MHIF FEATURED STUDY:

Heart EXPAND CAP

OPEN AND ENROLLING:

EPIC message to *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACTS:	SPONSOR:
Heart Failure/Transplant	Karl Mudy, MD	Kari Thomas - Kari.M.Thomas@allina.com | 612-863-7493 Kari Williams - Kari.Williams@allina.com | 612-863-0027	TransMedics, Inc.

DESCRIPTION: a single-arm study evaluating the OCS™ Heart System and extended criteria donor hearts (those that are currently not transplanted or are seldom transplanted in the US)

CRITERIA LIST/ QUALIFICATIONS:

Donor Heart Inclusion

- Expected total cross-clamp time of ≥4 hours; **OR** expected total cross-clamp time of ≥2 hours PLUS one of the following risk factors:
  - Donor age 45-55 years, inclusive, with no coronary catheterization data
  - Donor age ≥55 years
  - Left ventricular septal or posterior wall thickness of >12 mm, but ≤16 mm
  - Reported down time of ≥20 min, with stable hemodynamics at time of final assessment
  - Left heart ejection fraction (EF) ≥40%, but ≤50% at time of acceptance of offer
  - Donor angiogram with luminal irregularities with no significant CAD (≤50%)
  - History of carbon monoxide poisoning with good cardiac function at time of donor assessment
  - Social history of alcoholism with good cardiac function at time of donor assessment
  - History of diabetes without significant CAD on angiogram (≤50%)

To date, MHIF has had four successful uses of the TransMedics Organ Care System (OCS™), aka "Heart in the Box"

MHIF FEATURED STUDY:

Heart DCD

PENDING APPROVAL:

EPIC message to *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACTS:	SPONSOR:
Heart Failure/Transplant	Karl Mudy, MD	Kari Thomas - Kari.M.Thomas@allina.com | 612-863-7493 Kari Williams - Kari.Williams@allina.com | 612-863-0027	TransMedics, Inc.

DESCRIPTION: To evaluate the effectiveness of the OCS Heart System to resuscitate, preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation.

A prospective, randomized and concurrent controlled, non-inferiority pivotal trial in which subjects who receive a DCD donor heart transplant will be compared to subjects who receive a standard criteria donor heart transplant (SOC1 and SOC2 - from both randomized and concurrent control groups), adjusting for differences in risk factors.

CRITERIA LIST/ QUALIFICATIONS:

Donor Heart Inclusion

- Maastricht Category III DCD donor, defined as expected death after the withdrawal of lifesupportive therapy (WLST)
- Donor age 18-49 years old inclusive
- Warm ischemic time (WIT) ≤ 30 mins, with warm ischemic time defined as: Time from when
- mean systolic blood pressure (SBP) is < 50 mmHg or peripheral saturation < 70% to aortic crossclamp
- and administration of cold cardioplegia in the donor.

To date, MHIF has had four successful uses of the TransMedics Organ Care System (OCS™), aka “Heart in the Box”

Barts Health NHS
NHS Trust

UCL

Rethinking Myocardial Imaging from Biology to Outcomes

Professor James Moon
Clinical Director Imaging
Barts Heart Centre UCL, London

Minneapolis Heart Institute

What does the heart have to do? (My list)

Be built
Grow
Low energy at rest
High output at stress
Adapt
Evolutionary toolkit

2

Cardiology is being left behind by other domains eg Cancer

Measurement is imprecise

Not measuring biology and pathways

Not reaching all patients

Poor Standardization

Poor linking to therapy

Poor integration with other data

Myocardium – the single greatest opportunity in medicine

The heart of cardiology
- an emergent problem

Precision therapy?
- Not one approved myocardium targeted therapy
- millions get the same 4 drugs
- our studies fail

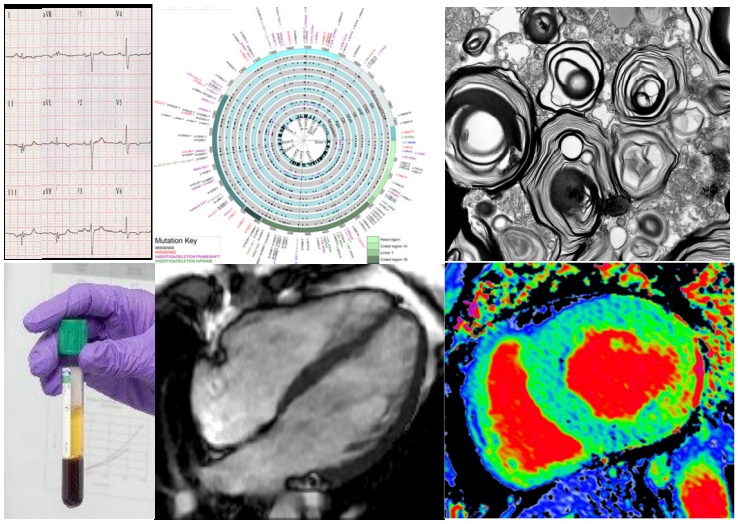
Control not cure
- cardiology becoming un-investable

Other domains transformed
- cancer: industralized, linked, redefined, biofluids, personalized therapies

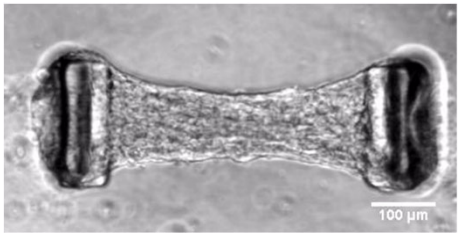
Cardiology silos
- no shared language: open source frameworks, “opinion based” domains
- genetics not actionned
- disease definitions imaging based
- 2 biofluid markers

We gamble
- massive endpoint phase III trials
- drug approvals falling

Exploration at many scales

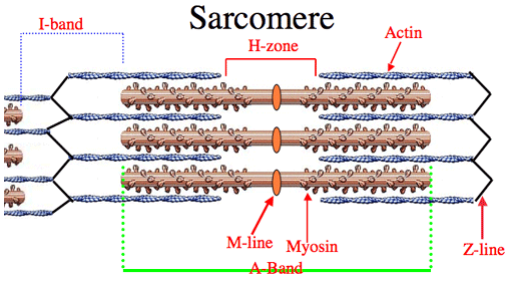


Structure and function
Tissue characterisation
Genetics
Blood biomarkers
ECG



Normal vs titin

The Myocyte

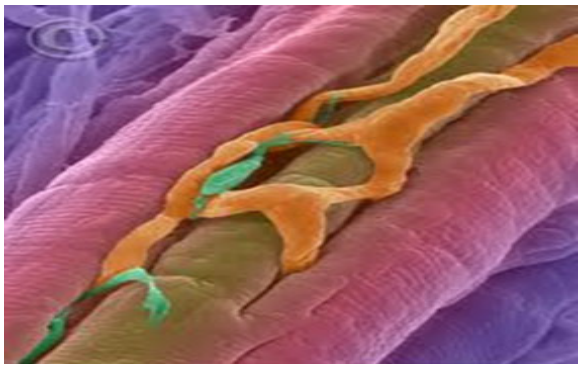


~13 contractile proteins
5000 proteins
Of ~26000 genes
Mutate each one: 15% - cardiac phenotype

6

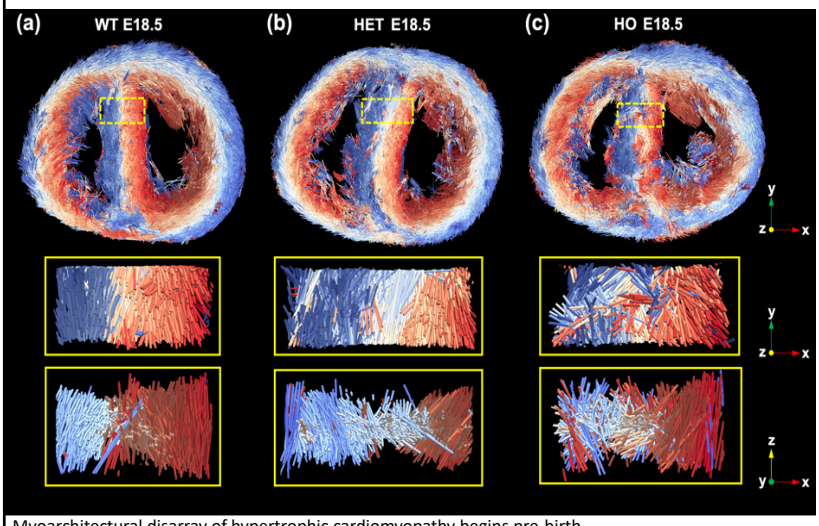
A pair of cells: the Myocyte and Capillary

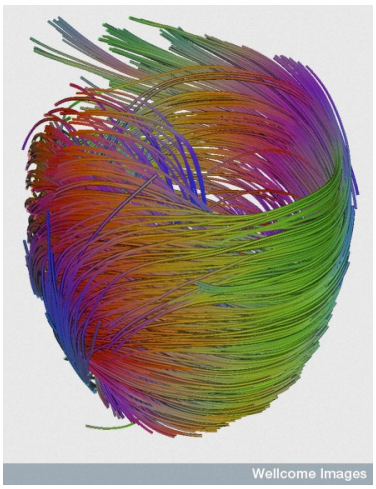
Fundamental building block



Am J Respir Crit Care Med. 2017 Oct 15;196(8):1075-1077.
Right Ventricle Vasculature in Human Pulmonary Hypertension Assessed by Stereology.
Graham BB[1].. Tuder RM[1].

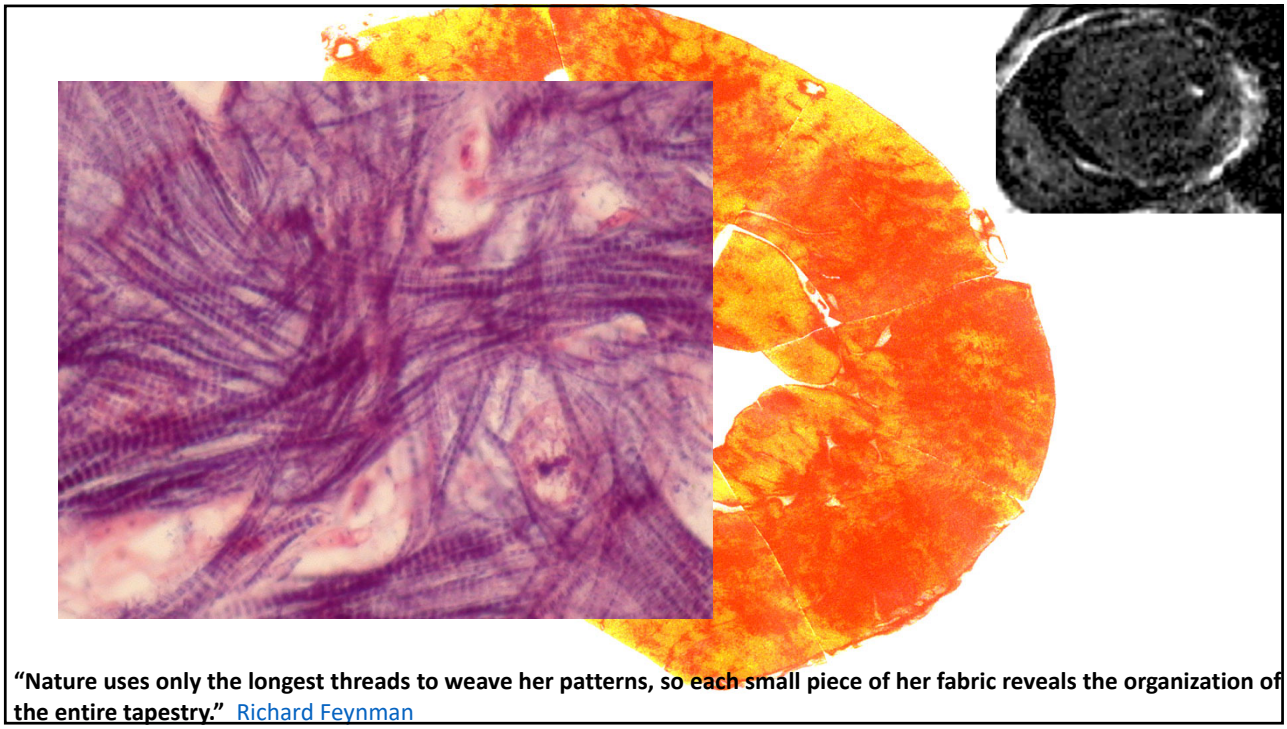
Myocytes into Fibrils



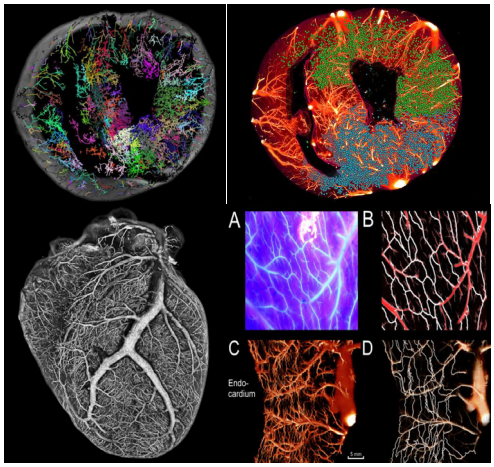


Myoarchitectural disarray of hypertrophic cardiomyopathy begins pre-birth
Canadilla….Moon.. Captur G. J Anatomy 2019

8



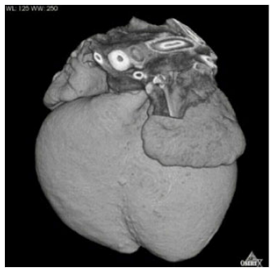
"Nature uses only the longest threads to weave her patterns, so each small piece of her fabric reveals the organization of the entire tapestry." Richard Feynman

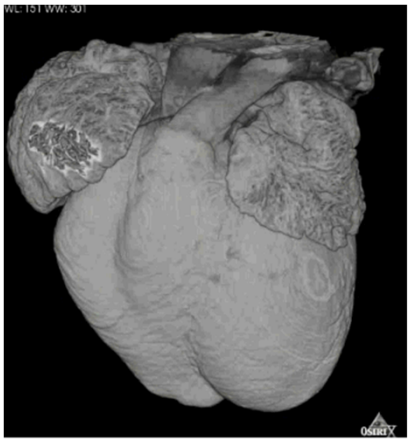


Coronary Circulation and Microcirculation

Maria Siebes, PhD
Dept. of Biomedical Engineering & Physics

Cardio-morphogenesis: Building a heart



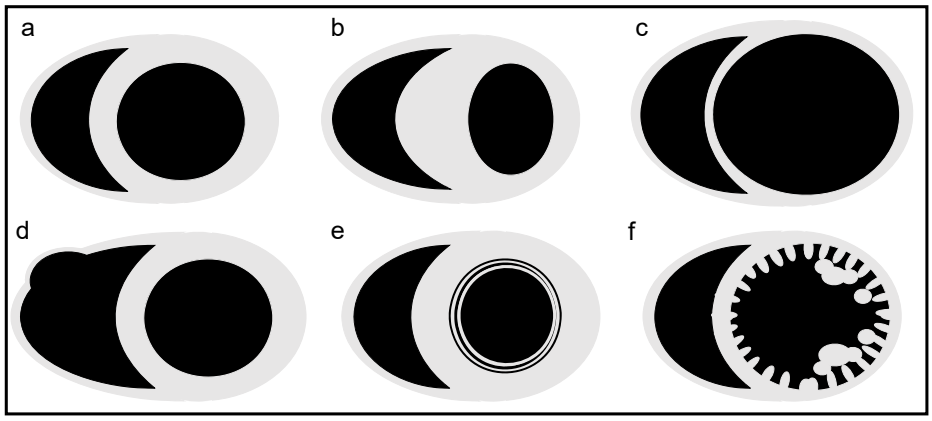


Post septation
Compaction

Episcopic microscopy. E14.5 to 16.5 mouse embryo (1mm long) Acknowledgements: Gaby Captur

