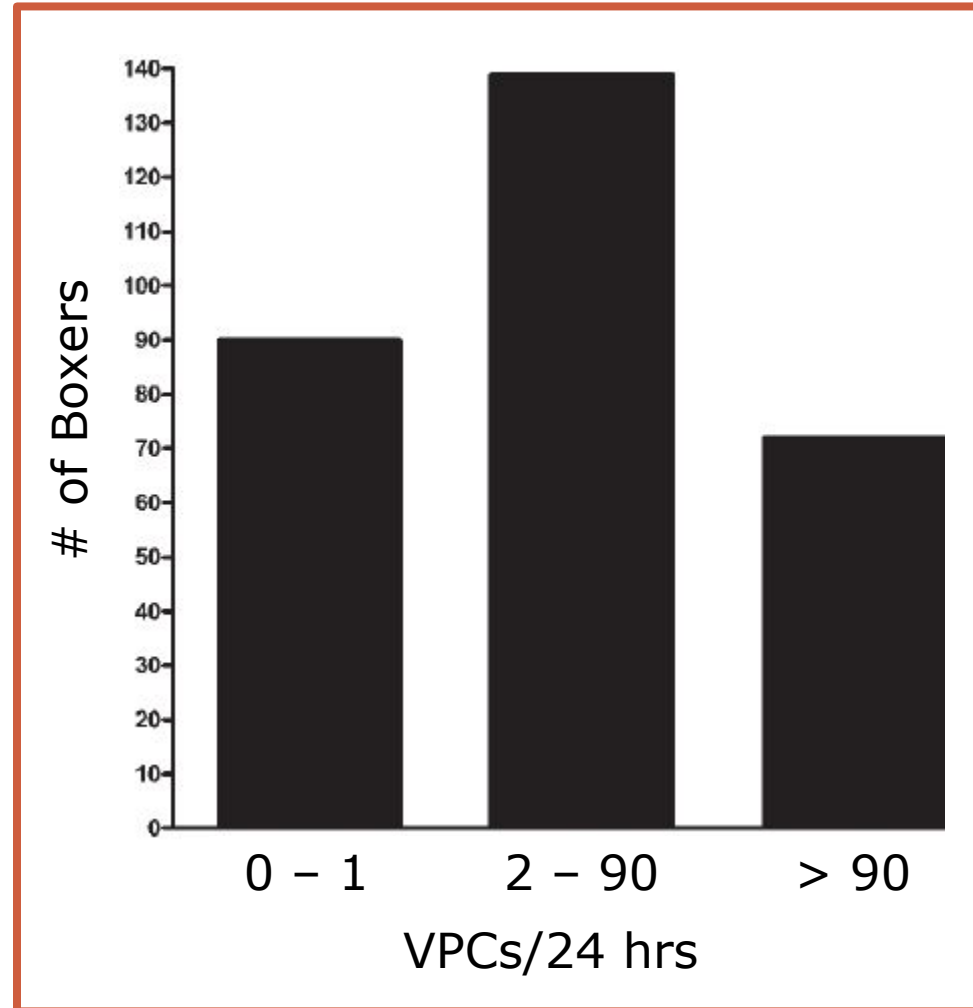
Supplements

- Fatty acids
 - Fish oils reduce # VPCs/24 hrs
 - EPA/DHA 100 mg/10 lb
- L-carnitine: 50 mg/kg PO BID to TID
 - May improve systolic function

ARVC

Prevalence

- Prevalence unknown
- Very few studies
 - 301 Asymptomatic Boxers Holtered
 - 23% of Boxers had > 90 VPCs/24 hrs



Neurocardiogenic Collapse

- Common in *young* Boxers
- Vasovagal events

The pathophysiology of neurally mediated bradycardia is incompletely understood.³⁻¹³ Episodes can be triggered by activities or situations that result in either a sympathetic surge or a parasympathetic surge. The latter triggers result in situational syncope.^{9,14-16} Surges of sympathetic activity can trigger intracardiac receptors that respond to loading or contractile conditions by evoking reflex vagal afferent traffic to the brainstem. The final common pathway associated with either sympathetic- or parasympathetic-initiated triggers is afferent vagal stimulation of the medullary vasomotor (vasodepressor) center. This center then responds with sympathetic withdrawal and mild or severely accentuated vagal efferent traffic.^{3,5,9,10,14-16}

Neurocardiogenic Collapse

- Brief loss of consciousness
 - Decreased cerebral blood flow
- Spontaneous recovery
- Normal ECG, Holter, echo
 - Some Boxers may have concurrent ARVC

Neurocardiogenic Collapse

- Treatment varies
 - May not be needed
 - Behavioral modifications
 - Beta-blockers and sotalol often worsen collapse events
 - Pacemaker alone often ineffective
 - Consider anti-cholinergic therapies
- Prognosis depends on quality of life

