Cardiac Biomarkers
Uses and Limitations

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Outline

- Introduction
- Testing Strategies
- Clinical Use
  - and limitations
- Biologic Variability
- Summary

INTRODUCTION

What is a Biomarker?

- Measurable substance that indirectly informs about organ health
  - Specific to the organ / tissue
  - Released in proportion to the degree of disease
    - greater damage = greater amounts measured

Organ-specific biomarkers

- Liver biomarker
  - Alanine transferase (ALT)
- Cardiac biomarker
  - B-type natriuretic peptide (BNP)
  - N-terminal pro-B-type natriuretic peptide (NTproBNP)
  - Cardiac troponin I (cTnI)
  - Atrial natriuretic peptide (ANP), and N-terminal pro-Atrial natriuretic peptide (NTproANP)

Liver disease

- How can we know how healthy a patient's liver is?
  - Abdominal palpation
  - Abdominal radiographs
  - Abdominal ultrasonography
  - Blood values such as ALT
  - Liver biopsy
    - Fine-needle aspirate
    - Laparoscopic biopsy
    - Laparotomy to obtain biopsy

ALT

- Present primarily in the hepatocyte cytosol
- ALT released with hepatocyte damage
  - circulates in the systemic blood stream
- ↑↑↑ ALT = ↑↑↑ Liver Damage

Cardiac disease

- How can we assess cardiac health/disease?
  - Cardiac auscultation
  - Thoracic radiographs
  - Echocardiography (cardiac ultrasound)
  - Blood markers such as cTnI or BNP
  - Cardiac Magnetic Resonance Imaging
  - Endomyocardial biopsy

Cardiac biomarkers

- N-terminal pro B-type Natriuretic Peptide (NTproBNP)
- cardiac troponin I (cTnI)
- B-type Natriuretic Peptide (BNP)
- N-terminal pro Atrial Natriuretic Peptide (NTproANP)
- Atrial Natriuretic Peptide (ANP)

Cardiac biomarkers

- *N-terminal pro B-type Natriuretic Peptide (NTproBNP)*
- *cardiac troponin I (cTnI)*
- B-type Natriuretic Peptide (BNP)
- N-terminal pro Atrial Natriuretic Peptide (NTproANP)
- Atrial Natriuretic Peptide (ANP)

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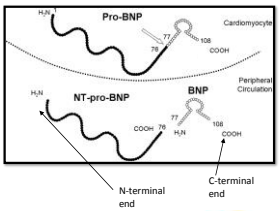
Natriuretic peptides (NP)

- pro-BNP and pro-ANP stored as granules
  - mostly atrial tissue
  - lesser degree in ventricular tissue
- Many pro-ANP peptides stored as granules
  - pro-BNP peptides production upregulated in ventricular m.
- C-terminal end is the <u>active hormone</u>



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Natriuretic peptides

- Volume Overload = Atrial/Ventricular Stretch
- NPs released to excrete Sodium/Water
- Chronic volume overload = ↑ BNP/ANP production in myocardium

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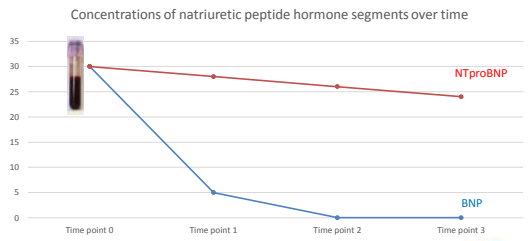
Natriuretic peptides



Half-life: BNP = 90 seconds; NTproBNP = 20 minutes

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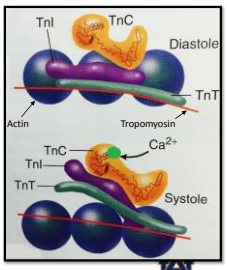
Cardiac troponin I (cTnI)

- Troponin subunits are associated with tropomyosin
  - Both cardiac and skeletal muscle
    - troponin subunits C and T
  - the I subunit = only cardiac



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Cardiac troponin I

- cTnI mostly bound to the contractile unit
  - Only ~3% cTnI found free in cytosol
- Cardiomyocyte damage = cTnI leaks into the interstitium
  - taken up by cardiac lymphatics
- cTnI then present in systemic circulation
  - lymphatics overwhelmed
- Likely excreted passively by kidneys

