HCM-arrangement – Maine Coonklubben og Norsk Skovkattering Marts 2007

Jørgen Koch
Lektor, dyrlæge ph.d.
IMHS, LIFE, KU

Velkommen til LIFE

- Dagens program
  - 1800-1900 (JK&MN)
    - Foredrag om HCM ved Jørgen Koch og Mia Nyberg
      - Sygdom
      - Diagnostik
      - Genetik
  - 1900-2100 (JK,SG,JW&MN)
    - Demo – ekko og rundvisning på Hospital for Mindre Husdyr
      - Grupper?
    - Stand/walk and talk
    - Kaffe, Te og kage……..

Spørgsmål til opdrætter og katteejere af Maine Coon, Norske skovkat, British Shorthair, Perser, Ragdolls, Hellig Birma og mange andre racer!

- Er du vidende om din katterace hyppigt rammes af hjertesygdom?
- Undersøger du din kat for hjertesygdom før anvendelse i avlen?
- Accepterer du, at din kat/dit opdræt evt. dør alt for tidligt?
- Fortæller du dine killingekøbere om risikoen?
- Eller er hjertesygdom bare en del af det at have netop din race?

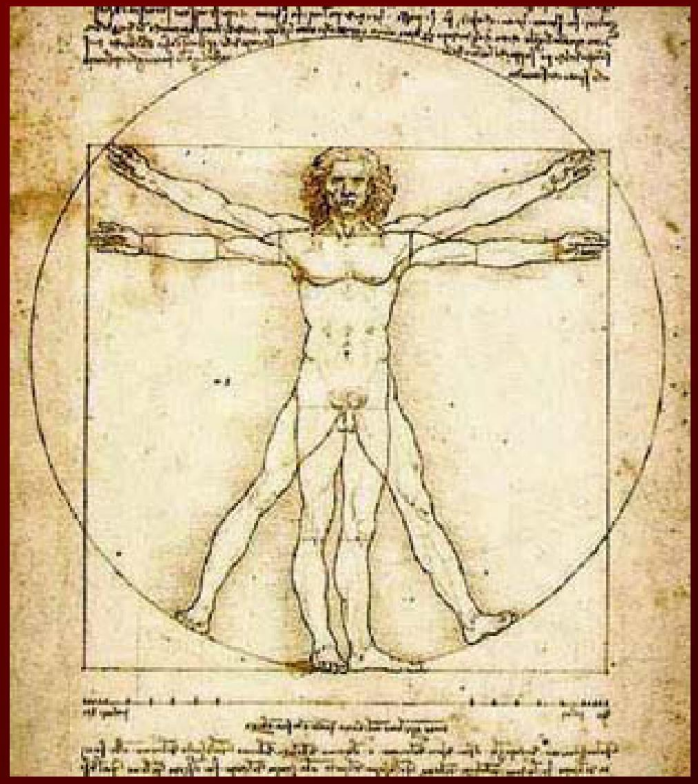
JA

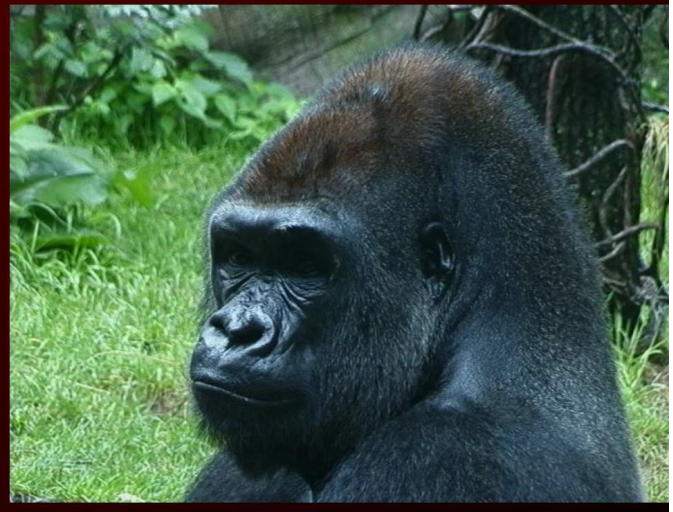
Efter min opfattelse er der en betydelig bedre moral i katteverdenen end hos fætter hund!

Projektgruppe HCM

- Overlæge Michael Christiansen, SSI
- Molekylærbiolog Mia Nyberg, SSI/LIFE
- Dyrlæge Sara Granström, LIFE
- Dyrlæge Jakob Willesen, LIFE
- Dyrlæge Jørgen Koch, LIFE
- Veterinærsygeplejerske Michelle Dupont, LIFE

Komparativ Kardiovaskulær Genetik
"Breaking the Code"





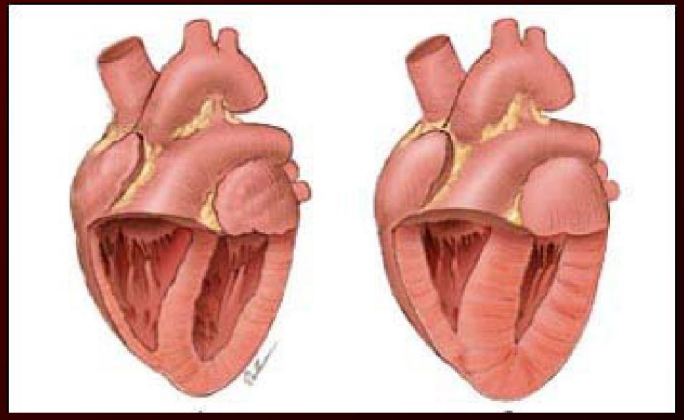
Spørgsmål ?

- De dummeste spørgsmål er dem, der ikke bliver stillet !

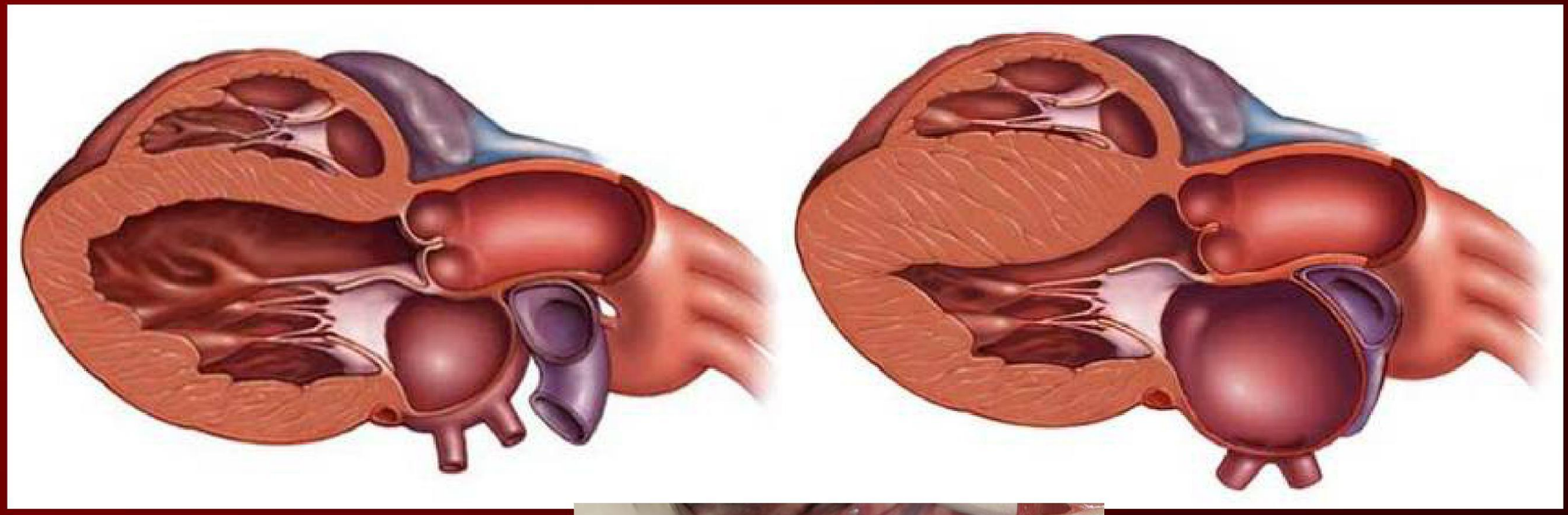
Hypertrofisk kardiomyopati hos kat = hyppigste hjertesygdom!

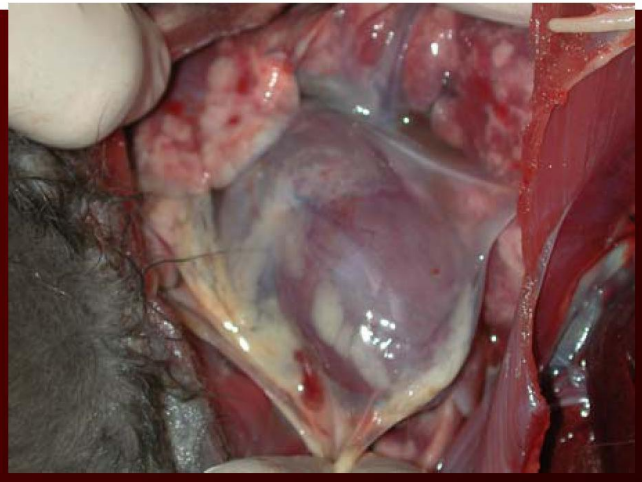
Hvad er HCM?