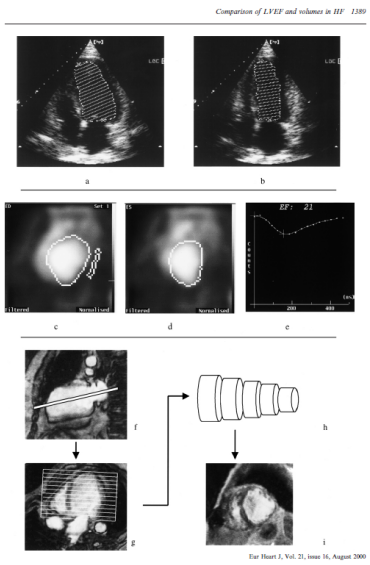
Imaging underpins cardiac care
Imaging modalities

Structure and function - Defined by morphology/function



Structure/function a long way away from biology

The basics: not well done

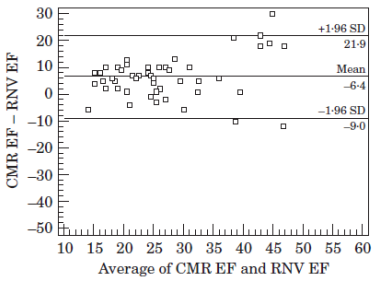


Echo

MUGA

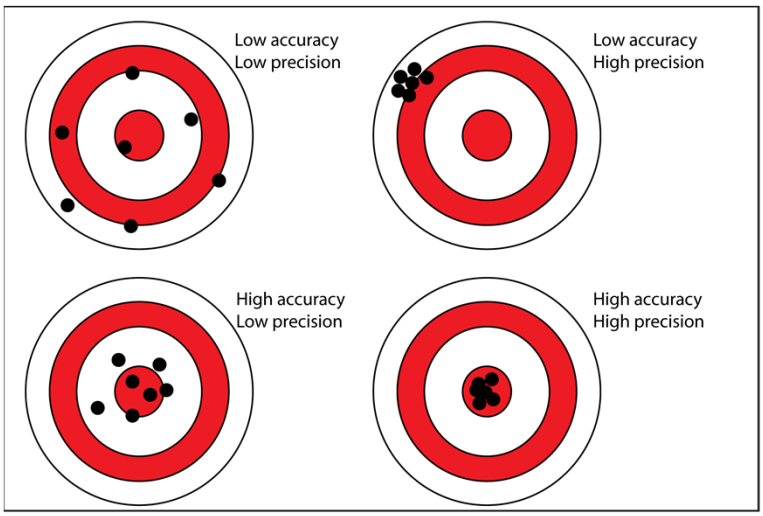
CMR

Parameter	Number	Mean ± SD
M-mode echo		
LV end-diastolic diameter	45	59 ± 11 mm
LV end-systolic diameter	45	50 ± 16 mm
Fractional shortening	45	16 ± 13%
Ejection fraction by cube	45	39 ± 22%
Ejection fraction by Teichholz	45	29 ± 15%
2D echo		
LV end-diastolic volume	36	136 ± 51 ml
LV end-systolic volume	36	98 ± 37 ml
EF by Simpson's biplane	36	31 ± 5%
RNV		
Ejection fraction	51	24 ± 21%
CMR		
LV end-diastolic volume	52	267 ± 106 ml
LV end-systolic volume	52	192 ± 98 ml
LV ejection fraction	52	30 ± 9%



Bellenger 2000

Accuracy vs Precision



Where am I now?

Vs

How have things changed?

Oncology patients undergoing screening for cardiotoxicity

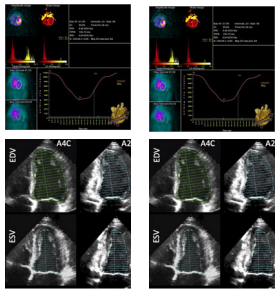
Referred for MUGA

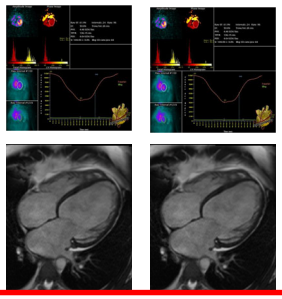
Referred for CMR/ echo

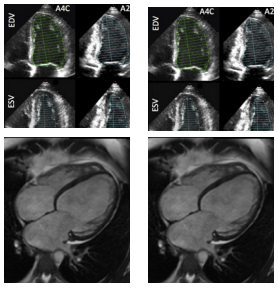
Group 1

Group 2

Group 3







Precision
Test-rest
reproducibility of ejection fraction
N=78; 312 assessments

Charlotte Manisty

Precision: MUGA vs Echo vs CMR

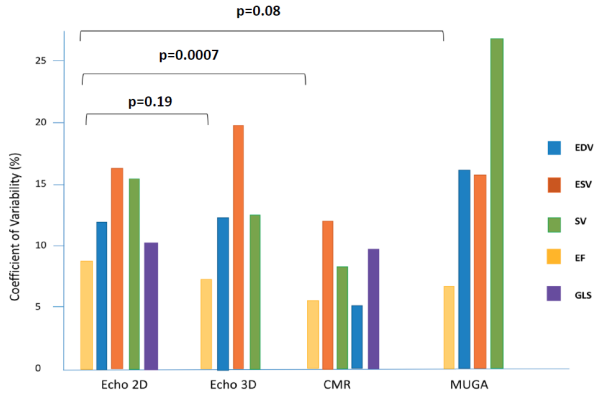


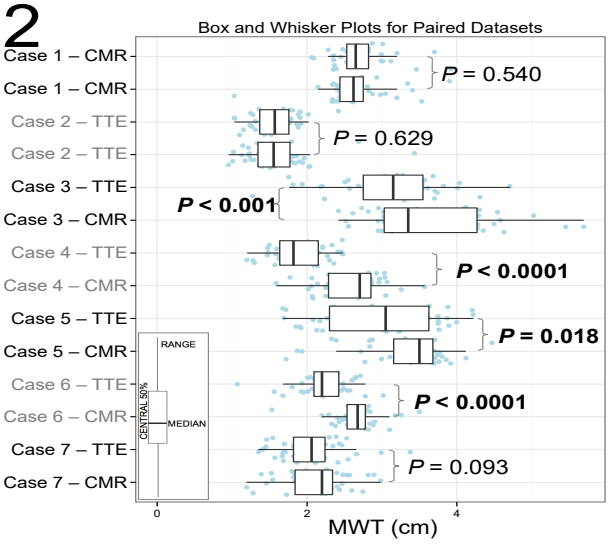
Figure 1: Coefficient of Variability for LV volumetric and functional assessment using 2DE, 3DE, MUGA and CMR

2D echo inadequate for detecting EF changes
But the others not that good

Menacho, Bhuva, Moon, Manisty submitted

Other parameters eg LVH?

2



10 perfect echo and CMR datasets
20 centres
69 experts

Conclusion:
Current wall thickness measurement:
Unacceptable as a clinical test

Or:
Global experts: talk not do (technicians)
Far more complex process occurring
(integrated opinion, then justify with 2D measurement

Submitted
Gaby Captur + 15 others

AI Revolution

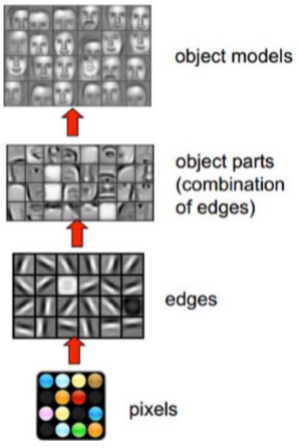
a world run by geeks

Medicine is lagging behind

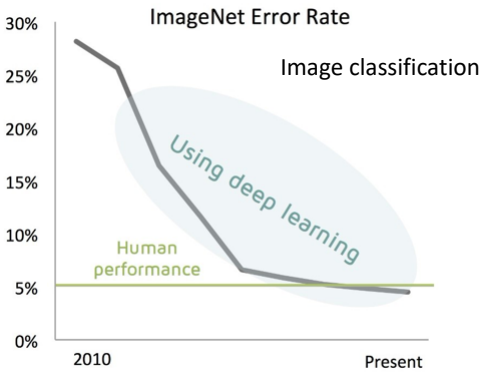
Images: Convolutional Neural Networks

Multilayered computation circuits copy the architecture of the visual cortex

CIFAR-10 :60,000 images
10 classes 32x32x3



No hard coding
learns features for itself



Best performance: <2% error rate

A revolution driven by multiple developments

Neuroscience

Compute power esp GPUs

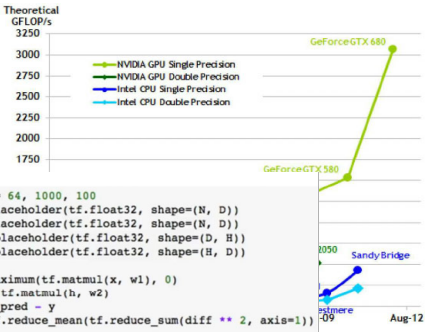
Data availability

Data sharing

New Computer languages
- Universities
- Industry

Competitions

Open publication arχive



TensorFlow: Neural Net

Running example: Train a two-layer ReLU network on random data with L2 loss

```
N, D, H = 64, 1000, 100
x = tf.placeholder(tf.float32, shape=(N, D))
y = tf.placeholder(tf.float32, shape=(N, D))
w1 = tf.placeholder(tf.float32, shape=(D, H))
w2 = tf.placeholder(tf.float32, shape=(H, D))

h = tf.maximum(tf.matmul(x, w1), 0)
y_pred = tf.matmul(h, w2)
diff = y_pred - y
loss = tf.reduce_mean(tf.reduce_sum(diff ** 2, axis=1))

grad_w1, grad_w2 = tf.gradients(loss, [w1, w2])

with tf.Session() as sess:
    values = {x: np.random.randn(N, D),
              w1: np.random.randn(D, H),
              w2: np.random.randn(H, D),
              y: np.random.randn(N, D),}
    out = sess.run([loss, grad_w1, grad_w2],
                   feed_dict=values)
    loss_val, grad_w1_val, grad_w2_val = ou
```

Fei-Fei Li & Justin Johnson & Serena Yeung Lecture 8 -4242 April 27, 2017 University

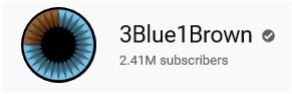
TX2080Ti:
res,

AI Revolution: not just classification segmentation

Object detection, labelling, pose, relationships, complex reasoning

Favourite resource:

1. Youtube: 3blue1brown series 3



Then

2. Youtube: CS231n lecture series Stanford

Progress is incredibly rapid

Youtube: Stanford course CS231n
GPU+vector based high level languages

www.kaggle.com/c/second-annual-data-science-bowl

Competitions Datasets Kernels Discussion Learn ••• kaggle

DATA SCIENCE BOWL

Second Annual Data Science Bowl

Transforming How We Diagnose Heart Disease

$200,000 · 773 teams · 3 years ago

Overview Data Kernels Discussion Leaderboard Rules

Overview

- Description
- Evaluation
- Prizes
- Timeline
- About The Dsb
- Resources
- Deep Learning Tutorial

We all have a heart. Although we often take it for granted, it's our heart that gives us the moments in life to imagine, create, and discover. Yet cardiovascular disease threatens to take away these moments. Each day, 1,500 people in the U.S. alone are diagnosed with heart failure—but together, we can help. We can use data science to transform how we diagnose heart disease. By putting data science to work in the cardiology field, we can empower doctors to help more people live longer lives and spend more time with those that they love.

Declining cardiac function is a key indicator of heart disease. Doctors determine cardiac function by measuring end-systolic and end-diastolic volumes (i.e., the size of one chamber of the heart at the beginning and middle of each heartbeat), which are then used to derive the ejection fraction (EF). EF is the percentage of blood ejected from the left ventricle with each heartbeat. Both the volumes and the ejection fraction are predictive of heart disease. While a number of technologies can measure volumes or EF, Magnetic Resonance Imaging (MRI) is considered the gold standard test to accurately assess the

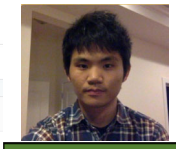
The National Heart, Lung, and Blood Institute (NHLBI) provided the MRI images for this competition. Special thanks to NHLBI Intramural Investigators Dr. Michael Hansen and Dr. Andrew Arai.