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Cardiac troponin I

- Healthy hearts do not have high concentrations in circulation
- Level of circulating cTnI in circulation corresponds to the degree of damage
  - cardiomyocyte specific

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TESTING STRATEGIES

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Screening

- Hypertrophic Cardiomyopathy in cats
- Dilated Cardiomyopathy in dogs
- Myxomatous Mitral Valve Disease in dogs
  - NOT NEEDED
  - ***AUSCULTATION PREFERRED***

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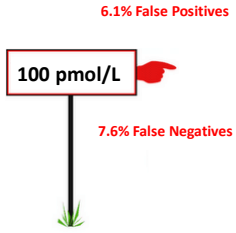
Screening - HCM

- NTproBNP in 201 cats (99 = normal)[1]
  - NTproBNP > 100 pmol/L detected HCM (92.4% sens. and 93.9% spec.)
  - Cats with NTproBNP <100 were unlikely to have HCM
- 92.4% of cats with the disease will test positive (> 100 pmol/L)
- 93.9% of cats without the disease will test negative (<100 pmol/L)



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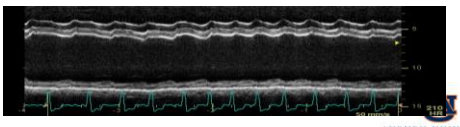
1. Vet Clin Pathol 2011;40:237-244

Screening - DCM

- NTproBNP in 155 Doberman Pinschers[1]
  - NTproBNP > 500 pmol/L = likely systolic dysfunction
  - NTproBNP < 500 pmol/L = likely normal LV function
  - Screening for Arrhythmia = ECG +/- Holter[1,2]



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1. J Vet Intern Med 2012;26:1330
2. J Vet Cardiol 2017;19:405

Testing strategy

- Not every animal needs cardiac biomarkers measured
- Minimizes false positive
- Clinical decision-making process
- False positives = worry and extra test

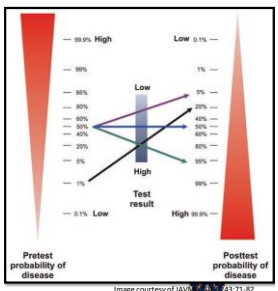

Image courtesy of JAVMA, Vol. 243, No. 1, July 1, 2013, pp. 71-82

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Testing strategy

- Consider case **A**
  - Very low likelihood of disease (1%) pretest
  - High positive only raises likelihood of disease a small amount
    - 1% -> 20%
  - 80% chance of false positive
    - case decision making
- A 1 yo DSH cat, clinically healthy without any history or physical exam signs of cardiovascular disease = low probability of disease
  - Not appropriate to measure NTproBNP as part of the pre-anesthetic bloodwork for this cat's spay

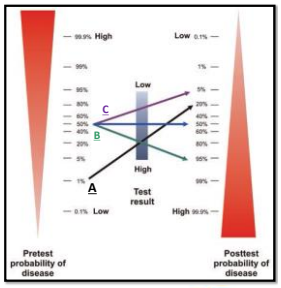

Image courtesy of JAVMA 2013;243:77

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Testing strategy

- Consider case **B**
  - Start with a 50/50 chance
    - Now test result = very helpful
  - High test result = 95% chance of disease
    - Case decision making
- Measuring NTproBNP in a cat with a murmur
  - A high NTproBNP value = Echocardiography good

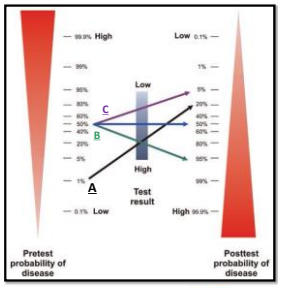

Image courtesy of JAVMA 2013;243:77

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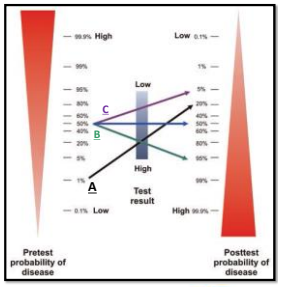
Testing strategy

- Consider case **C**
  - 50/50 chance of disease
  - Low test result = 5% chance of disease
- Adult cat with respiratory distress
  - Ddx: Congestive heart failure vs 1° resp. disease
  - Normal NTproBNP rules out CHF



