Cardiac Imaging in Acute MIS-C
Echo Based AI & its Applications

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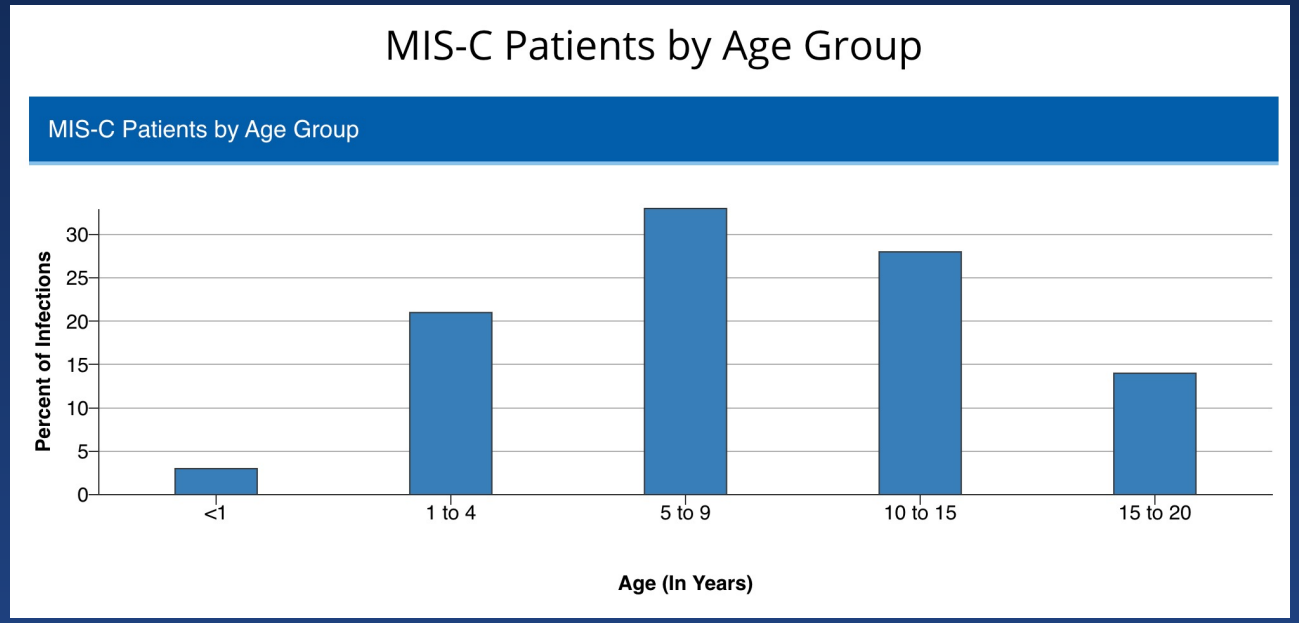
Introduction

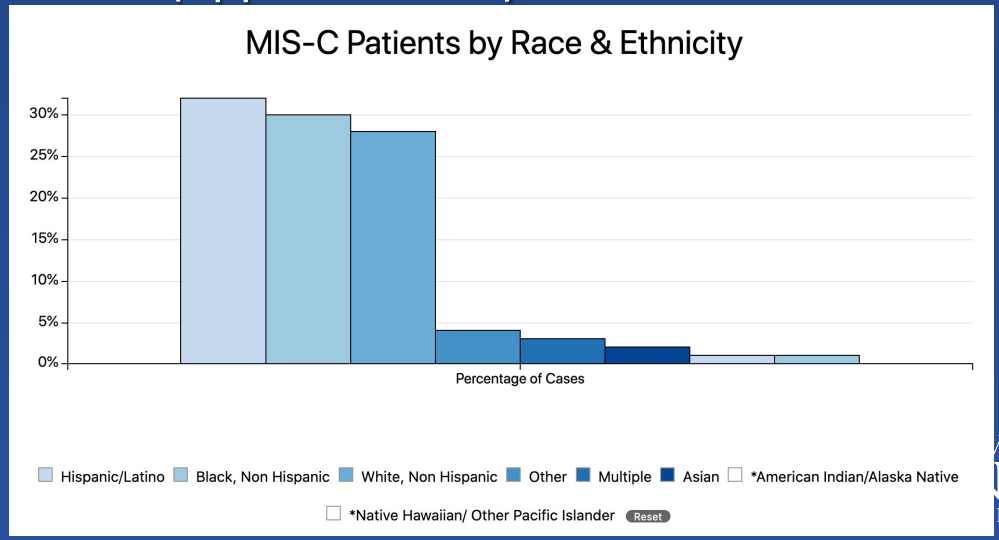
- Coronavirus (COVID-19) affected ~180 million people worldwide
  - ~3.9 million deaths
- Higher mortality noted in adults affected by COVID-19