ARVC Diagnosis

Screening Asymptomatic Boxers

- Early age: NCSU genetic testing
- 3 to 5 years old: annual echo & Holter



ARVC

Breeding Recommendations

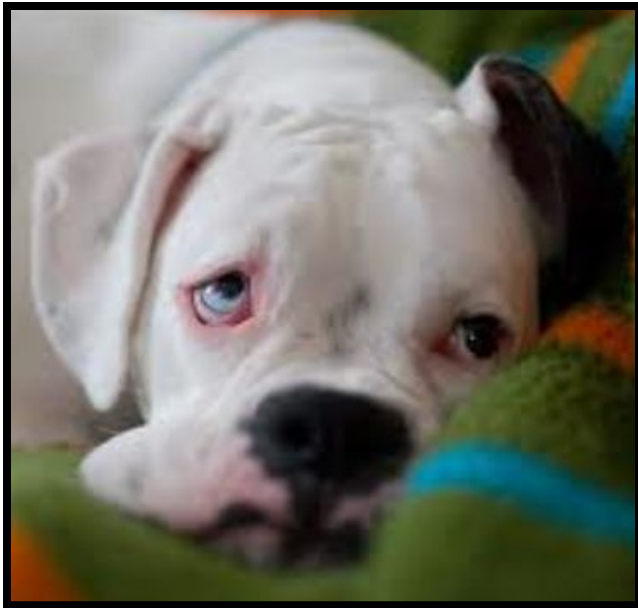
- Good breeding candidates
 - < 50 VPCs/24 hr
 - Two normal Holter monitors
 - ARVC mutation negative
 - ARVC mutation heterozygous
 - No evidence of disease
 - Breed to a mutation negative dog



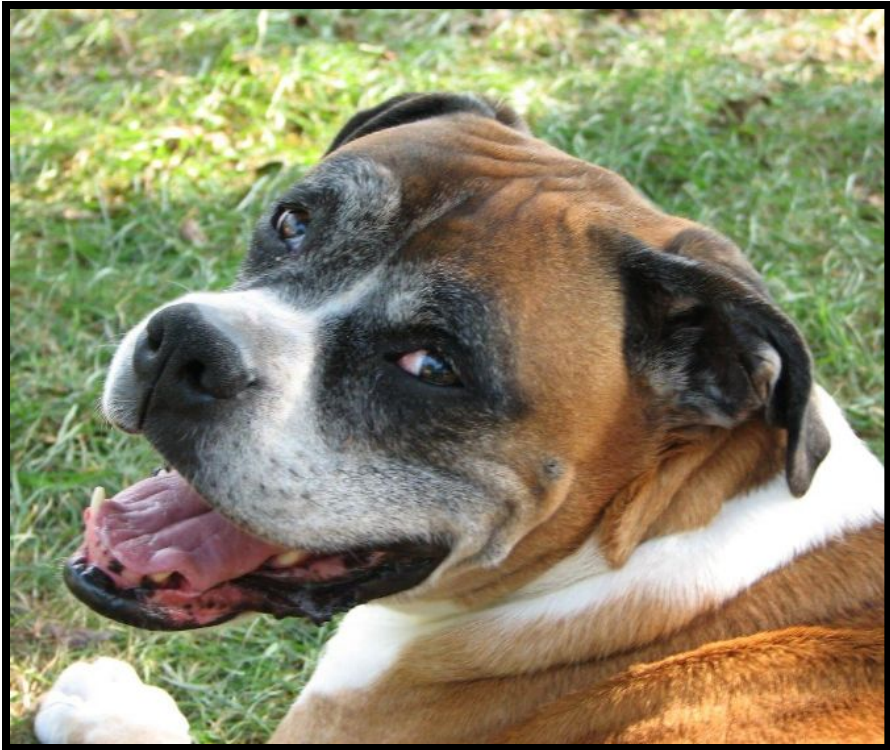
ARVC

Breeding Recommendations

- Cautious breeding/do not breed
 - 51 – 100 VPCs/24 hours
 - Re-evaluate in 6 months
- Remove from breeding programs
 - 100 – 300 VPCs/24 hours
 - ARVC heterozygous with evidence of ARVC
 - ARVC homozygous



ARVC Prognosis

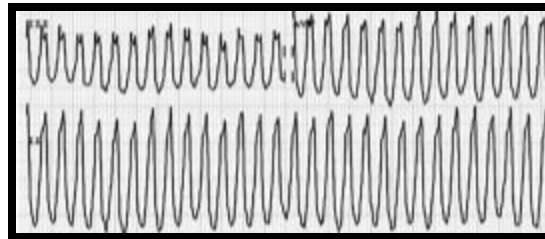


- Good to guarded to poor
- Unpredictable
 - Not all affected Boxers develop clinical signs
 - The complexity of the arrhythmia does not always relate to the prognosis

ARVC Prognosis

Negative Prognostics

- Ventricular tachycardia



ARVC Prognosis

Negative Prognostics

- Syncope
 - Collapsing Boxers survived 10 weeks
 - Non-collapsing Boxers survived 24 weeks
- Myocardial disease
 - Boxers with myocardial disease survived 17 weeks
 - Boxers with arrhythmias only survived 124 weeks
- CHF
 - Survival 3 – 9 months

ARVC Treatment

The Future

- Antiarrhythmics
- Veterinary specific defibrillators
- Gene therapy
- Immunomodulators
 - Wnt signaling



ARVC

Summary

- ARVC is an arrhythmogenic condition
 - Myocardial disease and CHF can occur
- Diagnosis can be difficult
 - Rule-out other illness
 - Non-invasive: ECG, Holter, genetic testing, echo
- Patient guided- therapy
 - Antiarrhythmics
 - Sudden death/decompensation may still occur
 - Address CHF

Thank You!



Any Questions?



Please Note:

CE credit certificates & presentation slides will be emailed to you. If you do not receive an email with this information within a week, contact Nichole - *nicholemanfredi@capecodvetspecialists.com*