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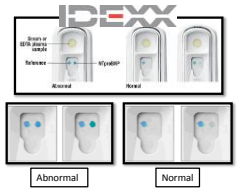
CLINICAL USE

NTproBNP in cats

- **SNAP® Feline Cardiopet® proBNP Test**
  - Results within 10 minutes
  - Requires just a few drops of blood
- Normal = < ~100 pmol/L[1]
- Abnormal = > ~270 pmol/L[1]
- *Normal results help rule out CHF*



1. J Vet Cardiol 2014;16:245

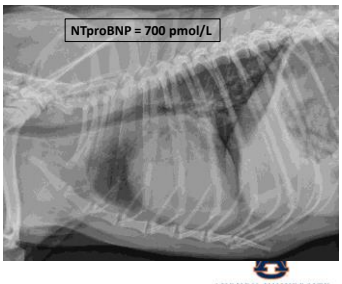
PREDICTing heart failure

- MMVD – ACVIM stage B2 dogs[1]
  - Thx rads, Echo, NTproBNP, BP
  - NTproBNP > 1500 pmol/L
    - ↑Risk of CHF within 6 months

1. J Vet Cardiol 2012;14:193

Clinical Case - MMVD

- 7 year old MN CKCS
- Tests:
  - Thx rads
  - Echo
  - BP
  - CBC/Panel/UA
- Follow-up:
  - Thx rads in 8 months
  - BP in 8 months



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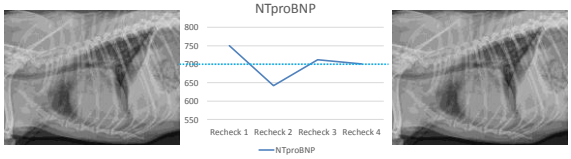
Clinical Case - MMVD

- Scenario #1



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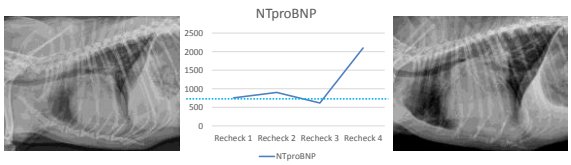
Clinical Case - MMVD

- Scenario #2



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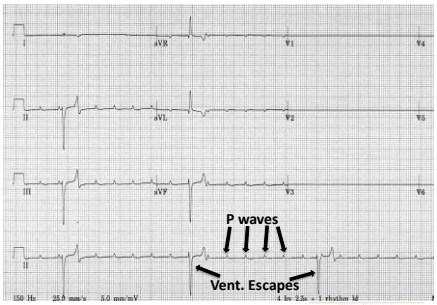
Clinical Case – 3° AVB

- 9 yo FS Labrador
- 3° AVB
- Echo normal



Clinical Case - 3° AVB

- Start with atropine response test
  - 0.04 mg/kg IV
  - Perform ECG for 5-10 minutes

No response → cardiac troponin I

Sinus tach ~180 bpm → Evaluate for systemic dz (ocular, resp, CNS, GI)

Clinical Case - 3° AVB

cardiac troponin I

0.008 ng/mL → No additional tests → Likely AV nodal fibrosis

5.3 ng/mL → Infectious tests* → Likely myocarditis

* Tick-bourne bacterial dz
Trypanosoma cruzi
Fungal myocarditis

Cardiac Troponin I

- **Remember!!**
  - each lab generates own reference range
  - different labs may not be comparable
  - Standard- vs. High-sensitivity assays
    - **Standard**: All Healthy dogs and 68% MMVD had undetectable values (below limit of detection)[1]
    - **High-sens**: 31% healthy and NO MMVD dogs had undetectable values[1]

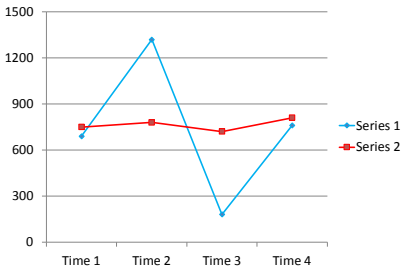
1. J Vet Cardiol 2017;19:124

BIOLOGIC VARIABILITY

Biologic Variability

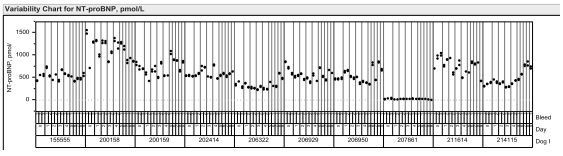
- The natural change that occurs in an analyte value, independent of disease severity progression
  - E.g. changes in biomarker values in a healthy dog
  - E.g. changes that occur over some time period in a dog with stable (non-progressive) disease
- Within-subject, between-subject, analytical variation
  - Critical Change Value %