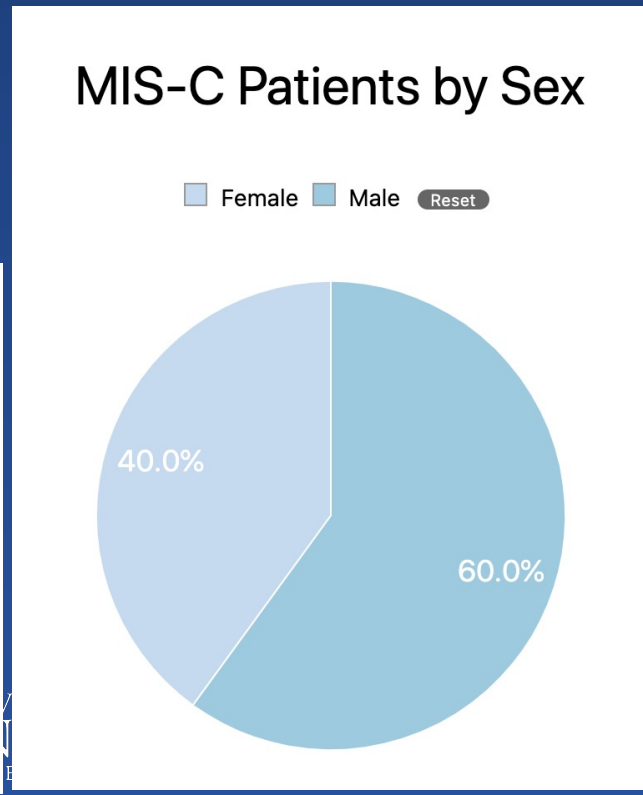
Demographics

- MIS-C is a rare complication of the COVID-19 infection in children occurring in <1% of children with SARS-CoV-2 infection.