- Sarkomer-kardiomyopati
  - Koncentrisk hypertrofi af venstre ventrikel
  - Familiær autosomal dominant
    - MYBPC3 mutation hos Maine Coon (Meurs 2005)
  - De novo?
  - Progressiv heterogen hjertemuskelsygdom
    - Variabel penetrans og ekspressivitet
    - 12 gener (humant)
- HCM varierer i sværhedsgrad
  - Fra godartet til pludselig død i en ung alder
  - Udvikling af hjertesvigt



Hypertrofi af hjertet (forstørret hjerte)



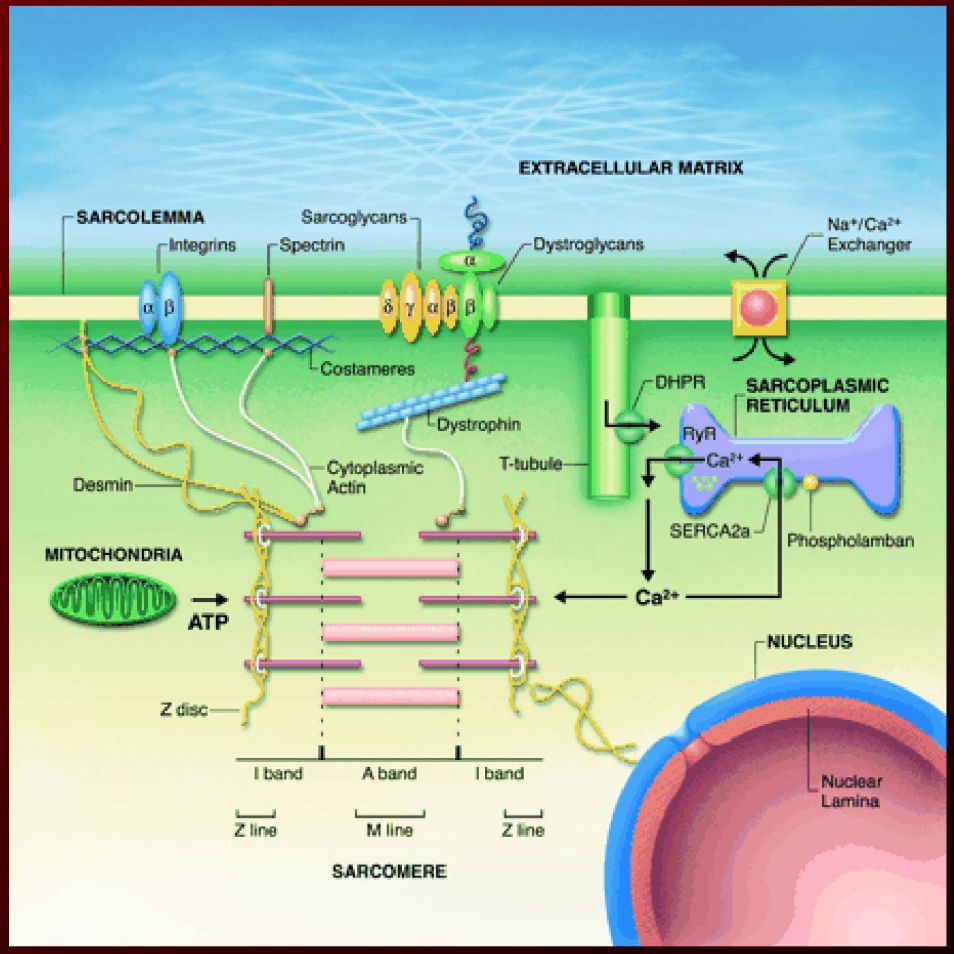


HCM!?

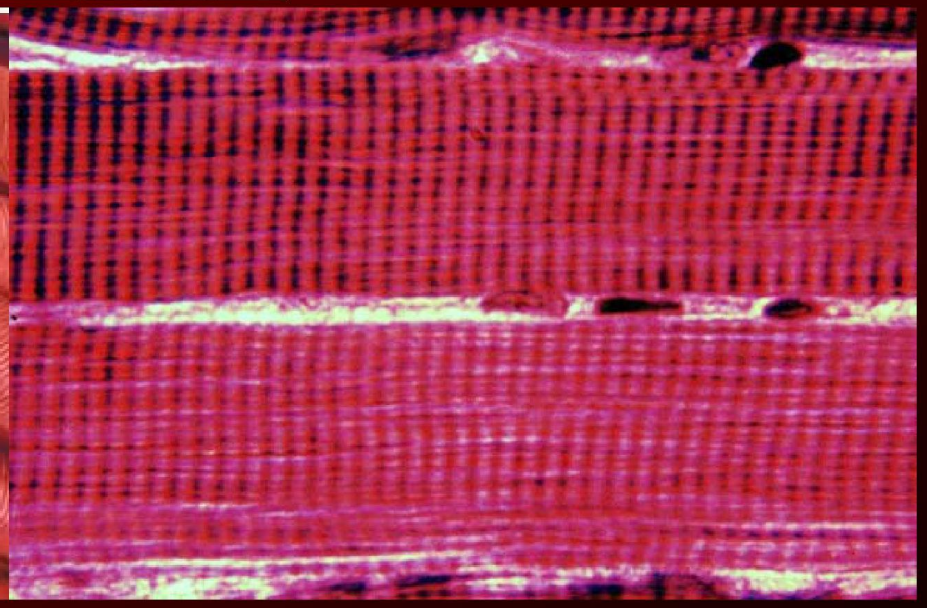
- HYPPIGSTE FÆNOTYPE – NORMAL HJERTE!?
  - Manifest fænotype: Venstre hjertemuskel hypertrofi, myofibrillær disarray, fibrose (bindevævsindlejring), karforandringer
- Samme fænotype fra forskellige mutationer indikerer en fælles patogenetisk mekanisme
- → Spørgsmål: Hvad er den fælles mekanisme?

Underliggende Mekanisme?!?

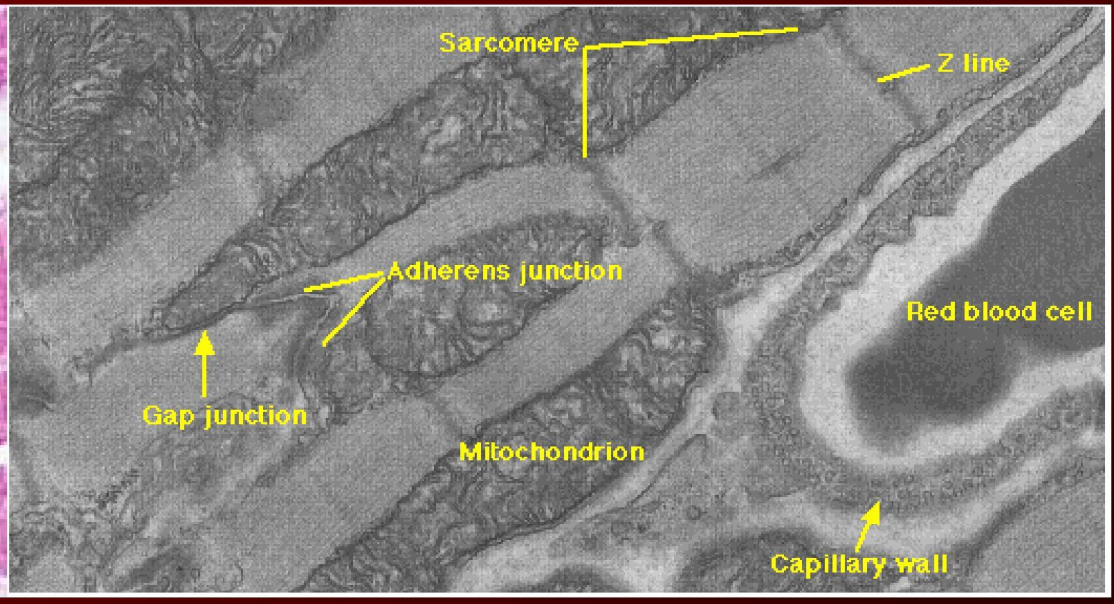
- Kompensatorisk respons pga sarkomer dysfunktion
  - Øget energibehov ifm kraftproduktion
    - Force per hydrolysis of ATP
  - Ændret Ca2+ homeostase og aktivering af "signaling pathways" for Ca2+-afhængig hypertrofi
  - **"Poison** peptide **theory"**- muteret protein bygges ind i sarkomerstrukturer og virker som et "poison polypeptide" og forstyrrer "wild-type" proteinfunktionen