Scientific Line Graph



NTproBNP in Normal Dogs

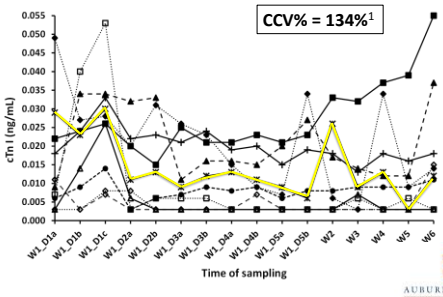
CCV% = 71%[1]



1. J Vet Cardiol 2017;19:124

cTnI in Normal Dogs

CCV% = 134%[1]



1. Vet Clin Pathol 2017;46:299

BV in MMVD dogs

1

Disease state	Dogs (N)	Samples (N)	CCV-95% (95% CI)
Healthy	10	160	70.8% (62.3–82.1%)
MMVD B1	10	40	73.4% (64.6–85.2%)
MMVD B2	10	40	51.4% (45.2–59.6%)
MMVD C-stable	8	32	53.3% (46.9–61.9%)
All MMVD	28	112	58.2% (51.2–67.5%)

NTproBNP
CCV = 58%

2

	Dogs (*n*)	Samples (*n*)	CV_I cTnI	CCV*
Healthy	10	111	48%	134%
MMVD B1	10	40	42%	118%
MMVD B2	10	40	33%	91%
MMVD C—stable	8	32	44%	121%
All MMVD	28	112	40%	110%

cTnI
CCV = 110%

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1. J Vet Cardiol 2017;19:124
2. Vet Clin Pathol 2017;46:299

How to Apply BV

- Revisit PREDICT study (MMVD)[1]
  - NTproBNP > 1500 pmol/L associated with development of CHF at or prior to next visit
- Normal BV for MMVD is <58% for NTproBNP[2]

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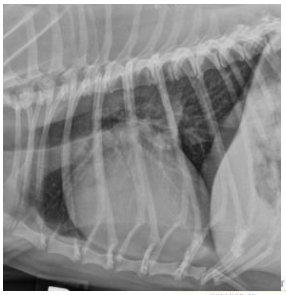
1. J Vet Cardiol 2012;14:193
2. J Vet Cardiol 2017;19:124

Patient 1
NTproBNP change of 40%

CCV = 58%

Previous Visit:
NTproBNP = 1000 pmol/L



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Patient 1

CCV = 58%

NTproBNP change of 40%

Previous Visit:
NTproBNP = 1000 pmol/L

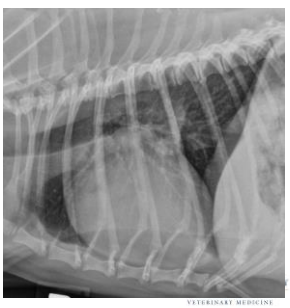
Today's Visit:
NTproBNP = 1400 pmol/L

Patient 2

CCV = 58%

NTproBNP change of 60%

Previous Visit:
NTproBNP = 800 pmol/L



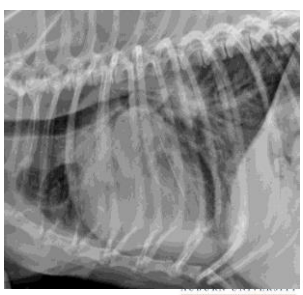
Patient 2

CCV = 58%

NTproBNP change of 60%

Previous Visit:
NTproBNP = 800 pmol/L

Today's Visit:
NTproBNP = 1280 pmol/L



Summary

- Cardiac biomarkers aren't for every patient
  - Screen for HCM in cats and DCM in Dobies
  - Test to minimize false positives
- Higher values = greater disease
  - Helps determine follow-up tests or referral
- Monitor trends
  - Helps predict prognosis
- Biologic variability important to consider

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Questions?