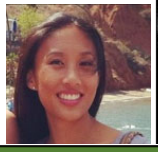
WINNER LICENSE TYPE: Open Source License

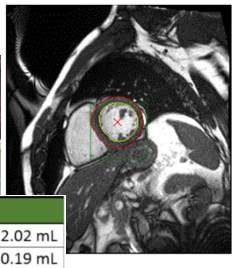
1000 patient volume studies, EF

The total prize pool for this competition is $200,000, distributed as follows:

- 1st place - $125,000
- 2nd place - $50,000
- 3rd place - $25,000







RMS Error		
Tencia_Woshialex	Diastolic	12.02 mL
	Systolic	10.19 mL
	E Fraction(%)	4.88 %

Richard Waters in San Francisco MARCH 30, 2016

Hedge funds + Add to myFT

Hedge fund 'quants' win heart diagnosis challenge

Tencia Lee and Qi Liu formulate algorithm to spot cardiac disease on MRI images

Paper 1

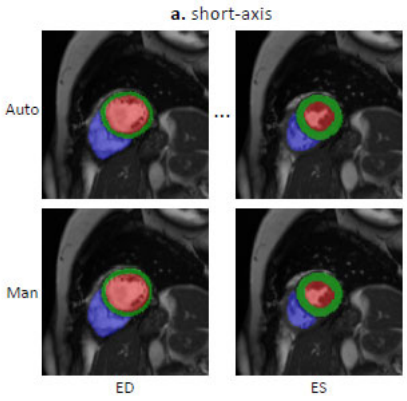
Accepted for publication by Journal of Cardiovascular Magnetic Resonance

RESEARCH

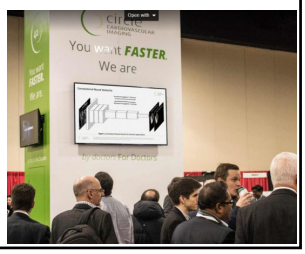
Automated cardiovascular magnetic resonance image analysis with fully convolutional networks

Wenjia Bai[1*], Matthew Sinclair[1], Giacomo Tarroni[1], Ozan Oktay[1], Martin Rajchl[1], Ghislain Vaillant[1], Aaron M. Lee[2], Nay Aung[2], Elena Lukaschuk[3], Mihir M. Sanghvi[2], Filip Zemrak[2], Kenneth Fung[2], Jose Miguel Paiva[2], Valentina Carapella[3], Young Jin Kim[3], Hideaki Suzuki[4], Bernhard Kainz[1], Paul M. Matthews[4], Steffen E. Petersen[2], Stefan K. Piechnik[3], Stefan Neubauer[3], Ben Glocker[1] and Daniel Rueckert[1]

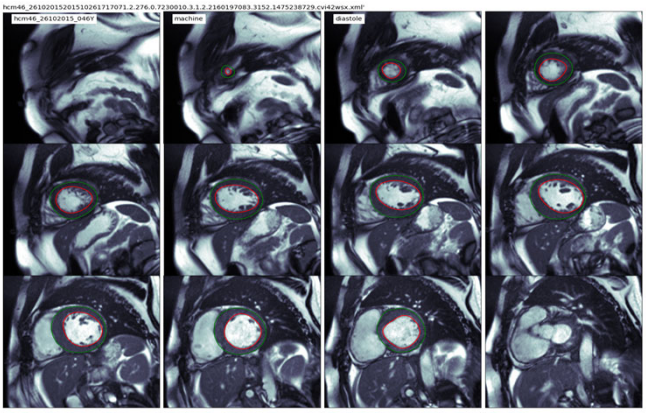
N=5000
Health
Single magnet
Comparison with human contours

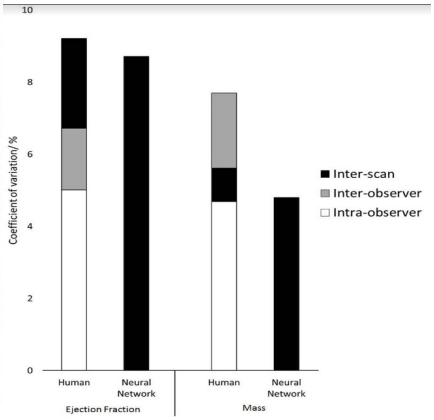


To product – for speed



Paper 2,3,4 – generalise, measure and improve performance

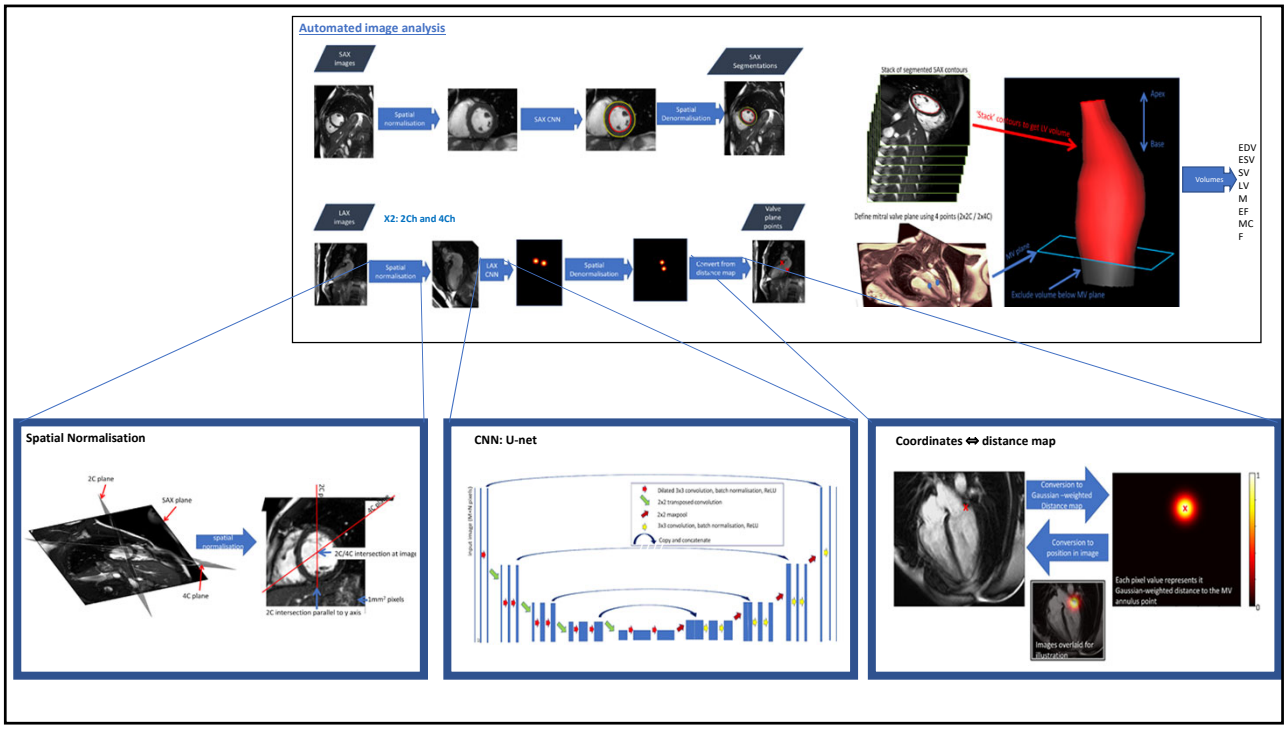


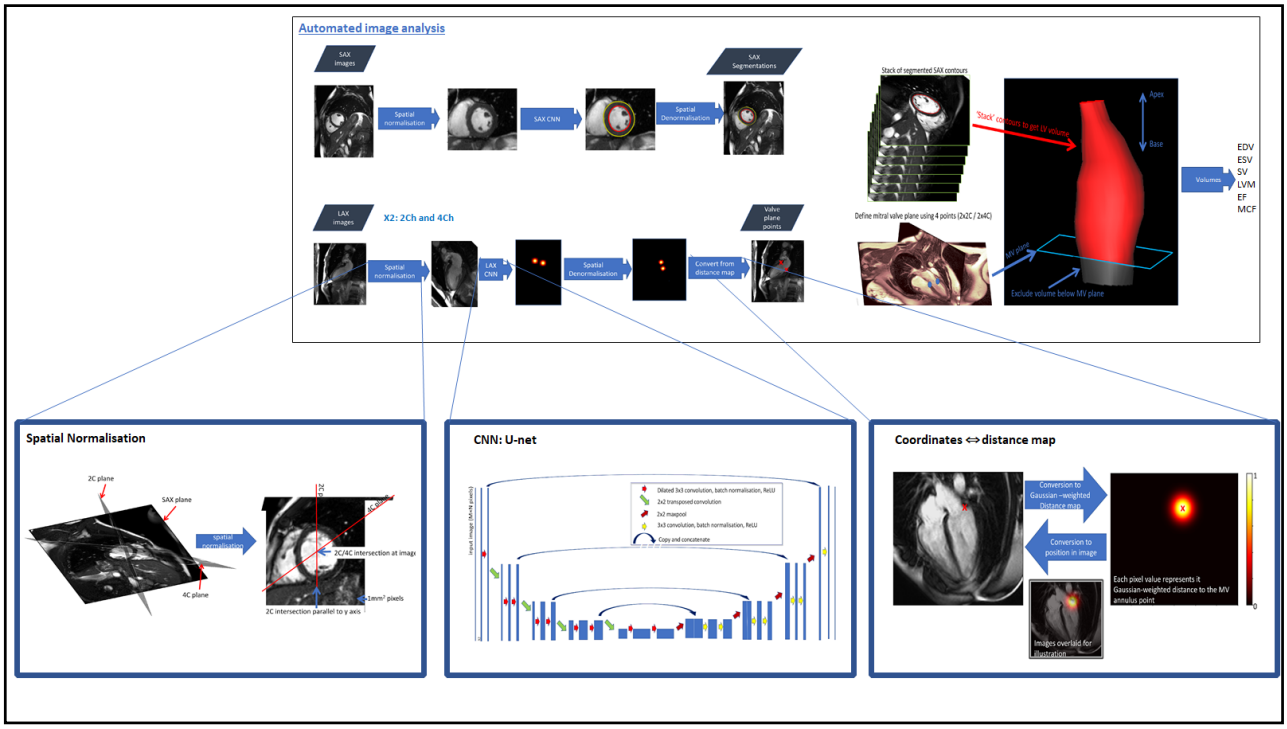


Performance equalling human – any disease

Bhuva A..Manisty C. In press Circ Imaging 2019

Can AI be Superhuman?


Automated image analysis
SAX images
Spatial normalisation
SAX CNN
SAX Segmentations
Spatial Denormalisation
Stack of segmented SAX contours
'Stack' contours to get LV volume
Apex
Base
Volumes
EDV
ESV
SV
LV
M
EF
MC
F
LAX images
X2: 2Ch and 4Ch
LAX CNN
Valve plane points
Convert from distance map
Define mitral valve plane using 4 points (2x2C / 2x4C)
MV plane
Exclude volume below MV plane
Spatial Normalisation
2C plane
SAX plane
4C plane
2C/4C intersection at image
2C intersection parallel to y axis
CNN: U-net
Dilated 3x3 convolution, batch normalisation, ReLU
2x2 transposed convolution
2x2 maxpool
3x3 convolution, batch normalisation, ReLU
Copy and concatenate
Coordinates ⇔ distance map
Conversion to Gaussian -weighted Distance map
Conversion to position in image
Each pixel value represents it Gaussian-weighted distance to the MV annulus point
Images overlaid for illustration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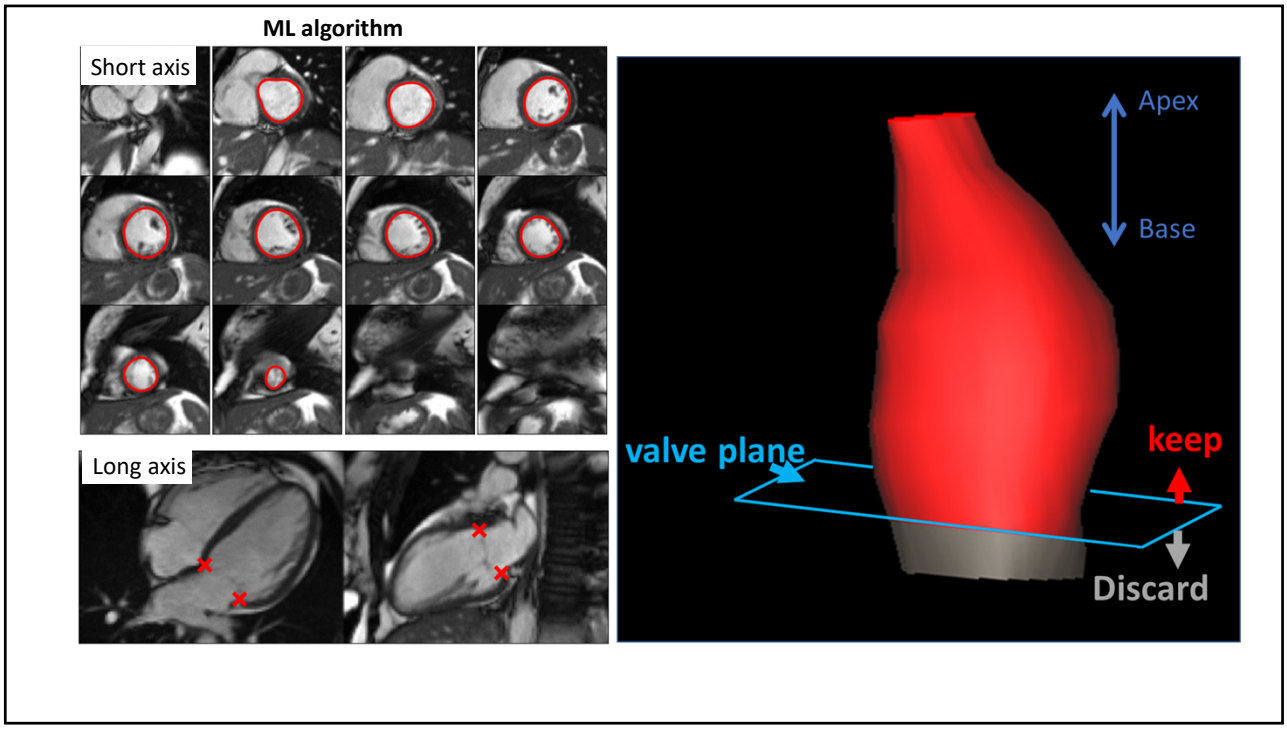
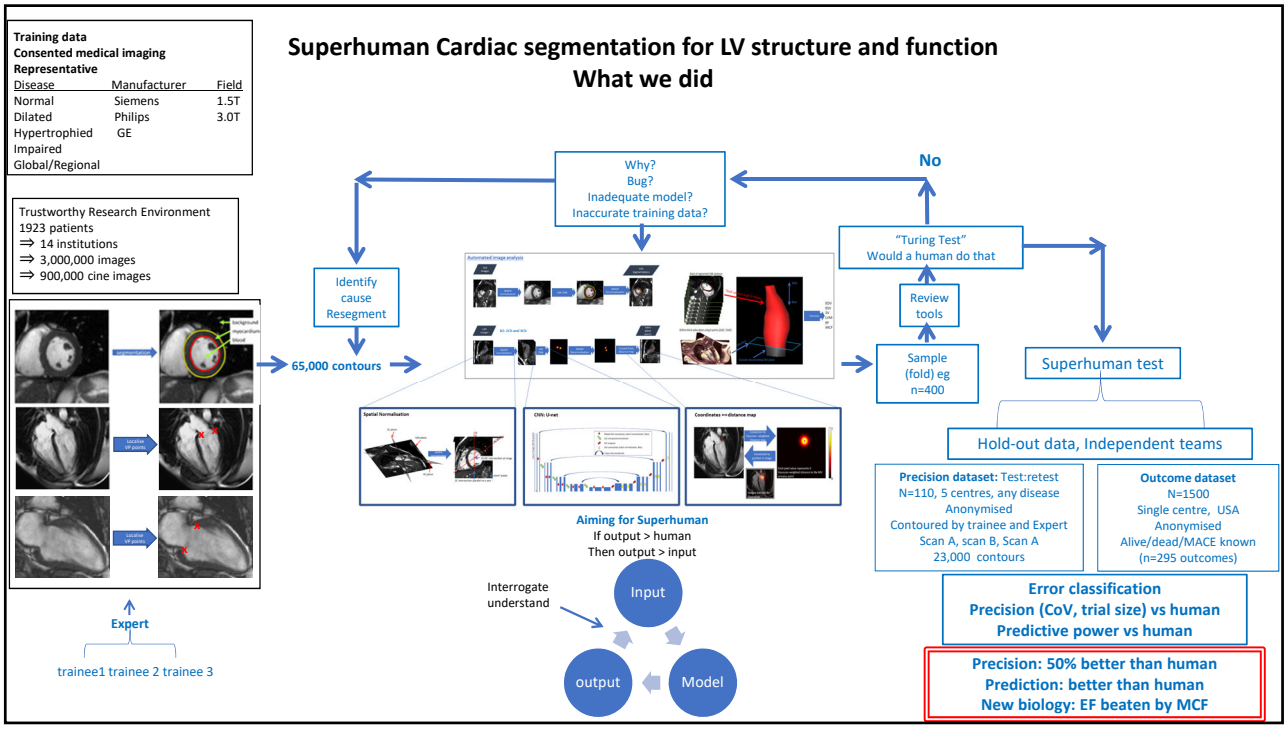
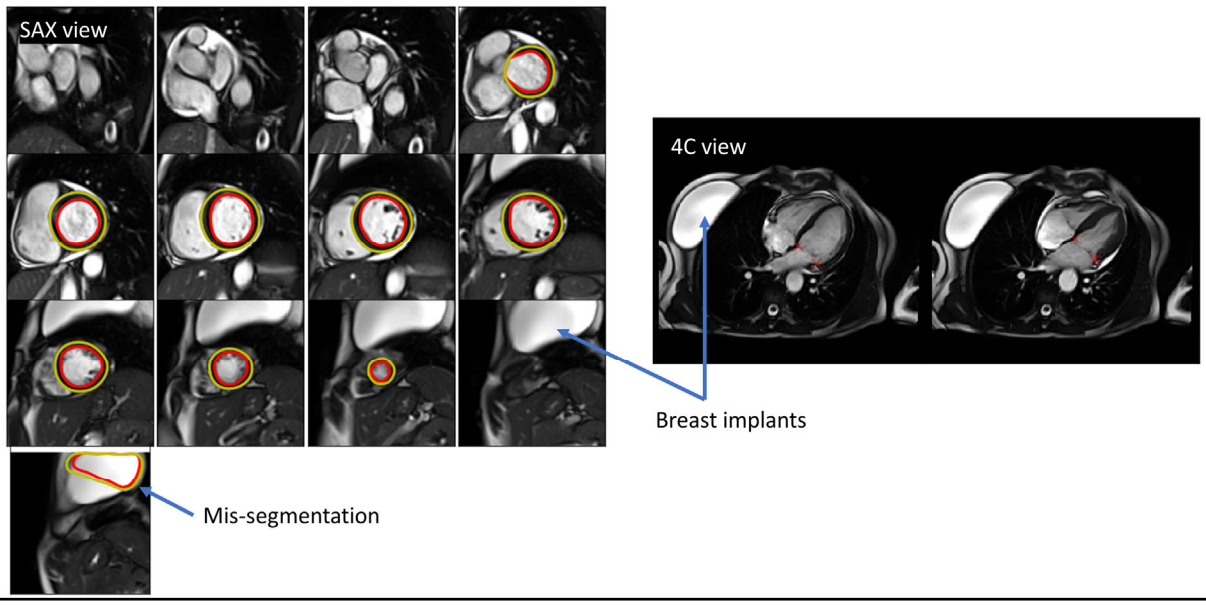
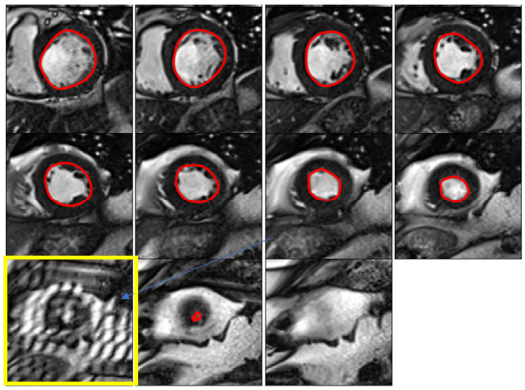
Stack of segmented SAX contours
'Stack' contours to get LV volume
Apex
Base
Volumes
EDV
ESV
SV
LVM
EF
MCF
LAX images
X2: 2Ch and 4Ch
LAX CNN
Valve plane points
Convert from distance map
Define mitral valve plane using 4 points (2x2C / 2x4C)
MV plane
Exclude volume below MV plane
Spatial Normalisation
2C plane
SAX plane
4C plane
2C/4C intersection at image
2C intersection parallel to y axis
CNN: U-net
Dilated 3x3 convolution, batch normalisation, ReLU
2x2 transposed convolution
2x2 maxpool
3x3 convolution, batch normalisation, ReLU
Copy and concatenate
Coordinates ⇔ distance map
Conversion to Gaussian -weighted Distance map
Conversion to position in image
Each pixel value represents it Gaussian-weighted distance to the MV annulus point
Images overlaid for illustration