Rød tværstribet muskulatur

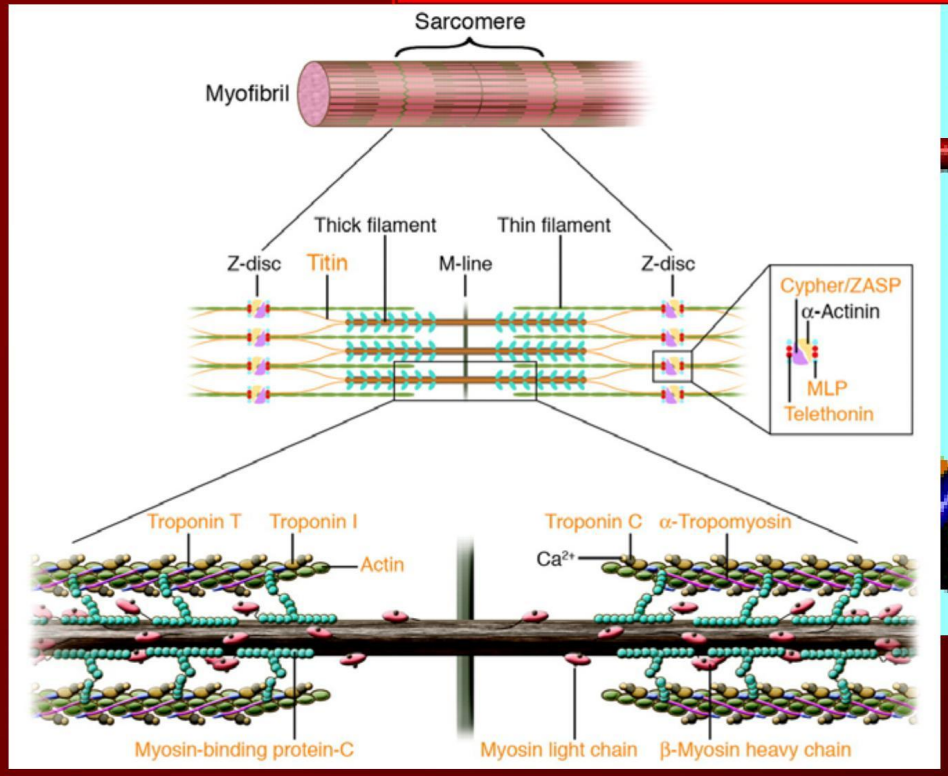


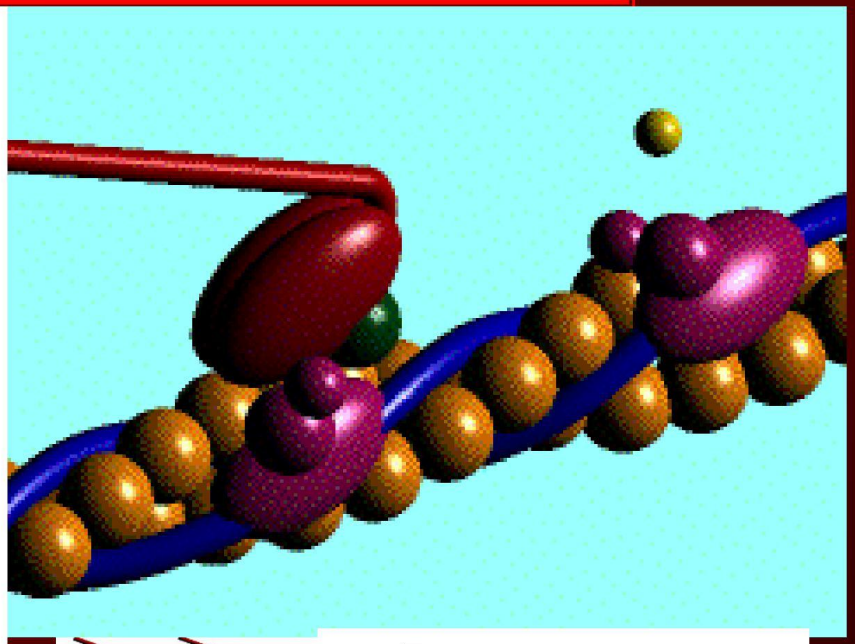
Hjertemuskel

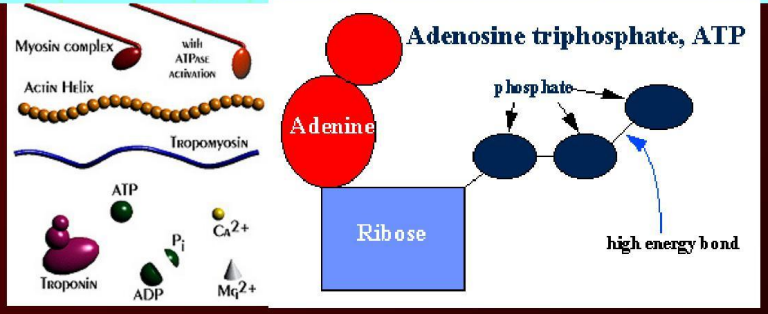


The heart is made of specialized muscle tissue with some similarities to both smooth and skeletal muscle. It is involuntary and mononucleate as is smooth muscle. It is striated like skeletal muscle which means that it has microscopically visible myofilaments arranged in parallel with the sarcomere structure. Cardiac muscle fibers branch and have a single nucleus per cell. Another difference in cardiac muscle is the presence of intercalated discs that are specialized connections between one cardiac muscle cell and another. These tight connections allow for almost completely free movement of ions so that action potentials can freely pass from one cell to another.

Muscle Contraction



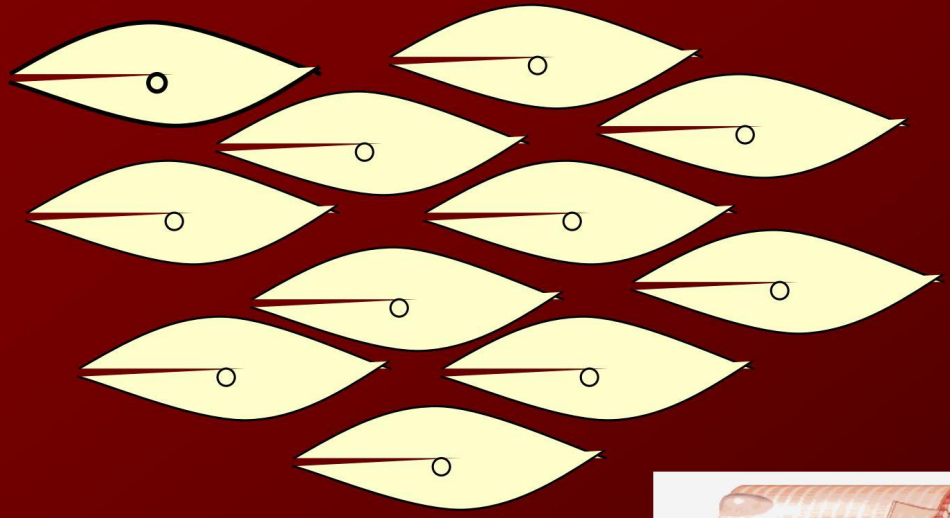




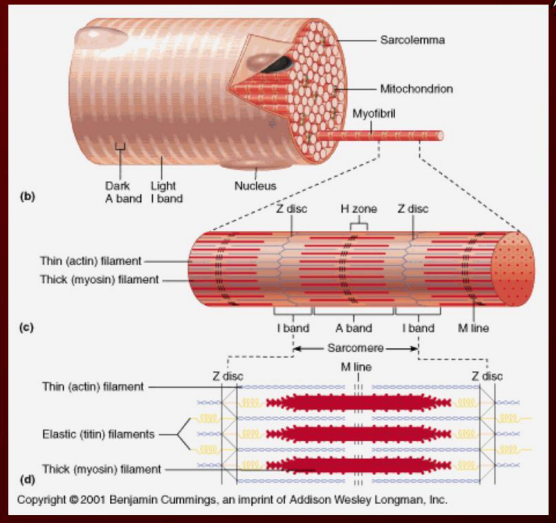
Cardiac myosin binding protein-C is a 137 kD polypeptide that has structural and regulatory functions in the sarcomere.

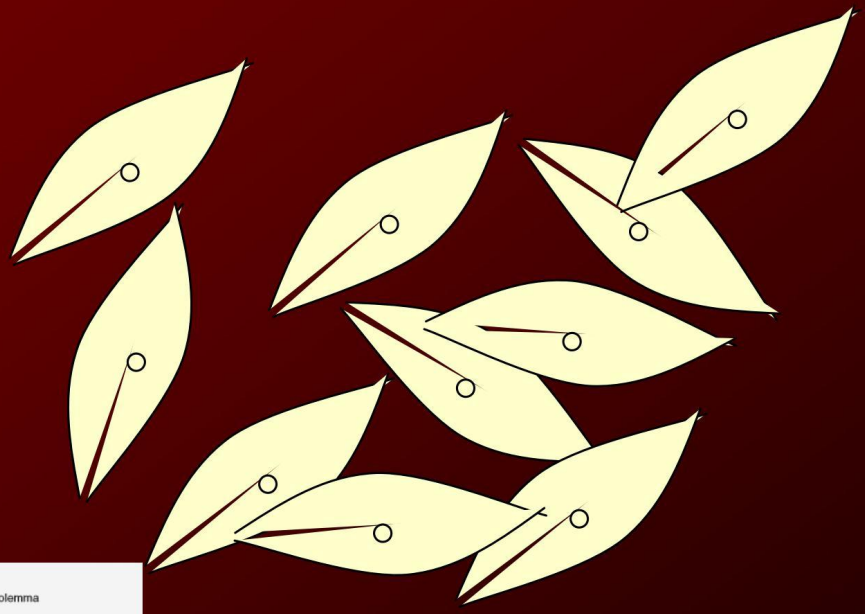
- Located in middle 1/3 of each half A-band
- Myofibrillogenesis (embryogenesis)
- Dynamic regulation of cardiac contraction in response to adrenergic stimuli

Hjertemuskel



Normal muskelstruktur
(parallelle celler)

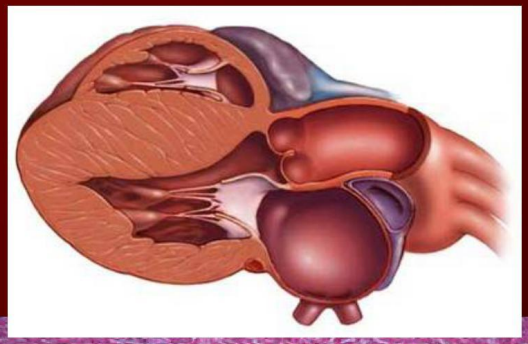


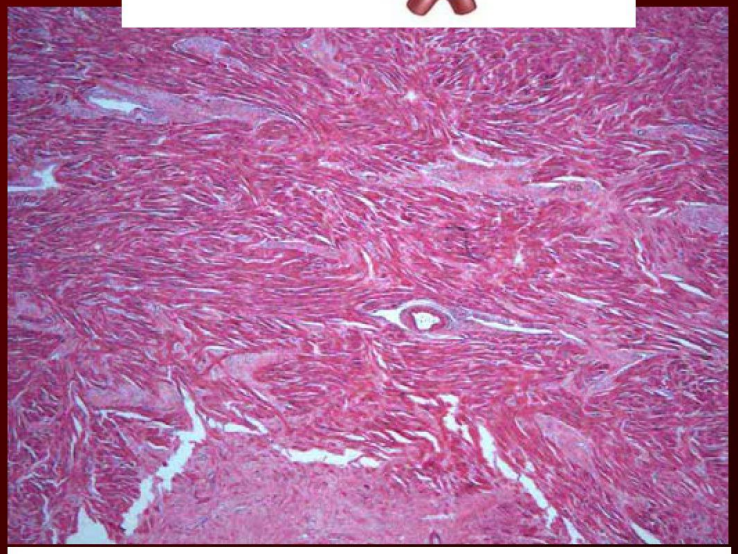


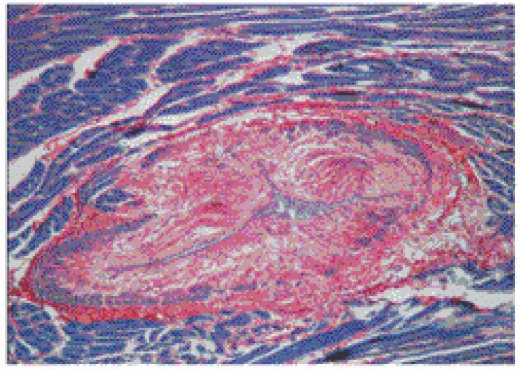
HCM – Myokardiestruktur
"myofibrillar disarray"
Uorganiseret struktur

Patologi

1. Koncentrisk hypertrofi af venstre hjertekammer
   - Myofiber disarray with bundles running in all directions. Unfortunately, disarray is not pathognomic of HOCM
   - Interstitial fibrosis is also present with abnormal, disorganized, and thickened collagen matrix. Unfortunately, disarray is not pathognomic of HOCM.







◀ *Figur 4: Udsnit af venstre ventrikels fri-væg. Der ses fortyk-ket væg og forsnævr-et lumen pga. intramural-arterie. PTAH-farvning. Forstørrelse: x 100.*

HCM hos kat

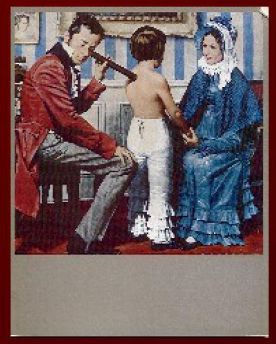
- Patologi:
  - Mål hjertets vægt! (normalt < 20 g hos 5 kg kat)

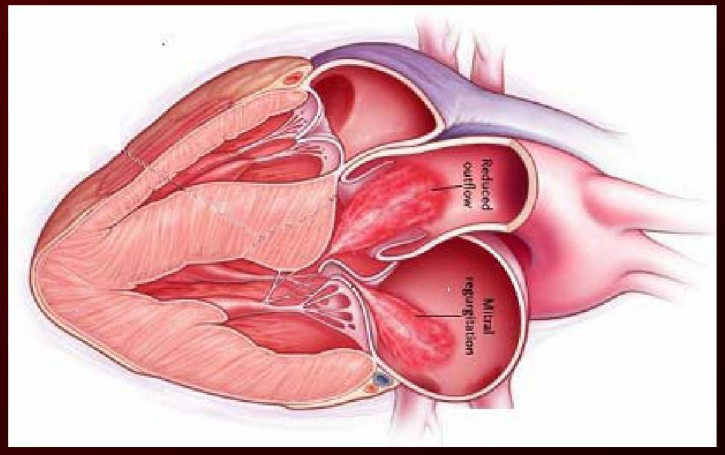
Differentialdiagnoser

- Aortastenose
- Hyperthyreoidisme
- Hypertension
  - nyresygdom
- Akromegali

Klinik (HCM)

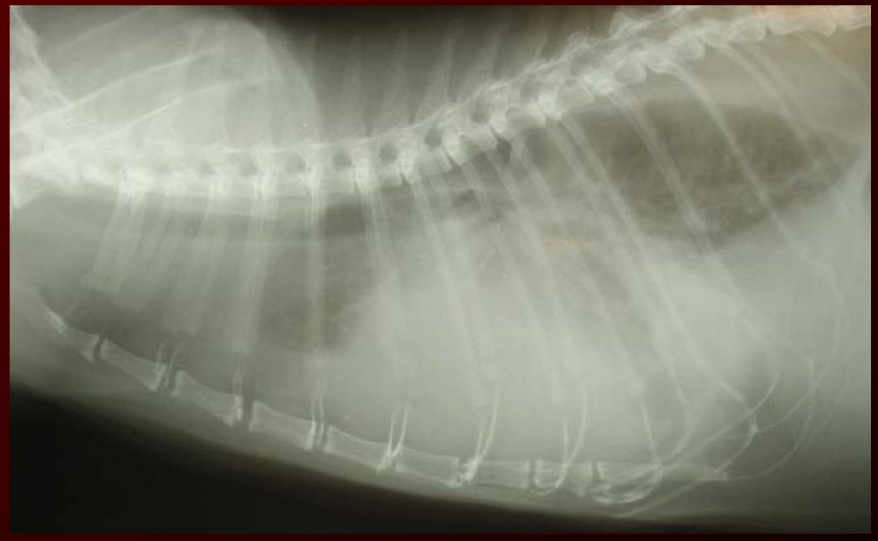
- Mislyd
- Galoplyd?
- Åndenød
- Nedstemt og anoreksi
- Pludselig død (besvimelsesanfald?)