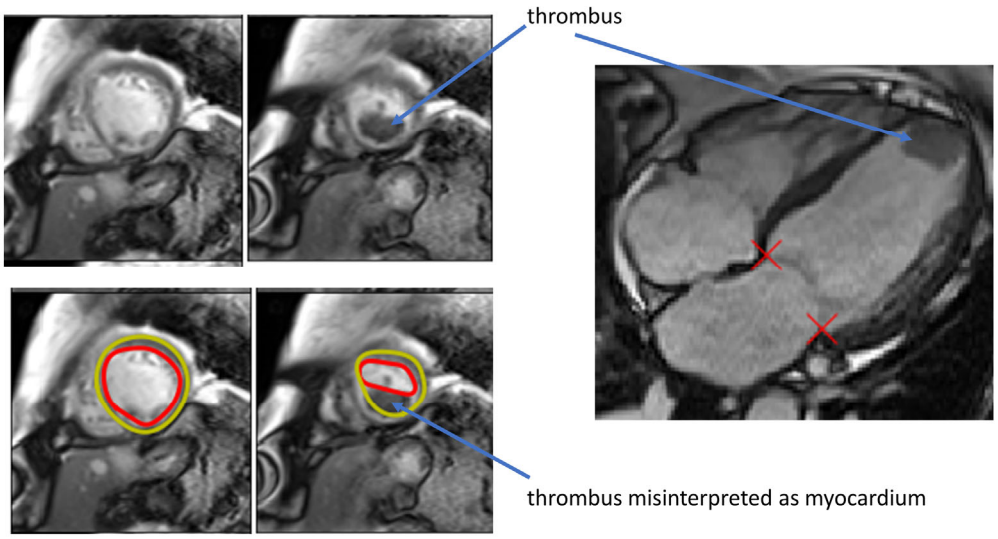

ML algorithm
Short axis
Long axis
Apex
Base
valve plane
keep
Discard


Training data
Consented medical imaging
Representative
Disease
Manufacturer
Field
Normal
Siemens
1.5T
Dilated
Philips
3.0T
Hypertrophied
GE
Impaired
Global/Regional
Trustworthy Research Environment
1923 patients
⇒ 14 institutions
⇒ 3,000,000 images
⇒ 900,000 cine images
Expert
trainee1 trainee 2 trainee 3
65,000 contours
Superhuman Cardiac segmentation for LV structure and function
What we did
Why?
Bug?
Inadequate model?
Inaccurate training data?
No
Identify cause Resegment
"Turing Test"
Would a human do that
Review tools
Sample (fold) eg n=400
Superhuman test
Hold-out data, Independent teams
Precision dataset: Test:retest
N=110, 5 centres, any disease
Anonymised
Contoured by trainee and Expert
Scan A, scan B, Scan A
23,000 contours
Outcome dataset
N=1500
Single centre, USA
Anonymised
Alive/dead/MACE known
(n=295 outcomes)
Aiming for Superhuman
If output > human
Then output > input
Interrogate understand
Input
output
Model
Error classification
Precision (CoV, trial size) vs human
Predictive power vs human
Precision: 50% better than human
Prediction: better than human
New biology: EF beaten by MCF

Latest work: Almost never wrong







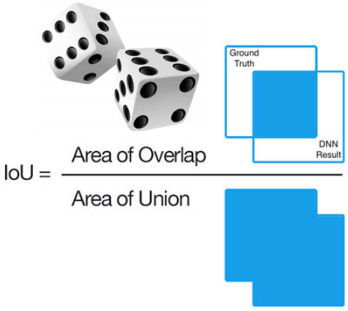
How do you Evaluate Model Performance?

- Measure agreement of model vs human
  - e.g. DICE metric, Haussdorf distance

But… are humans always right?

Hold-out validation datasets

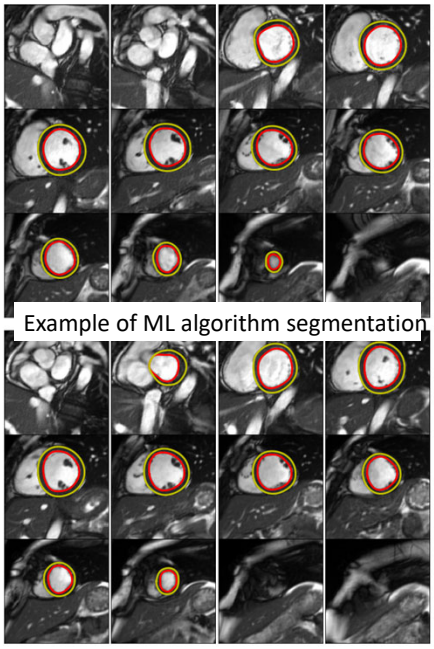
- 1. Precision
- 2. Prediction clinical outcomes



Precision

- 110 patients
- Multi-institution
- Multiple pathologies
- Scanned
  - then scanned again
- Expert vs machine

Scan
EF 56%



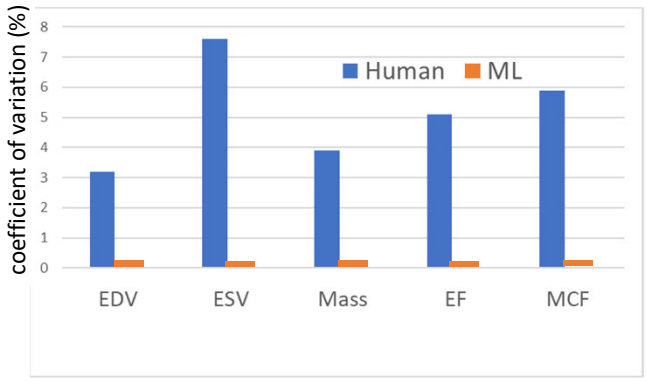
Example of ML algorithm segmentation

Rescan
EF 58%

https://thevolumesresource.com

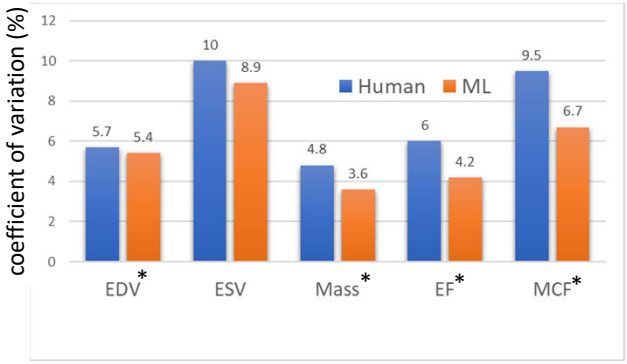
Precision: Intra-observer Reliability

Exact same images twice
ML algorithm has no variatic
same image ⇒ same answe



https://thevolumesresource.com

Precision: Scan Re-scan Repeatability



Translates to clinical trials:

- to detect 3% change in EF
  ⇒ need 40% fewer subjects

https://thevolumesresource.com

Predicting Clinical Outcome

- 1,277 patients
- Clinical service
- CMR
- Clinical outcomes
  - Death
  - Hospital admission with heart failure
- 5.5 year median follow-up
  - 29% event rate

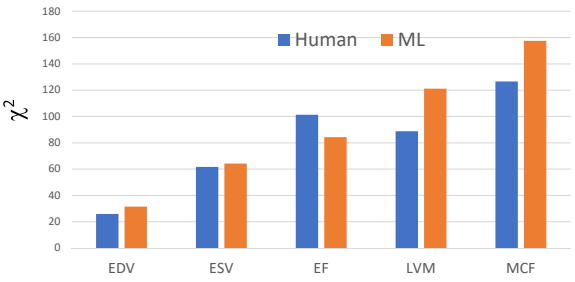
Predciting Clinical Outcome

- Cox regression analysis
  - LV metrics *vs* outcome
  - $\chi^2 \propto$ strength of association

Multivariate

Human expert	ML algorithm	
χ^2 = 167	χ^2 = 191	p<0.01

Univariate

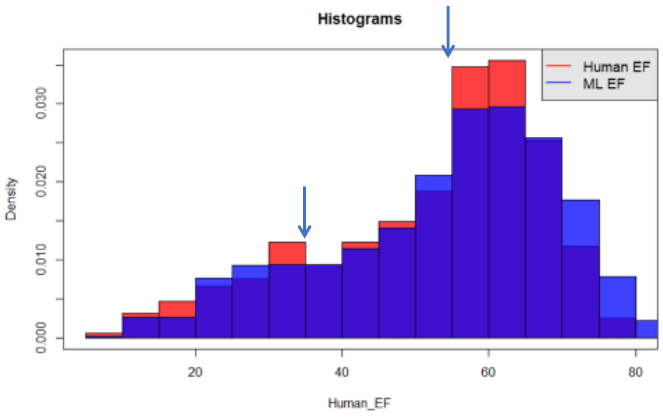


$$myocardial\ contraction\ fraction\ (MCF) = \frac{stroke\ volume}{myocardial\ volume}$$

AI: a mirror to see ourselves

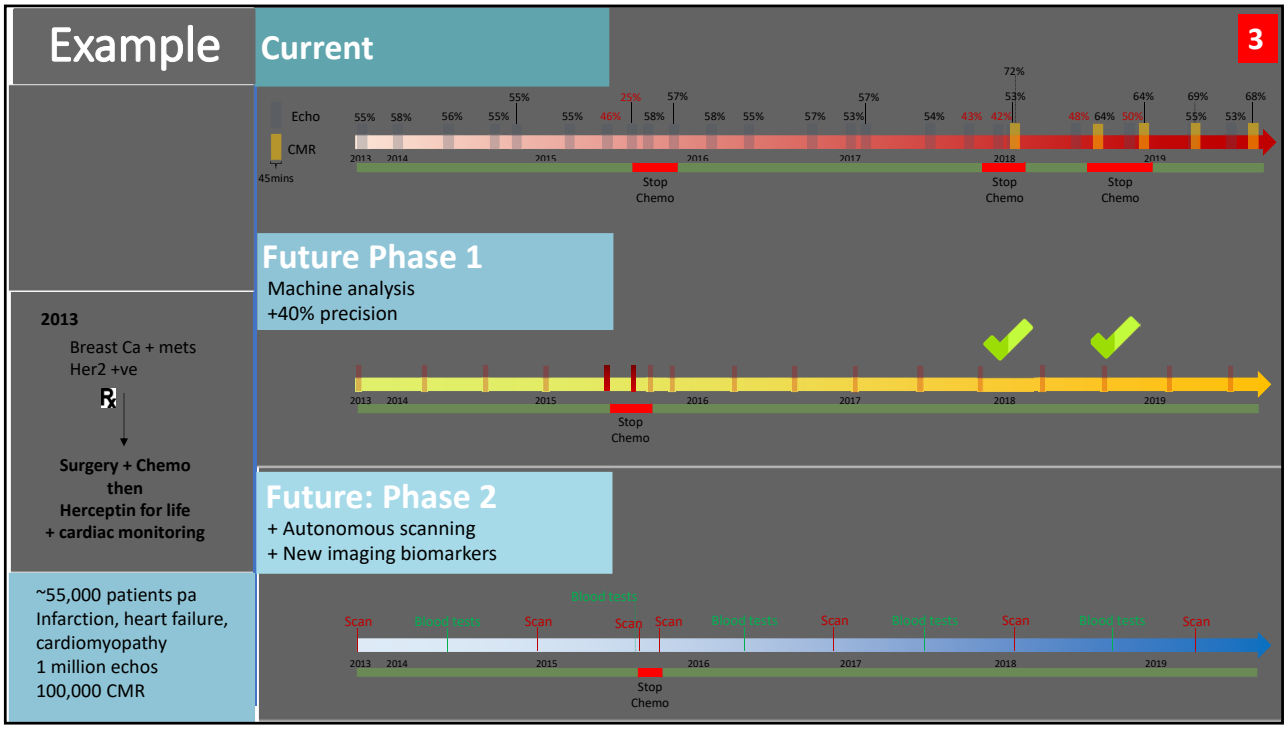
AI approach:

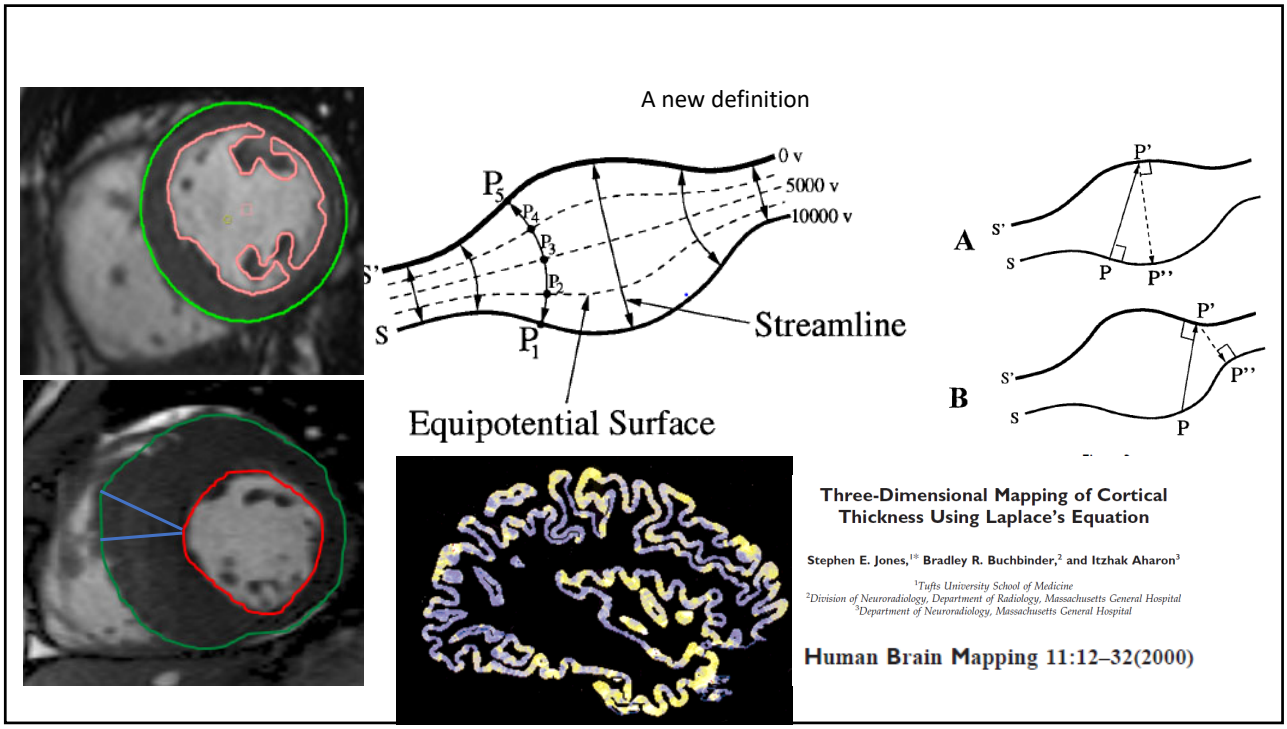
- more precision, all parameters
- Prognosis better prediction for overall model
  - MCF beats EF
- one outlyer: human EF beats machir



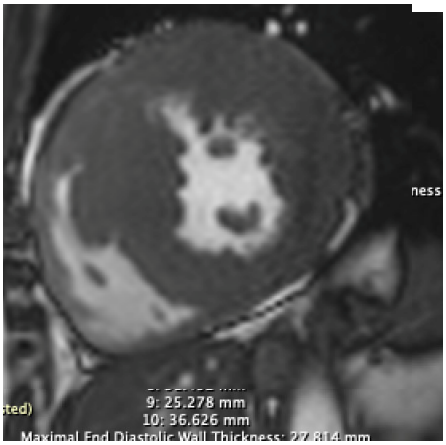
Humans primary task is are not measuring EF

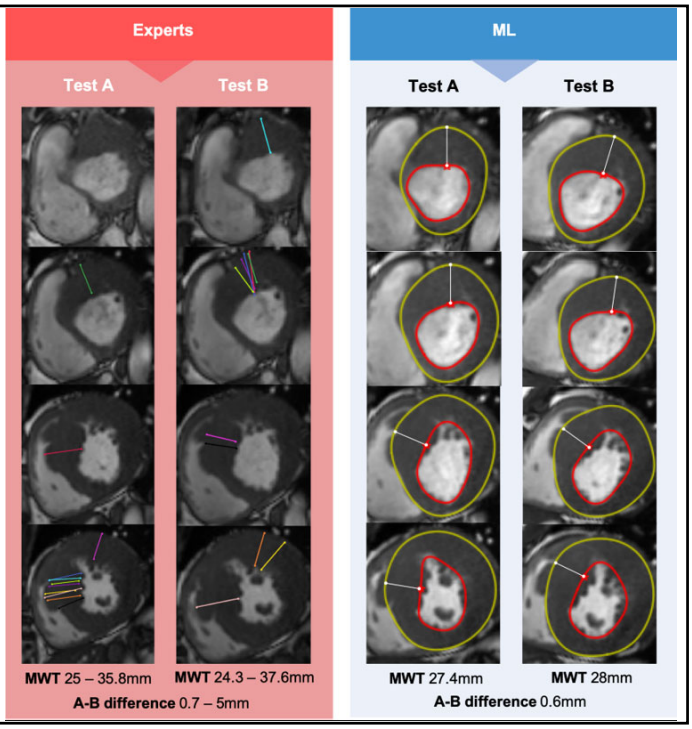
- a service
- integration of datasources
- trying to influence decision making


Example
Current
3
Echo
CMR
45mins
Stop Chemo
Future Phase 1
Machine analysis
+40% precision
2013
Breast Ca + mets
Her2 +ve
Surgery + Chemo
then
Herceptin for life
+ cardiac monitoring
Future: Phase 2
+ Autonomous scanning
+ New imaging biomarkers
Scan
Blood tests
~55,000 patients pa
Infarction, heart failure, cardiomyopathy
1 million echos
100,000 CMR


A new definition
0 v
5000 v
10000 v
Streamline
Equipotential Surface
A
B
Three-Dimensional Mapping of Cortical Thickness Using Laplace's Equation
Stephen E. Jones, Bradley R. Buchbinder, and Itzhak Aharon
Human Brain Mapping 11:12–32(2000)

Wall thickness – preliminary results





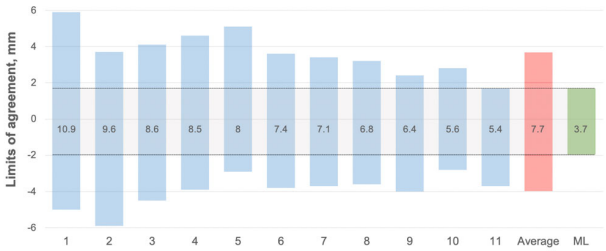
Cardiac Wall Thickness

Measuring heart maximum wall thickness
12 credible international experts
- 4 continents

in60 HCM patients
- scanned twice
- 5 different scanners
- multiple institutions

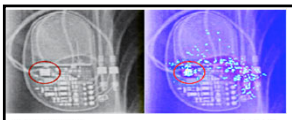
AI beats not just one human, but all humans

Figure 4. Test:retest Bland-Altman limits of agreement (LOA, mean bias ± 1.96 SD) for each expert (1 – 11, blue) and machine learning (ML, green). The average LOA for all experts is shown in red. The difference between the upper and lower LOAs is displayed in each bar. The LOA for ML was less than half of the average expert LOA.



Joao Augusto pending submission

Initial success:



Cardiac Rhythm Device Identification Using Neural Networks

RESEARCH

Automated cardiovascular magnetic res
image analysis with fully convolutional

Wenjia Bai[1*], Matthew Sinclair[1], Giacomo Tarroni[1], Ozan Oktay[1], Martin Rajchl[1], Ghislain Vaillant[1], Aaron M. Lee[2], Nay Aung[2], Elena Lukaschuk[3], Mihir M. Sanghvi[2], Filip Zemrak[2], Kenneth Bernhard Kainz[1], Ben Glocker[1] and

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

A Multicenter, Scan-Rescan, Human and Machine Learning CMR Study to Test Generalizability and Precision in Imaging Biomarker Analysis

See Editorial by Colletti

Improving the generalizability of convolutional neural network-based segmentation on CMR images

Chen Chen[1,2]†, Wenjia Bai[2,3], Rhodri H. Davies[4], Anish N. Bhuva[4,5], Charlotte Manisty[4,5], James C. Moon[4,5], Nay Aung[3,6], Aaron M.Lee[6], Mihir M. Sanghvi[3,6]*, Kenneth Fung[3,6], Jose Miguel Paiva[6], Steffen E. Petersen[3,6], Elena Lukaschuk[7], Stefan K. Piechnik[7], Stefan Neubauer[7], and Daniel Rueckert[1]

[1]Biomedical Image Analysis Group, Department of Computing, Imperial College London, London, UK
[2]Data Science Institute, Imperial College London, London, UK
[3]Department of Medicine, Imperial College London, London, UK
[4]Institutes for Cardiovascular Science, University College London, London, UK
[5]Department of Cardiovascular Imaging, Barts Heart Centre, St Bartholomew's Hospital, London, UK
[6]NIHR Biomedical Research Centre at Barts, Queen Mary University of London, London, UK
[7]NIHR BRC Oxford, Division of Cardiovascular Medicine, Radcliffe, Department of Medicine, University of Oxford, Oxford, UK.

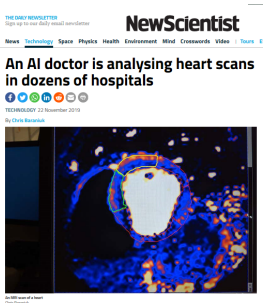
Deep Residual Grappa (DeepGrappa): A General Purpose Self-calibrated AI based MR Reconstruction

Hui Xue[1], Jaime Moon[2], and Peter Kellman[1]
[1]NHLBI, NIH, Bethesda, MD, United States, [2]Barts Heart Centre, Barts Health NHS Trust, London, United Kingdom

Mol Cell Proteomics Papers in Press. Published on June 26, 2019 as Manuscript RA119.001586

Identification of a Multiplex Biomarker Panel for Hypertrophic Cardiomyopathy using Quantitative Proteomics and Machine Learning

Authors: Gabriella Captur[1,2†] MD PhD MRCP MSc, Wendy E Heywood[2,4†] PhD BSc, Caroline Coats[3,5†] MBBS MRCP PhD, Stefania Rosmini[3] MD, Vimal Patel[5] MBBS MD MRCP PhD, Luis R Lopes[2,5] MD PhD, Richard Collis[5] MBBS MRCP PhD, Nina Patel[2,4] BSc, Petros Syrris[5] PhD, Paul Bassett[6] MSc, Ben O'Brien[7,8] MD PhD (Habil) FRCA FFICM MHBA, James C Moon[2,5] MD MBBS MRCP, Perry M Elliott[2,5†] MBBS MD FRCP FESC FACC, Kevin Mills[1,4*†] BSc PhD



NewScientist

An AI doctor is analysing heart scans in dozens of hospitals

TECHNOLOGY 22 November 2019

By Chris Baraniuk

BACKGROUND: Automated analysis of ca using machine learning (ML) has great poti by poor generalizability. Comparison is trac a reference, ignoring inherent human inter ensuring that ML cannot demonstrate supe (scan:rescan reproducibility) addresses this. and humans using a multicenter, multi-dise magnetic resonance data set

Automated Inline Analysis of Myocardial Perfusion MRI with Deep Learning

Hui Xue[1], Rhodri Davies[2], Louis Brown[3], Kristopher D Knott[2], Tushar Kotecha[4], Marianna Fontana[4], Sven Plein[3], James C Moon[2], Peter Kellman[1]

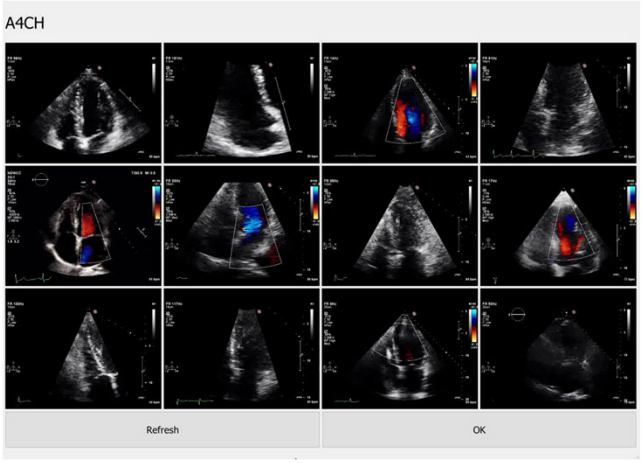
1. National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA
2. Barts Heart Centre, Barts Health NHS Trust, London, UK
3. Multidisciplinary Cardiovascular Research Centre (MCRC) & Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds
4. National Amyloidosis Centre, Royal Free Hospital, London, UK

Automated Detection of Left Ventricle in Arterial Input Function Images for Inline Perfusion Mapping using Deep Learning: A study of 15,000 Patients

Hui Xue[1], Ethan Tseng[1], Kristopher D Knott[2], Tushar Kotecha[3], Louise Brown[4], Sven Plein[4], Marianna Fontana[3], James C Moon[2], Peter Kellman[1]

1. National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA
2. Barts Heart Centre, London, UK
3. National Amyloidosis Centre, Royal Free Hospital, London, UK
4. Department of Biomedical Imaging Science, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK

Fast feedback tools for AI
Expert imagers needed – capturing what you do
Democratising process



Here fast training "which view is 4ch"

Francis DP group, Imperial

AI in imaging will cascade benefit through cardiology

Solutions generalise

Faster

More accurate, more precise

Humans stop mundane per patient analysis processes

Instead 2 things:
a) Quality control and oversight
b) Training: not just junior doctors, but networks

Things no-one tells you: engineering:clinicial
1. Medicine is about unique outliers not big data: I want outlyers not big data
2. Missing data is missing for a reason
3. Your language is not my language (precision?)
4. Doctors are not doing what they say they are doing

AI penetration of healthcare currently low
But this is changing:
Imaging: All our research now has AI in it