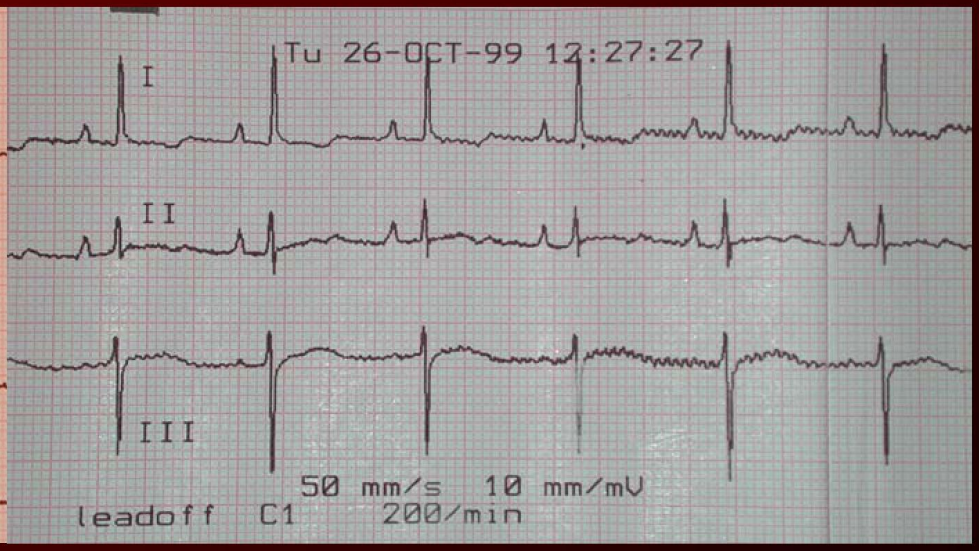
Diagnosticering af HCM

- Røntgen
  - Hjerteformet i DV projektion
  - Kongestion

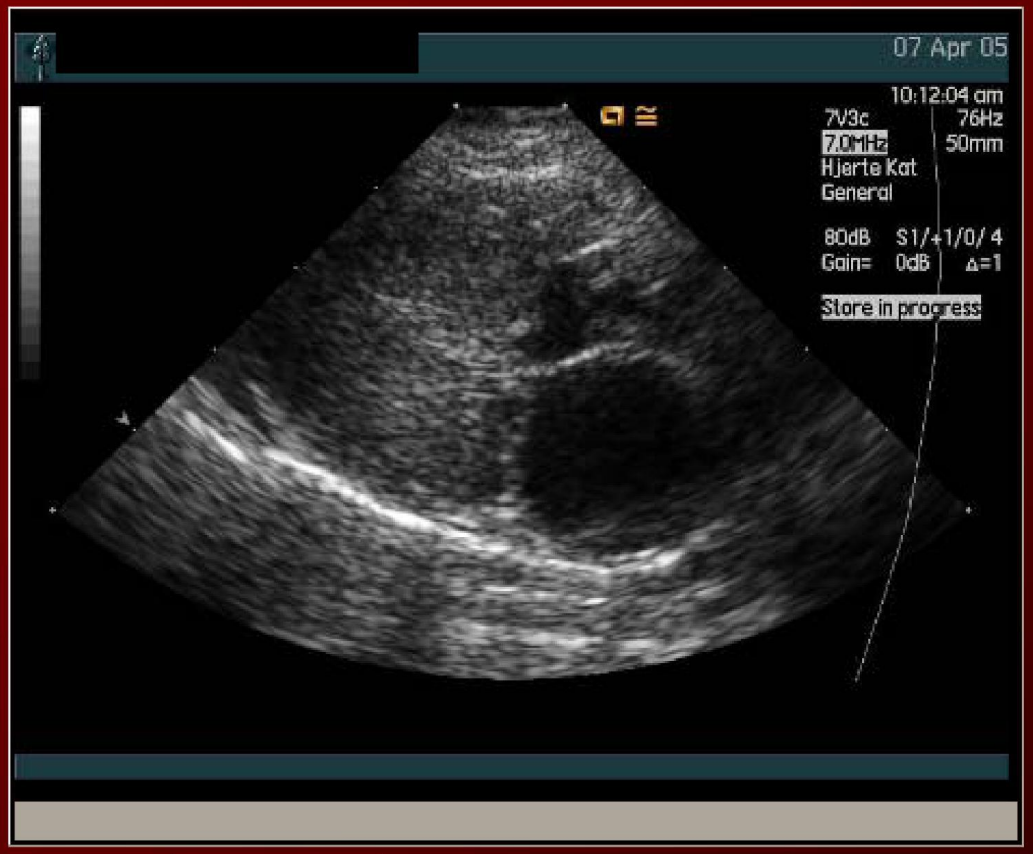


Diagnosticering af HCM

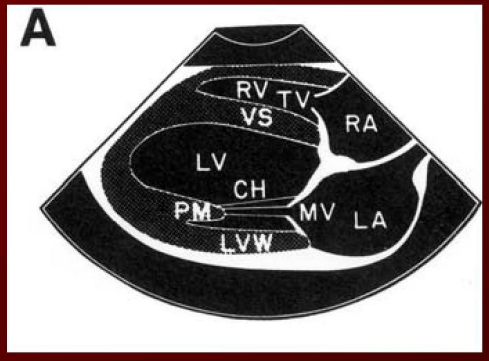
- EKG - Forstørrelsesmønstre
  - Fasikulært blok?

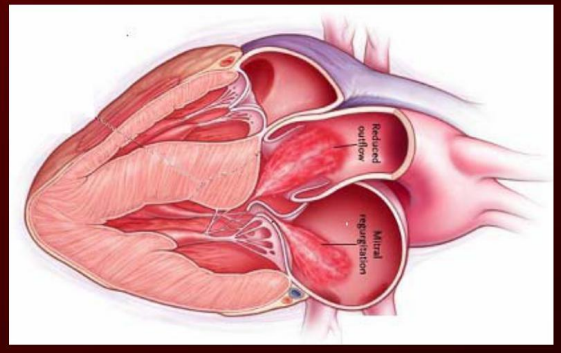


HCM in Cats



Echo:
2-D Right Parasternal
Long Axis View

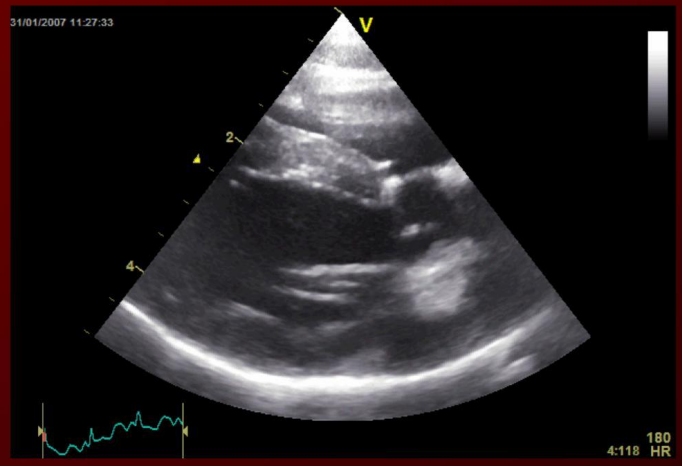


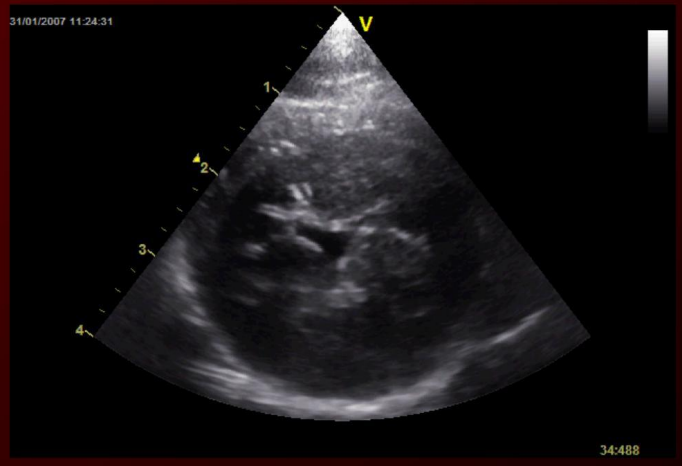


MRI – human HOCM

Diagnosticering af HCM

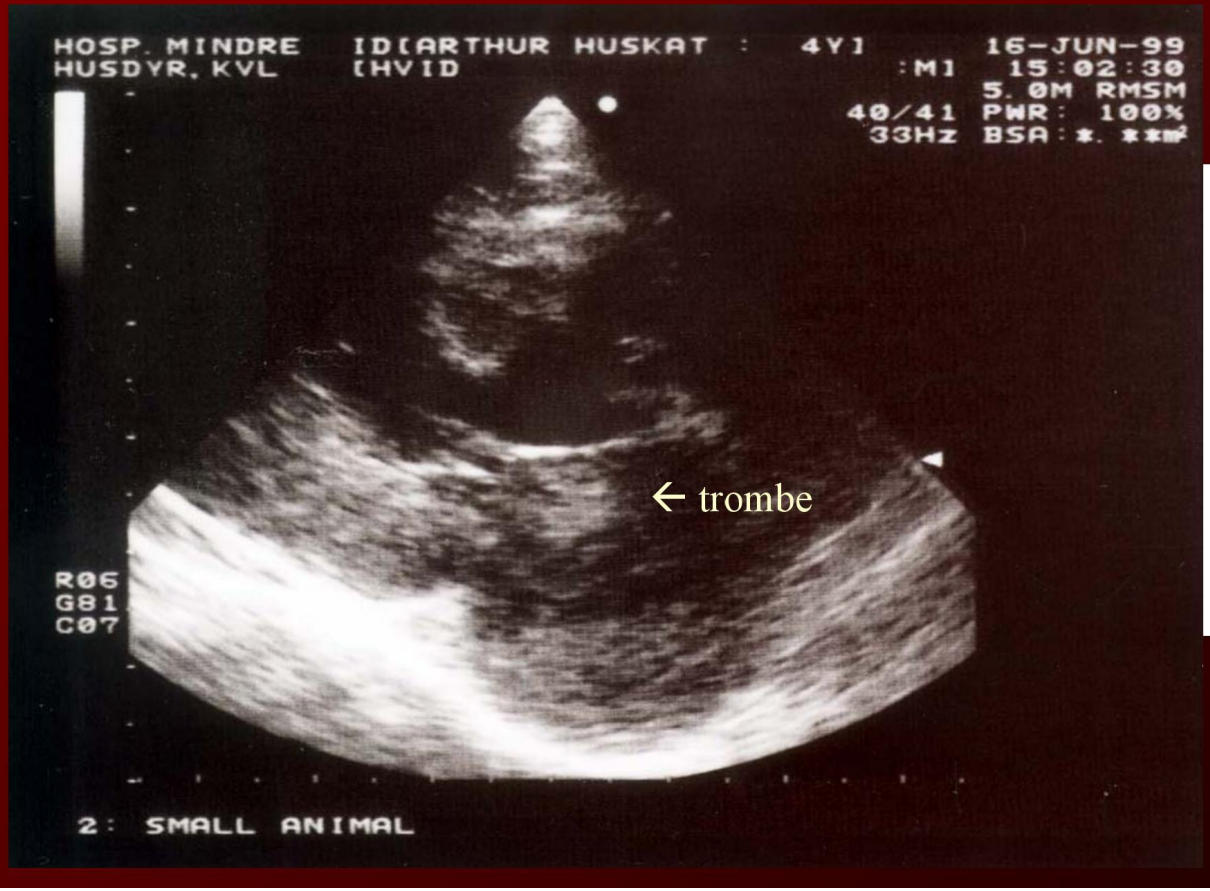
- Ekkokardiografi (hypertrofi, SAM)
  - Ventrikelvæg
    - Septum og frivæg i diastole > 6 (5) mm
  - SAM
  - Obliteration
  - LA/AO-ratio
  - Papillarmuskler

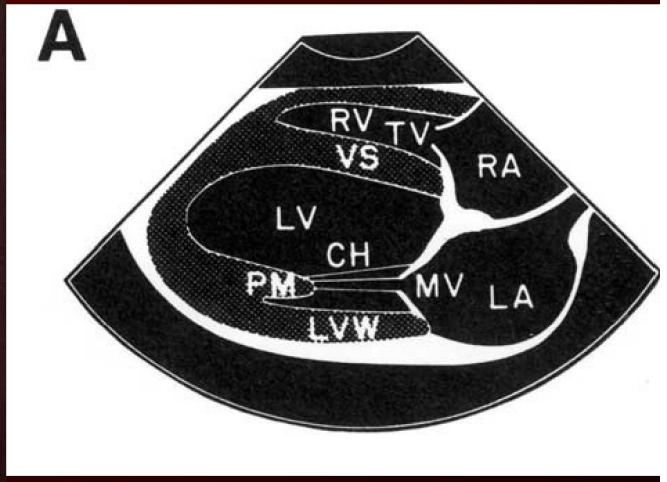




HCM hos kat

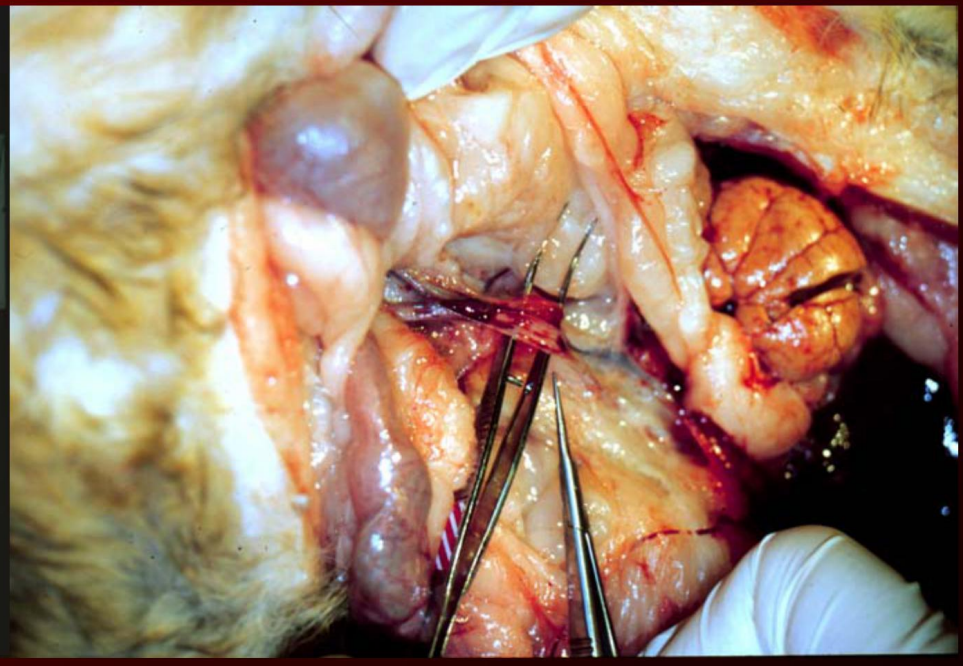
- Ekkokardiografi
  - 2-D længdeakse





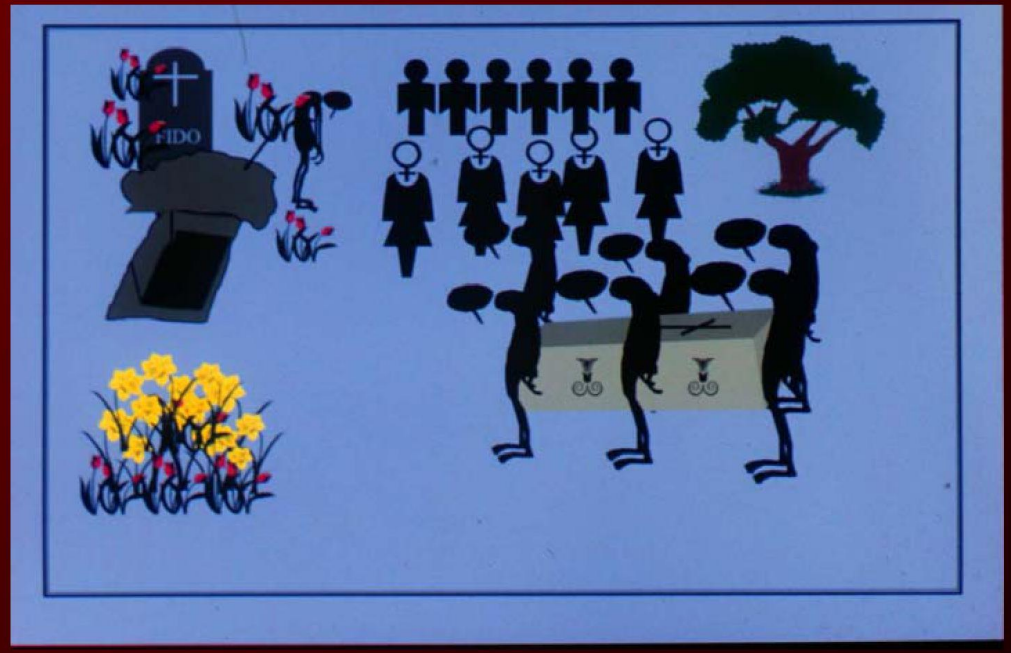
Klinik (HCM)

- Trombeembolisme (”saddel-trombe”) ved aorta´s trifurcation med følgende lammelse af dyrets bagparti (eller højre forben og cerebrum)



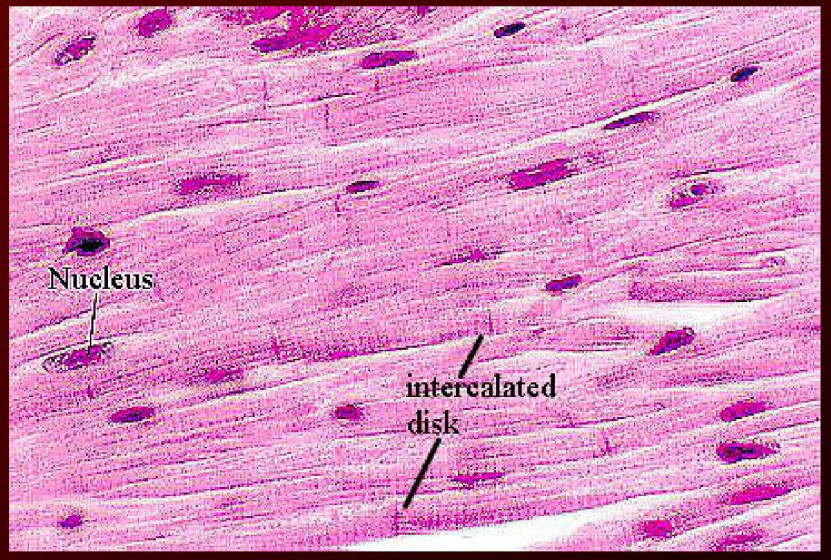
Prognose ved HCM

- Asymptomatisk i årevis
  - Benign?
- Pludselig død
- Hjertesvigt
- Blodprop
- ??