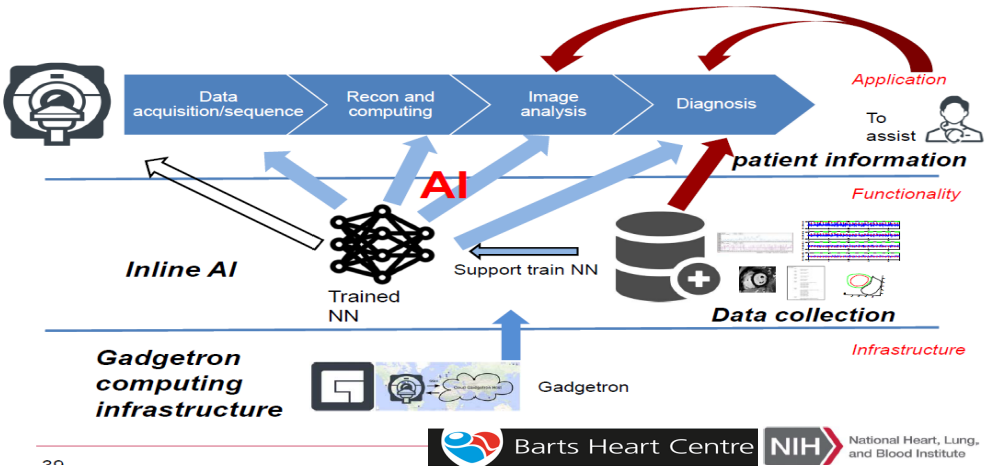


Image acquisition

Reconstruction

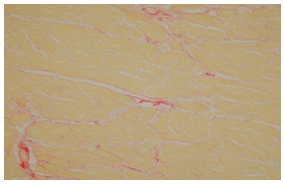
Analysis

Interpretation

Linking to other data

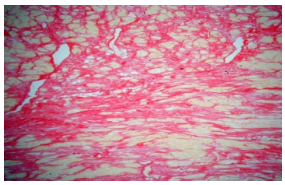
Peter Kellman Hui Xue, Rhodri Davies. NIH: Barts

Myocardial biology – processes

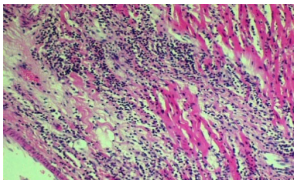


normal

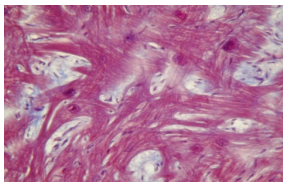
infarction



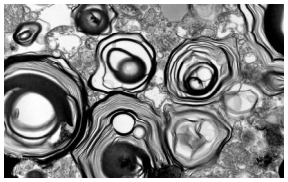
diffuse fibrosis



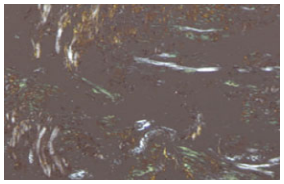
myocarditis



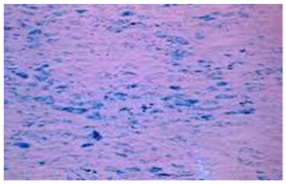
disarray



Fabrys



amyloid



iron

Dozens more types. Different stains, different cameras

Speakers own cases

Framework for Pathological processes

Primary Processes

Direct Myocardial Storage
- myocytes (subtypes)
- endothelial cells
- fibroblasts, smooth muscle, immune

Remote disease
- autonomic
- vascular
- renal

Other effects
- non-storage toxic effect (systemic/paracrine)

→

Secondary Processes

Key pathways
- "Buffering"
- hypertrophy
- cell death
- inflammation
- fibrosis
- 100x other pathways

Impact classification
- adaptive/maladaptive
- reversible/irreversible
- druggable/non druggable

Modifiers
- Age
- Sex
- Multimorbidity
- Therapy

→

Primary Consequences

Mechanical
- Gain/loss of function
- Adaptability
- Efficiency

Electrical
- Space - Conduction system
- Time – de-/re-polarisation

Secondary Consequences

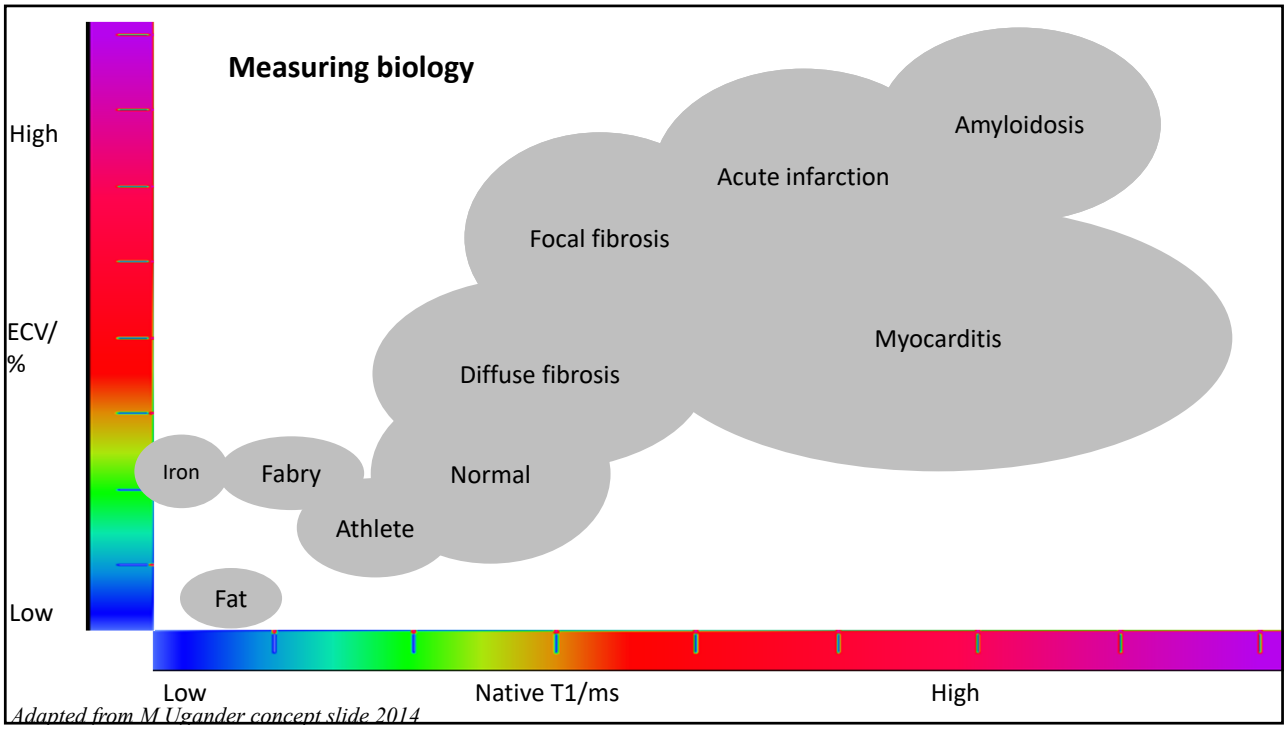
Symptoms
- Fatigue
- Exercise limitation
- Chest pain

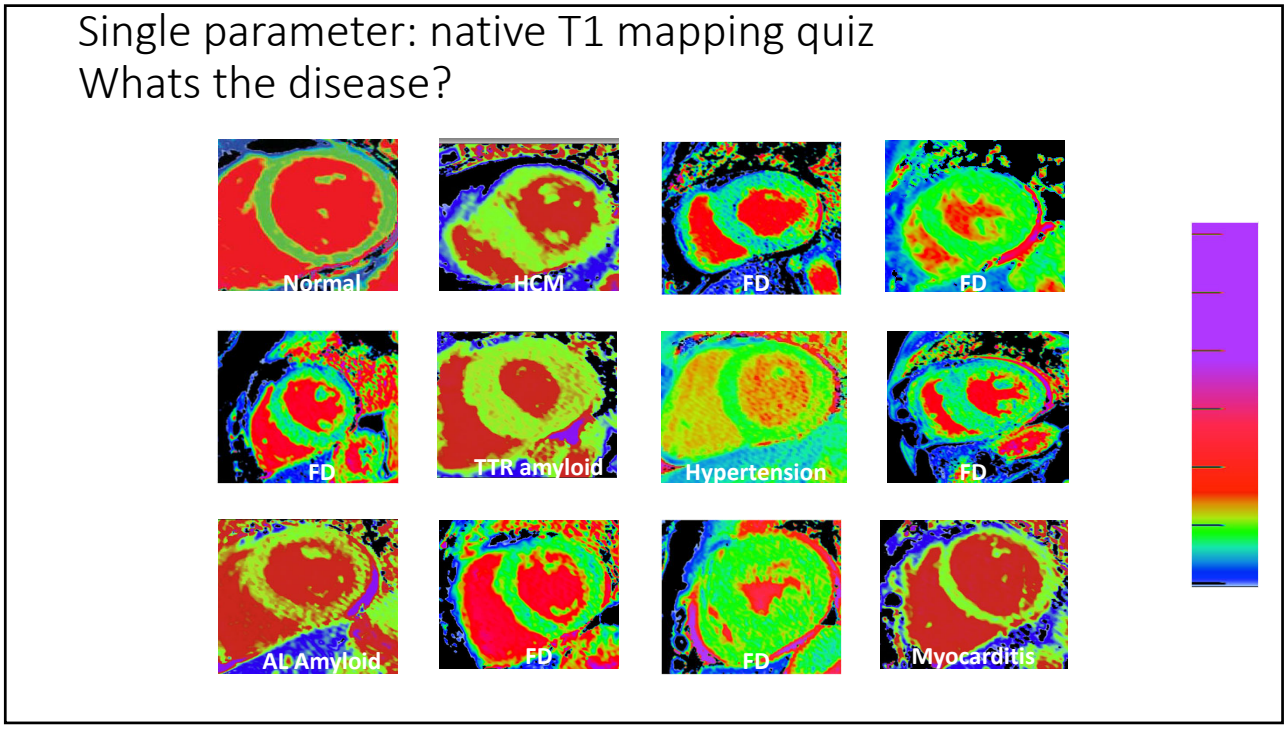
Risk

Heart failure

Sudden death

Here Fabrys


Measuring biology
High
ECV/
%
Low
Amyloidosis
Acute infarction
Focal fibrosis
Myocarditis
Diffuse fibrosis
Iron
Fabry
Normal
Athlete
Fat
Low
Native T1/ms
High
Adapted from M Ugander concept slide 2014


Single parameter: native T1 mapping quiz
Whats the disease?
Normal
HCM
FD
FD
FD
TTR amyloid
Hypertension
FD
AL Amyloid
FD
FD
Myocarditis

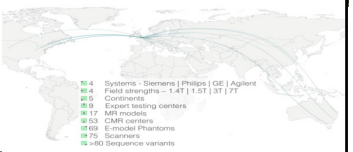
SERIAL T1 MULTI-CENTER DATA – 1.5T

1.5 T Longitudinal multi-site, multi-vendor T1 mapping T1MES data*

Temp-adjusted (21°C) CoV/tube for 1.5 T T1 mapping sequences according to vendor/scheme/WIP#

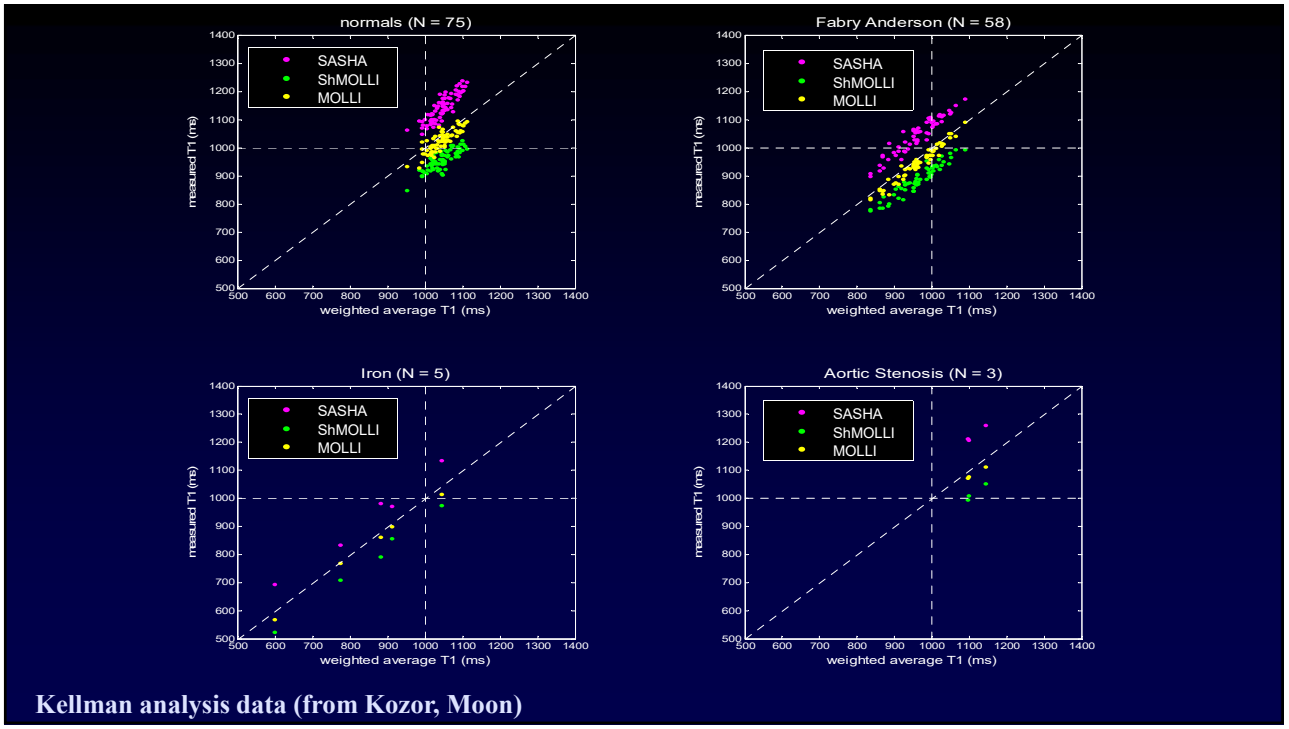
Vendor | sequence ranking order by CoV (1.5 T)

SIEMENS	MOLLI 5s(3s)3s [448B]	0.27	BEST CoV
PHILIPS	MOLLI 3s(3s)5s	0.54	
SIEMENS	SASHA	0.56	
SIEMENS	SHMOLLI [1041B]	0.64	
PHILIPS	SASHA	0.92	
PHILIPS	ShMOLLI	1.04	
GE	MOLLI 5b(3s)5b	1.28	
GE	SMART	3.00	

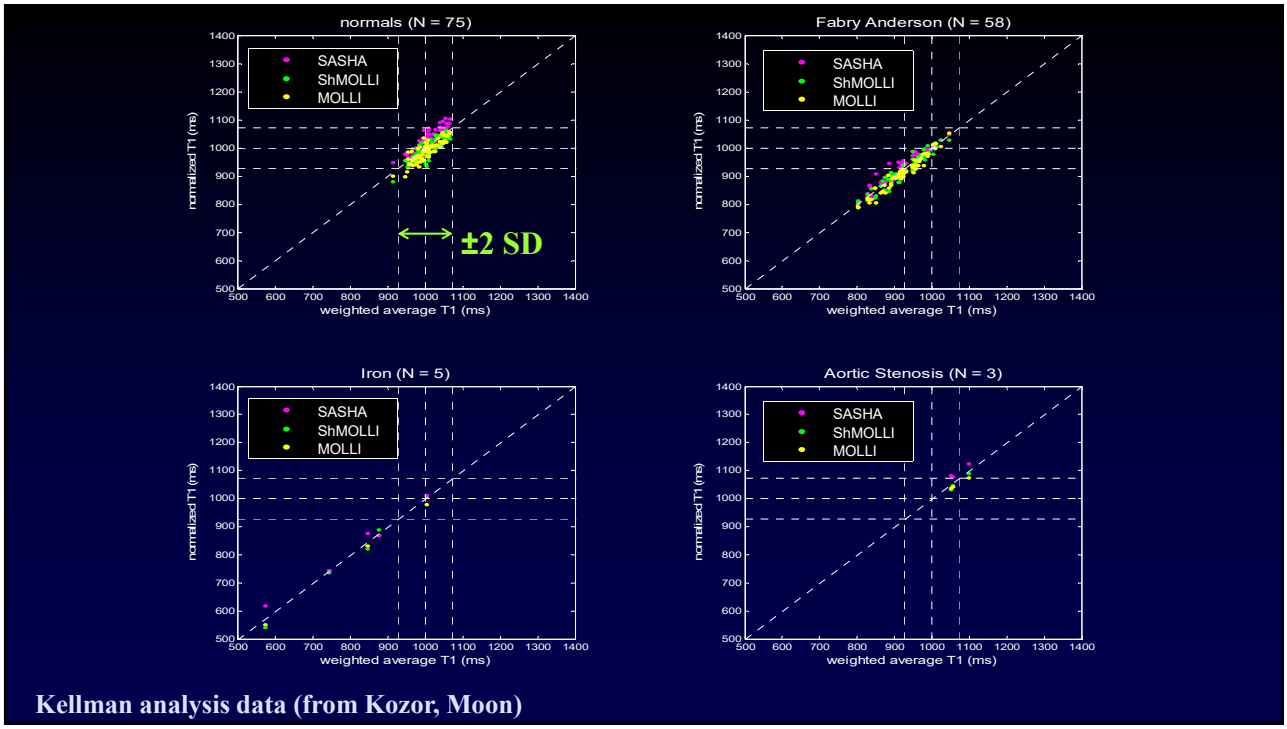


*Captur G, Moon JC + 50 others et al. in review #4

MRC | UCL

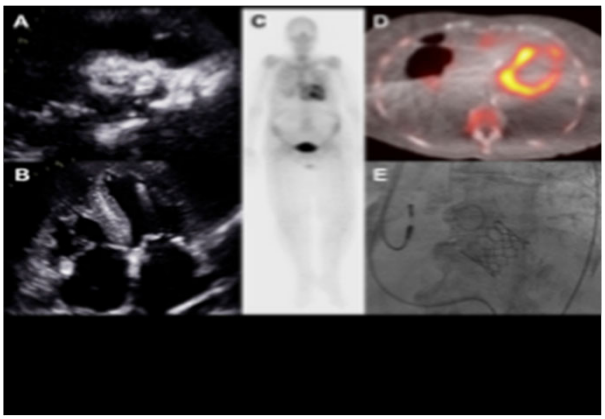


Kellman analysis data (from Kozor, Moon)



Kellman analysis data (from Kozor, Moon)

Not just CMR, not just mapping



Amyloid in 1 in 7 TAVR patients

JACC 2018
Castano EHJ 2017

ASNC

EXPERT CONSENSUS RECOMMENDATIONS

ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI EXPERT CONSENSUS RECOMMENDATIONS FOR MULTIMODALITY IMAGING IN CARDIAC AMYLOIDOSIS: PART 1 OF 2—EVIDENCE BASE AND STANDARDIZED METHODS OF IMAGING

ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI EXPERT CONSENSUS RECOMMENDATIONS FOR MULTIMODALITY IMAGING IN CARDIAC AMYLOIDOSIS: PART 2 OF 2—DIAGNOSTIC CRITERIA AND APPROPRIATE UTILIZATION

Multimodality approaches, published yesterday
https://doi.org/10.1007/s12350-019-01760-6

AS and AS-amyloid – a program

Single centre
Multicentre
Registry
Outcome
Therapy

Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis.
Treibel TA, Kozor R, Schofield R, Benedetti G, Fontana M, Bhuva AN, Sheikh A, López B, González A, Manisty C, Lloyd G, Kellman P, Díez J, **Moon JC**.
J Am Coll Cardiol. 2018 Feb 27;71(8):860-871. doi: 10.1016/j.jacc.2017.12.035.

Prevalence of Cardiac Amyloidosis in Patients Referred for Transcatheter Aortic Valve Replacement.
Scully PR, **Treibel** TA, Fontana M, Lloyd G, Mullen M, Pugliese F, Hartman N, Hawkins PN, Menezes LJ, **Moon JC**.
J Am Coll Cardiol. 2018 Jan 30;71(4):463-464. doi: 10.1016/j.jacc.2017.11.037. No abstract available.

Reappraising myocardial fibrosis in severe aortic stenosis: an invasive and non-invasive study in 133 patients.
Treibel TA, López B, González A, Menacho K, Schofield RS, Ravassa S, Fontana M, White SK, DiSalvo C, Roberts N, Ashworth MT, Díez J, **Moon JC**.
Eur Heart J. 2018 Feb 21;39(8):699-709. doi: 10.1093/eurheartj/ehx353.

Prevalence and Outcome of AS-Amyloid in Patients referred for TAVI
Paul R Scully[1,2], Kush P Patel[1,2], Thomas A Treibel[1,2], George D Thornton[1], Rebecca K Hughes[1,2], Sucharitha Chadalavada[1], Neil Hartman[3], Marianna Fontana[4], Francesca Pugliese[1,5,6], Nik Sabharwal[7], James D Newton[7], Andrew Kelion[7], Muhiddin Ozkor[1], Simon Kennon[1], Michael Mullen[1], Guy Lloyd[1,2,5], Leon J Menezes[1,8,9], Philip N Hawkins[4], James C Moon[1,2]
Accepted, EHJ

AS-amyloid–Dual pathology or novel disease?
A multimodality, multi-cohort assessment
Kush P Patel[1,2], Paul R Scully[1,2], Thomas A Treibel[2], George Joy[2], George Thornton[2], Rebecca Hughes[1,2], Suzanne Williams[3], Therese Tillin[3], Gabriella Captur[1,3], Liza Chako[4], Andrew Kelion[5], Nikant Sabharwal[5], Jim Newton[5], Simon Kennon[2], Mick Ozkor[2], Michael J Mullen[2], Philip Hawkins[4], Julian Gillmore[4], Leon Menezes[2], Francesca Pugliese[2,6], Alun Hughes[3], Marianna Fontana[4],Guy Lloyd[2], James C Moon[1,2]
Submitted Circulation

Tom Treibel

Joal Cavalcante

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 3, 2020

Extracellular Myocardial Volume in Patients With Aortic Stenosis

Russell J. Everett, MD, PhD,[a] Thomas A. Treibel, MD, PhD,[b] Miho Fukui, MD,[c] Heesun Lee, MD,[d] Marzia Rigolli, MD, DPhil,[e] Anvesha Singh, MD, PhD,[f] Petra Bijsterveld, MA,[g] Lionel Tastet, MSc,[h] Tarique Al Musa, MD,[g] Laura Dobson, MD,[g] Calvin Chin, MD, PhD,[i] Gabriella Captur, MD, PhD,[j] Sang Yong Om, MD,[k] Stephanie Wiesemann, MD,[l] Vanessa M. Ferreira, MD, DPhil,[e] Stefan K. Piechnik, PhD,[e] Jeanette Schulz-Menger, MD,[l] Erik B. Schelbert, MD,[c] Marie-Annick Clavel, DVM, PhD,[h] David E. Newby, MD, PhD,[g] Saul G. Myerson, MD,[e] Phillipe Pibarot, DVM, PhD,[h] Sahmin Lee, MD,[k] João L. Cavalcante, MD,[c] Seung-Pyo Lee, MD, PhD,[d] Gerry P. McCann, MD,[f] John P. Greenwood, MD, PhD,[g] James C. Moon, MD,[b] Marc R. Dweck, MD, PhD[g]

ESC European Society of Cardiology — European Heart Journal (2020) 0, 1–10 doi:10.1093/eurheartj/ehz905 — CLINICAL RESEARCH Heart failure/cardiomyopathy

Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis

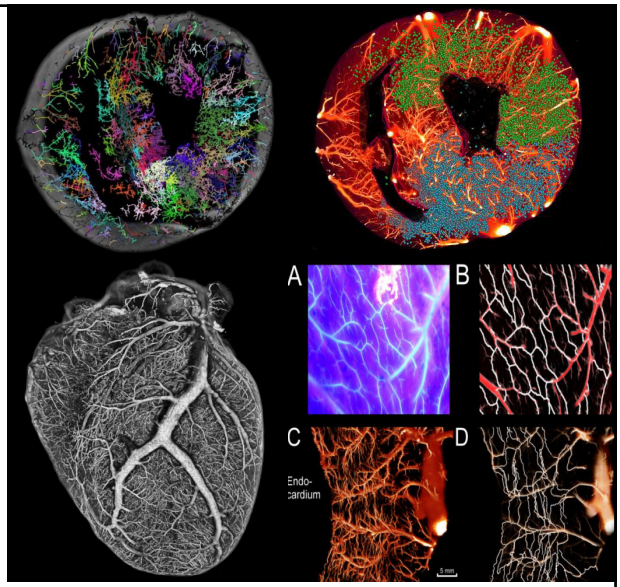
Liza Chacko[1†], Raffaele Martone[1,2†], Francesco Bandera[3,4], Thirusha Lane[1], Ana Martinez-Naharro[1], Michele Boldrini[1], Tamer Rezk[1], Carol Whelan[1], Cristina Quarta[1], Dorota Rowczenio[1], Janet A. Gilbertson[1], Tanakal Wongwarawipat[1], Helen Lachmann[1], Ashutosh Wechalekar[1], Sajitha Sachchithanantham[1], Shameem Mahmood[1], Rossella Marcucci[5], Daniel Knight[1], David Hutt[1], James Moon[6,7], Aviva Petrie[8], Francesco Cappelli[2], Marco Guazzi[3,4], Philip N. Hawkins[1], Julian D. Gillmore[1‡], and Marianna Fontana[1*‡]

Circulation

ORIGINAL RESEARCH ARTICLE

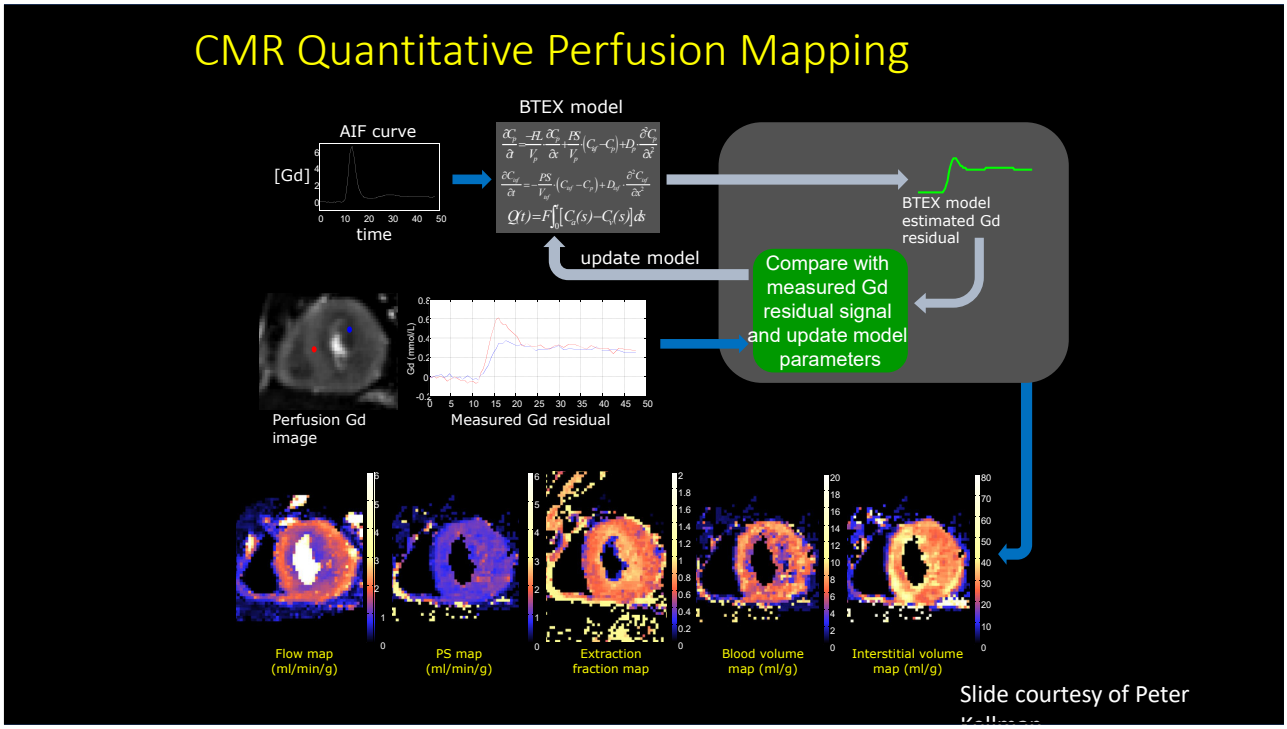
Myocardial Scar and Mortality in Severe Aortic Stenosis
Data From the BSCMR Valve Consortium

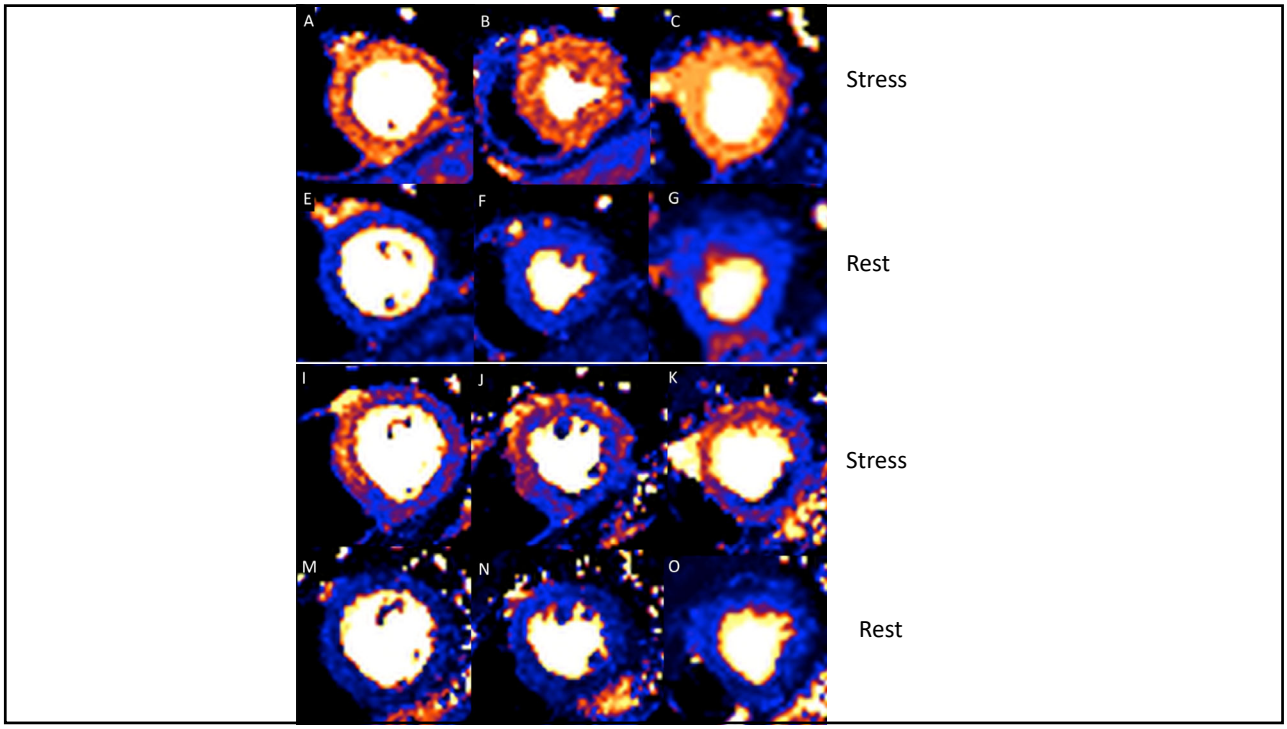
Sex differences in left ventricular remodelling, myocardial fibrosis and mortality after aortic valve replacement.
Singh A, Musa TA, **Treibel** TA, Vassiliou VS, Captur G, Chin C, Dobson LE, Pica S, Loudon M, Malley T, Rigolli M, Foley JRJ, Bijsterveld P, Law GR, Dweck MR, Myerson SG, Prasad SK, **Moon JC**, Greenwood JP, McCann GP.
Heart. 2019 Dec;105(23):1818-1824. doi: 10.1136/heartjnl-2019-314987. Epub 2019 Aug 29.