Sarkomer-gener ifm HCM: genotype-fænotype sammenhæng

- • AD males and females equally affected
- ~ 50% of offspring or affected subjects at risk of carrier status
- delayed age of onset (age-related penetrance)
- • β-MHC mutations (MYH7)
  - earlier onset
  - poor prognosis
  - severe hypertrophy
- • cTnT mutations
  - mild hypertrophy
  - poor prognosis (SD)
  - 20% without hypertrophy
- • MyBPC mutations
  - good prognosis
  - mild hypertrophy
  - late onset
- Possible selection bias: patients studied in referral centers



Terapi ved HCM hos kat

Asymptomatisk HCM/HOCM	Symptomatisk HCM/HOCM
Evt. Indendørs-kat ❖Atenolol: 6.25 mg 1 gang dagligt (monitorere hjertefrekvens) ❖+/- Magnyl •Baseres på atriestørrelse eller thrombefund ❖+/- Benazepril/ramipril/enalapril (VV-hypertrofi) ❖Undgå depotsteroider, væskeinfusion og ekstra saltet mad ❖Monitorering ved anæstesi før,under og efter ❖Nutraceuticals (taurin-carnitin-fiskeolie)?	Indendørskat ❖ Furosemid 5-10 mg 1-3 x dagligt, +/- Nitroglycerin and Oxygen ❖Diltiazem 7.5 mg 3 x dgl. og/eller atenolol AM, Atenolol PM)) ❖+/- Magnyl •Baseres på atriestørrelse eller thrombefund ❖+/- benazepril/ramipril/enalapril (VV-hypertrofi/pleural effusion) ❖Undgå depotsteroider, væskeinfusion og moderat salt restriktion ❖ Anæstesi risikovurdering med monitorering/oxygen ved anæstesi før,under og efter ❖Nutraceuticals (taurin-carnitin-fiskeolie)? ❖Elektrolyttilskud (kalium)

Screeningsprogram

- Avlsdyr
  - DNA-test
    - Homozygoter
    - Heterozygoter
    - Frie
  - Hjerteskanning
    - Manifest HCM
    - Equivocal
    - Frie (positiv DNA-test)
- Alder
  - DNA-test
  - Skanning
- Racer
- Hyppighed
- Krav til
  - Udstyr
  - Person
- Fejlkilder?

Ekkokardiografi

EKKOKARDIOGRAFI – Hjerteskanning

- Skanningsmetoder
  - M-mode
  - 2-D
  - Spectral Doppler
    - Pulsed, continous
  - Color Doppler
  - Tissue Doppler
    - Strain, Strain rate
  - 3-D
- Kombineret Duplex, triplex

- Fordele
  - Real-time
  - Hurtig
  - Noninvasiv
  - Relativt billigt
  - Transportabel
  - God temporal resolution (50 ms)
  - God spatial resolution (1 mm)

- Klinisk anvendelse
  - Anatomi
  - Blodflow
  - Funktion

- Ulemper
  - Luft (lunger) kan ikke penetreres
  - Knogler (ribben) kan ikke penetreres
  - Operatør afhængigt
  - Artefakter
  - Kræver "3-Dimensionalt" tænkning
  - Fund skal korreleres til andre kliniske data/test for at stille en diagnose

HCM screening within health programme

Participating clubs: Maine Coon-katten, Sällskapet Sibirisk Katt, Skogkattslingan, Rex United, Skogkattklubben Birka, Rasclub Maine Coon, Scandinavian Ragdoll Club, Birmasällskapet, SWEPEX (Svenska Perser & Exoticringen), Ragdollklubben
Visit http://www.pawpeds.com/healthprogrammes/ for more information

Patient Information

Owner's name

Cat's registered name

Address

Registration number

Postcode/City/State

ID number, microchip or tattoo

Country

Race

Phone (including country code)

Male Not altered
Female Altered

Email

Born (year-month-day)

I am aware that the results will be retained for the records of Maine Coon-katten. I authorize Maine Coon-katten to publicly release all results from this form

Sire

Signature Date

Dam

Examination

Examination date (year-month-day)

Sedated
Yes, with: No

Examination equipment

Weight _____ kg

Heart rate _____ bpm

Dehydrated Pregnant
Lactating Other, describe

Auscultation:
Normal Gallop
Murmur, characteristics
Grade: I II III IV V VI Dynamic Static
Timing: Systolic Diastolic Both Continuous
Location: Left apex (sternum) Left Base Other, describe

IVSd	_____	cm mm	M-mode	2-D
LVIDd	_____		M-mode	2-D
LVFWd	_____		M-mode	2-D
IVSs	_____		M-mode	2-D
LVIDs	_____		M-mode	2-D
LVFWs	_____		M-mode	2-D
SF	_____			
Ao	_____		M-mode	2-D
LA	_____		M-mode	2-D
LA/Ao	_____			

Subjective left atrial size
Normal
Mild enlargement
Moderate enlargement
Severe enlargement

Systolic anterior motion of the mitral valve yes no

If yes, LV outflow tract flow velocity (Doppler) _____

End-systolic cavity obliteration yes no

Papillary muscles
Normal
Abnormal, moderate enlargement
Abnormal, severe enlargement

Assessment (based on phenotype)

Comments

Normal
Equivocal
HCM Mild Moderate Severe
Other, describe

Veterinarian

Veterinarian's name, clinic's name and address

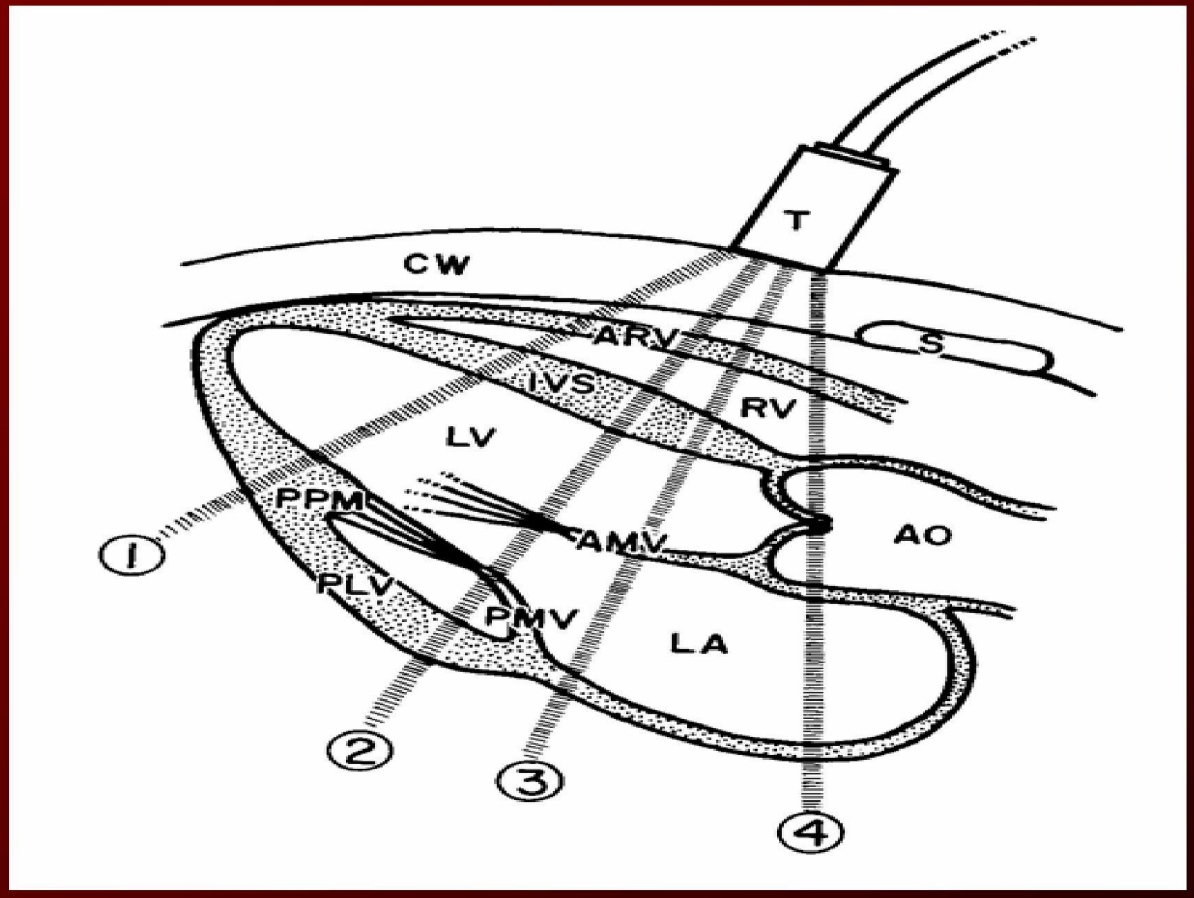
Cat's identity verified yes no, describe why not