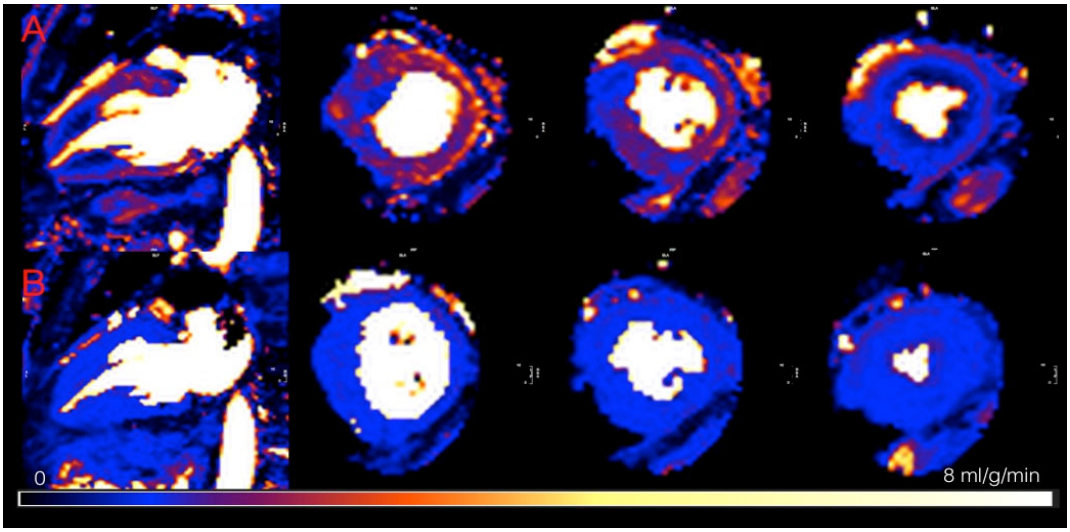
Coronary Circulation and Microcirculation

Maria Siebes, PhD
Dept. of Biomedical Engineering & Physics


CMR Quantitative Perfusion Mapping
BTEX model
AIF curve
[Gd]
time
update model
BTEX model estimated Gd residual
Compare with measured Gd residual signal and update model parameters
Perfusion Gd image
Measured Gd residual
Flow map (ml/min/g)
PS map (ml/min/g)
Extraction fraction map
Blood volume map (ml/g)
Interstitial volume map (ml/g)
Slide courtesy of Peter

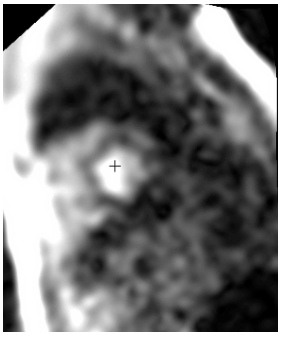

A
B
C
Stress
E
F
G
Rest
I
J
K
Stress
M
N
O
Rest

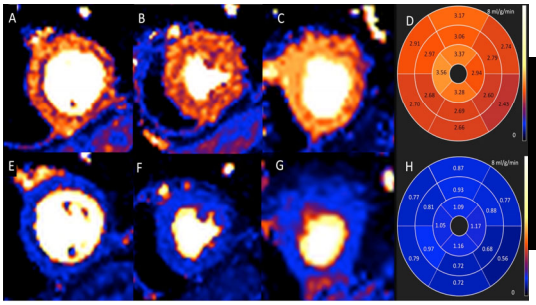
Hypertrophic cardiomyopathy - Apical



Stress

Rest





	Gadgetron Report
Stress HR	71
Pre-stress HR	102
HR increase	-30.0 %
AIF peak [Gd]	1.8 mmol/L
AIF first pass FWHM	11.8 sec
Respiratory	Heavy
WARNING !	Slow AIF detected

AI feature extraction

AI segmentation

technical reporting

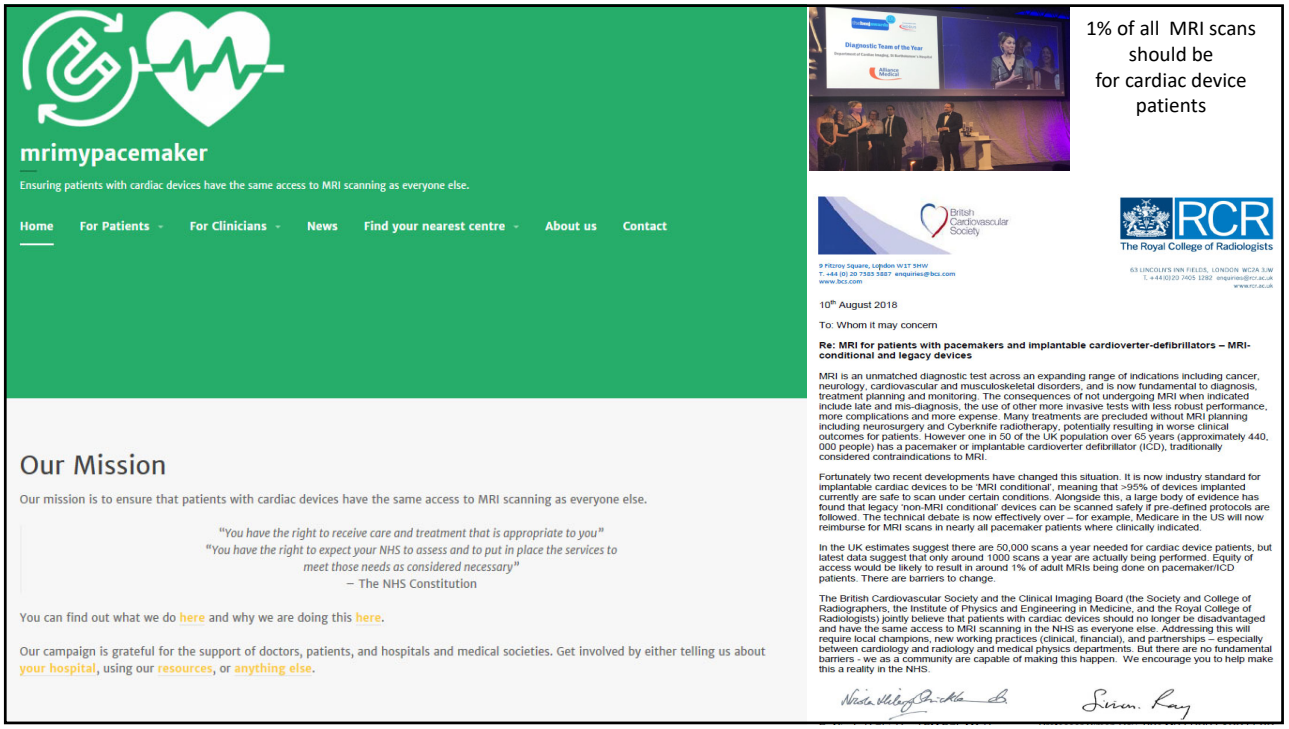
The Prognostic Significance of Quantitative Myocardial Perfusion – an Artificial Intelligence Based Approach Using Perfusion Mapping

Kristopher D Knott MBBS[a,b], Andreas Seraphim MBBS[a,b], Joao B Augusto MD[a,b], Hui Xue PhD[c], Liza Chako MBBS[a,d], Nay Aung MBBS[b,a], Steffen E. Petersen DPhil[b,a], Jackie A. Cooper MSc[a], Charlotte Manisty PhD[a,b], Anish N Bhuva MBBS[a,b], Tushar Kotecha MBChB[a,d], Christos V. Bourantas PhD[a,b], Rhodri H Davies[a,b] PhD, Louise AE Brown MBChB[d], Sven Plein MD PhD[d], Marianna Fontana PhD[a,d], Peter Kellman PhD[c], James C Moon MD[a,b].

Circulation – 14th February

Reaching more patinets

More information per study
Faster
Cheaper
Easier
More available
More situations



1% of all MRI scans should be for cardiac device patients

British Cardiovascular Society

RCR The Royal College of Radiologists

10th August 2018

To: Whom it may concern

Re: MRI for patients with pacemakers and implantable cardioverter-defibrillators – MRI-conditional and legacy devices

MRI is an unmatched diagnostic test across an expanding range of indications including cancer, neurology, cardiovascular and musculoskeletal disorders, and is now fundamental to diagnosis, treatment planning and monitoring. The consequences of not undergoing MRI when indicated include late and mis-diagnosis, the use of other more invasive tests with less robust performance, more complications and more expense. Many treatments are precluded without MRI planning including neurosurgery and Cyberknife radiotherapy, potentially resulting in worse clinical outcomes for patients. However one in 50 of the UK population over 65 years (approximately 440, 000 people) has a pacemaker or implantable cardioverter defibrillator (ICD), traditionally considered contraindications to MRI.

Fortunately two recent developments have changed this situation. It is now industry standard for implantable cardiac devices to be 'MRI conditional', meaning that >95% of devices implanted currently are safe to scan under certain conditions. Alongside this, a large body of evidence has found that legacy 'non-MRI conditional' devices can be scanned safely if pre-defined protocols are followed. The technical debate is now effectively over – for example, Medicare in the US will now reimburse for MRI scans in nearly all pacemaker patients where clinically indicated.

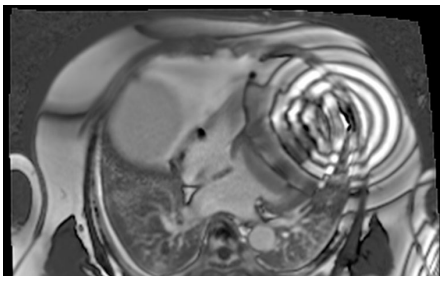
In the UK estimates suggest there are 50,000 scans a year needed for cardiac device patients, but latest data suggest that only around 1000 scans a year are actually being performed. Equity of access would be likely to result in around 1% of adult MRIs being done on pacemaker/ICD patients. There are barriers to change.

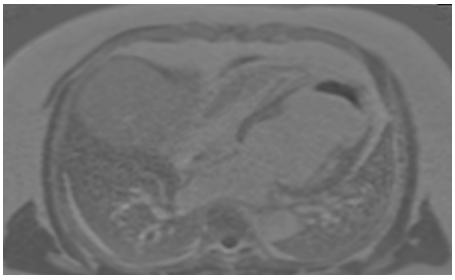
The British Cardiovascular Society and the Clinical Imaging Board (the Society and College of Radiographers, the Institute of Physics and Engineering in Medicine, and the Royal College of Radiologists) jointly believe that patients with cardiac devices should no longer be disadvantaged and have the same access to MRI scanning in the NHS as everyone else. Addressing this will require local champions, new working practices (clinical, financial), and partnerships – especially between cardiology and radiology and medical physics departments. But there are no fundamental barriers - we as a community are capable of making this happen. We encourage you to help make this a reality in the NHS.

MRI for any patient with any pacemaker or ICD

-

Wide Band LGE for ICD patients



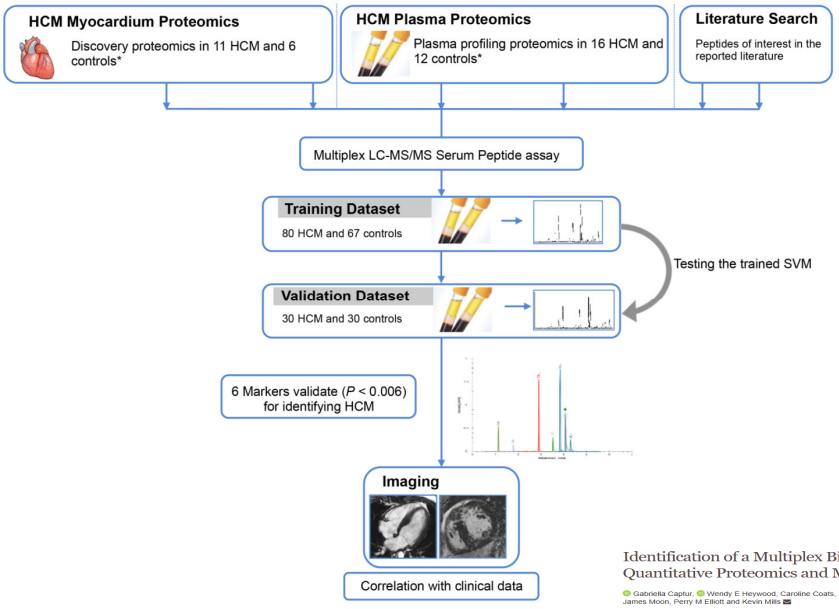


CMR in 10 minutes

Reaching new patients

Amna Abdel-Gadir and Hatai Ngamkasem (London/Thailand)

New biomarkers – integrating with imaging



6 biomarkers
10 µl plasma
10 minute LC-MS/MS

Predicts HCM (vs controls)
AUC 0.87
Correlates with:
wall thickness
4 biomarkers correlate with
NSVT
5 year predicted risk

Identification of a Multiplex Biomarker Panel for Hypertrophic Cardiomyopathy using Quantitative Proteomics and Machine Learning

Gabriella Captur, Wendy E Heywood, Caroline Coats, Stefania Rosmini, Vimal Patel, Luis R Lopes, Richard Collis, Nina Patel, Petros Syrris, Paul Bassett, Ben O'Brien, James Moon, Perry M Elliott and Kevin Mills
Molecular & Cellular Proteomics June 26, 2019, mcp.RA119.001586; https://doi.org/10.1074/mcp.RA119.001586

Conclusion

We have problems in Cardiology
- falling behind other fields for therapies
- our imaging not good as we think
- need to measure pathways and biology better

A framework for proceeding

AI is transforming imaging
- a revolution - stay on board
- all modalities
- changing imaging, changing cardiology

Other area:
- reaching more patients
- faster cheaper easier
- standardization

New frontiers:
- Integrating imaging with other datasources
- linking centres together

Transforming care

james@moonmail.co.uk