Signature Date

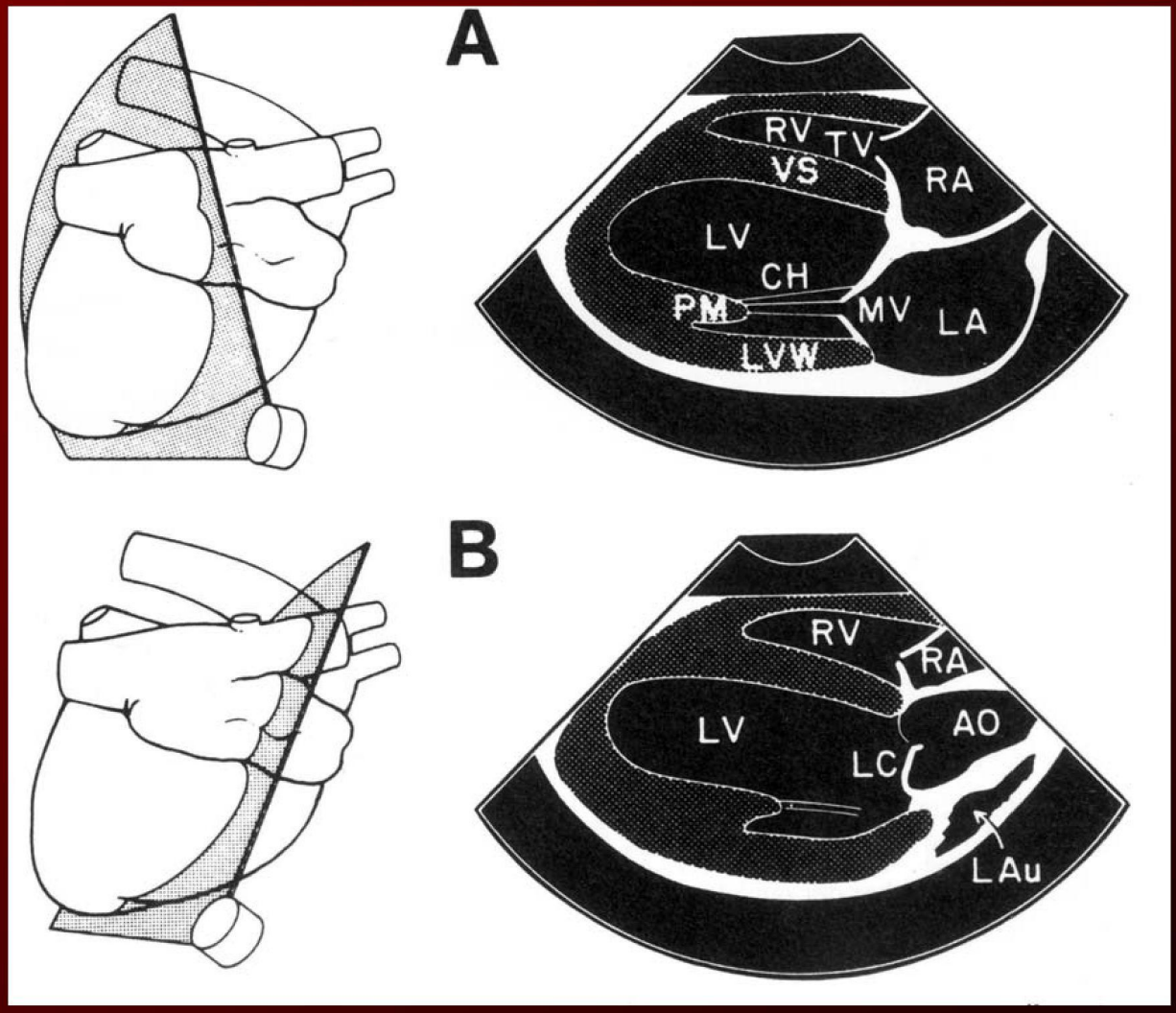
For registration of the result, the veterinarian shall send a copy of this form to:
Maine Coon-katten, c/o Anne N. Jensen, Landsvinget 5, Nejede, 3400 Hillerød, Denmark

Rev 1.5 (en) 2007-03-04

Hjerteskanning

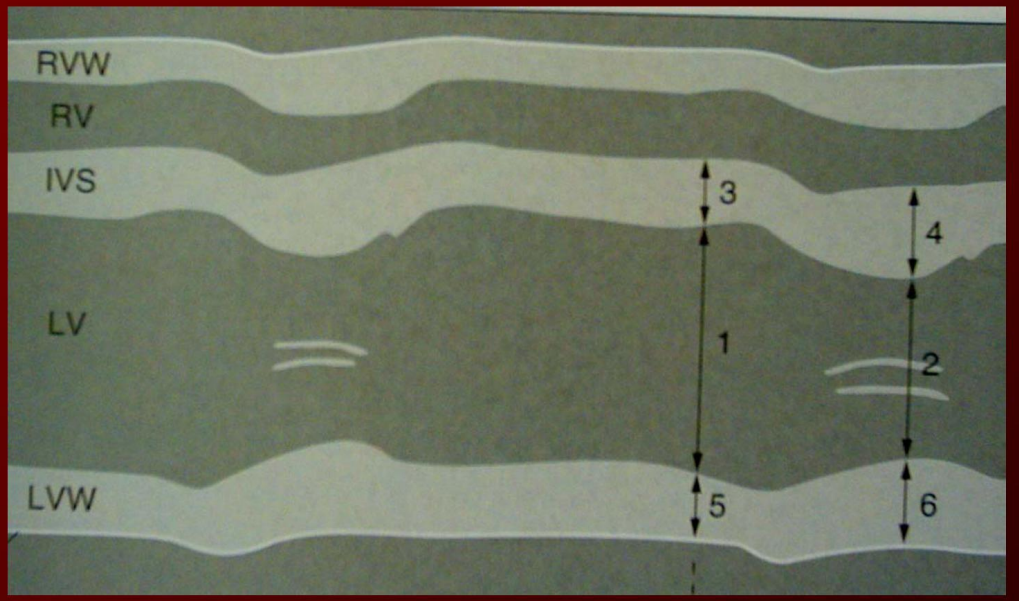


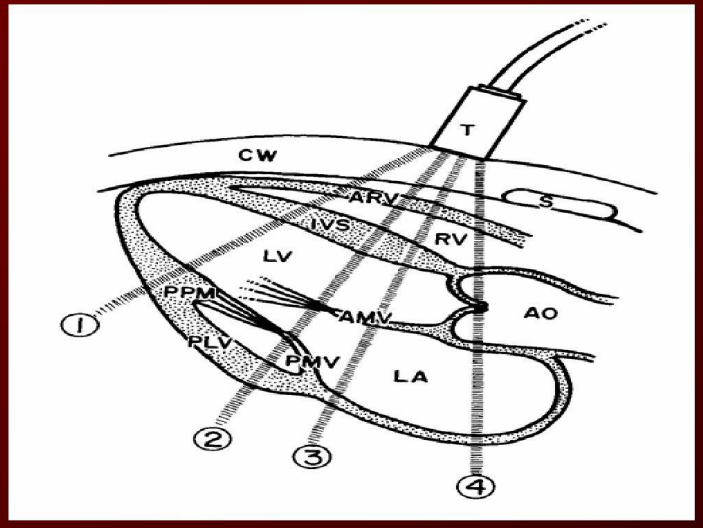
Hjerteskanning - længdeaksesnit

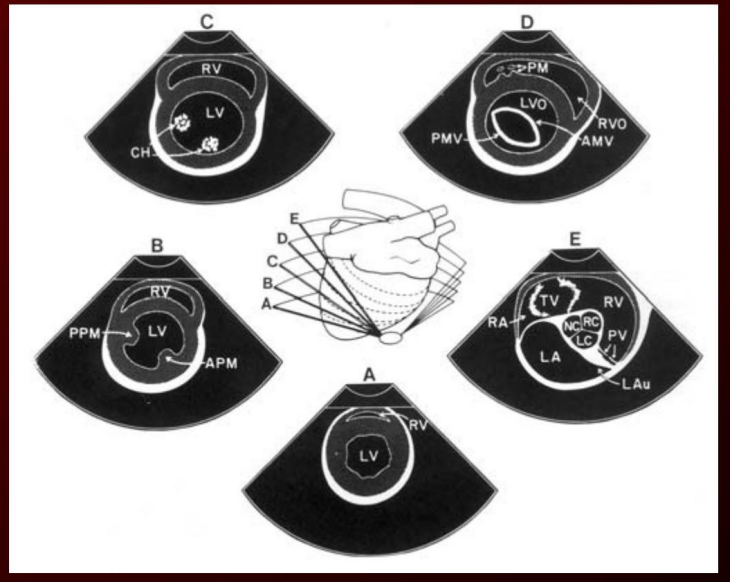


M-MODE

1. LV end-diastolic dimension = LVEDD
2. LV end-systolic dimension = LVESD
3. IVS end-diastolic = IVSED
4. IVS end-systolic = IVSES
5. LV wall end-diastolic = LVWED
6. LV wall end-systolic = LVWES







Ekkokardiografi - Color Doppler