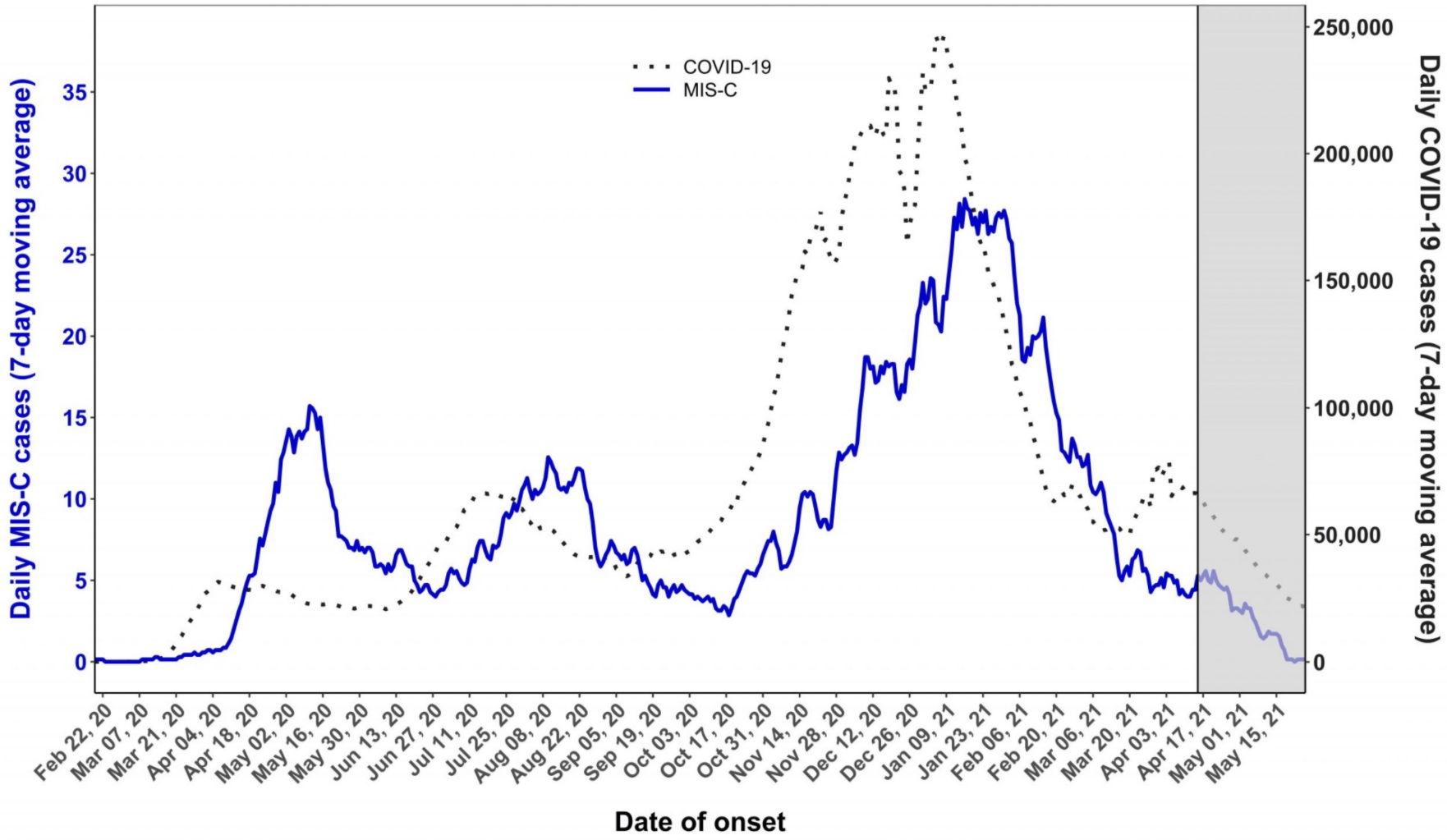
- As of June 2nd, 2021
  - 4018 cases + for MIS-C
  - 36 deaths
- Median age 9 y (5-13y)
- 60% male
- 62% are Hispanic or Latino, or Black or non-Hispanic
  - Lower in children of Asian descent (opposite of KD)







Daily MIS-C Cases and COVID-19 Cases Reported to CDC (7-Day Moving Average)



Number of included MIS-C cases: 4013. The graph shows the 7-day moving average number of COVID-19 patients and MIS-C patients with date of onset between February 19, 2020 and May 18, 2021.

- Mechanism of MIS-C not well understood
  - **Immune dysregulation** – with abnormal immune response to virus.
    - Similar to
      - Kawasaki Disease
      - Macrophage Activation Syndrome
      - Cytokine Release Syndrome
  - **SARS-CoV-2 virus**
    - Several children have negative antigen and positive antibody response – abnormal immune host response
  - **Myocardial injury**
    - Systemic Inflammation
    - Myocarditis, pericarditis
    - Stress cardiomyopathy

CDC definition – MIS-C

- Age <21 years presenting with
  - Fever
  - laboratory evidence of inflammation
  - evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)

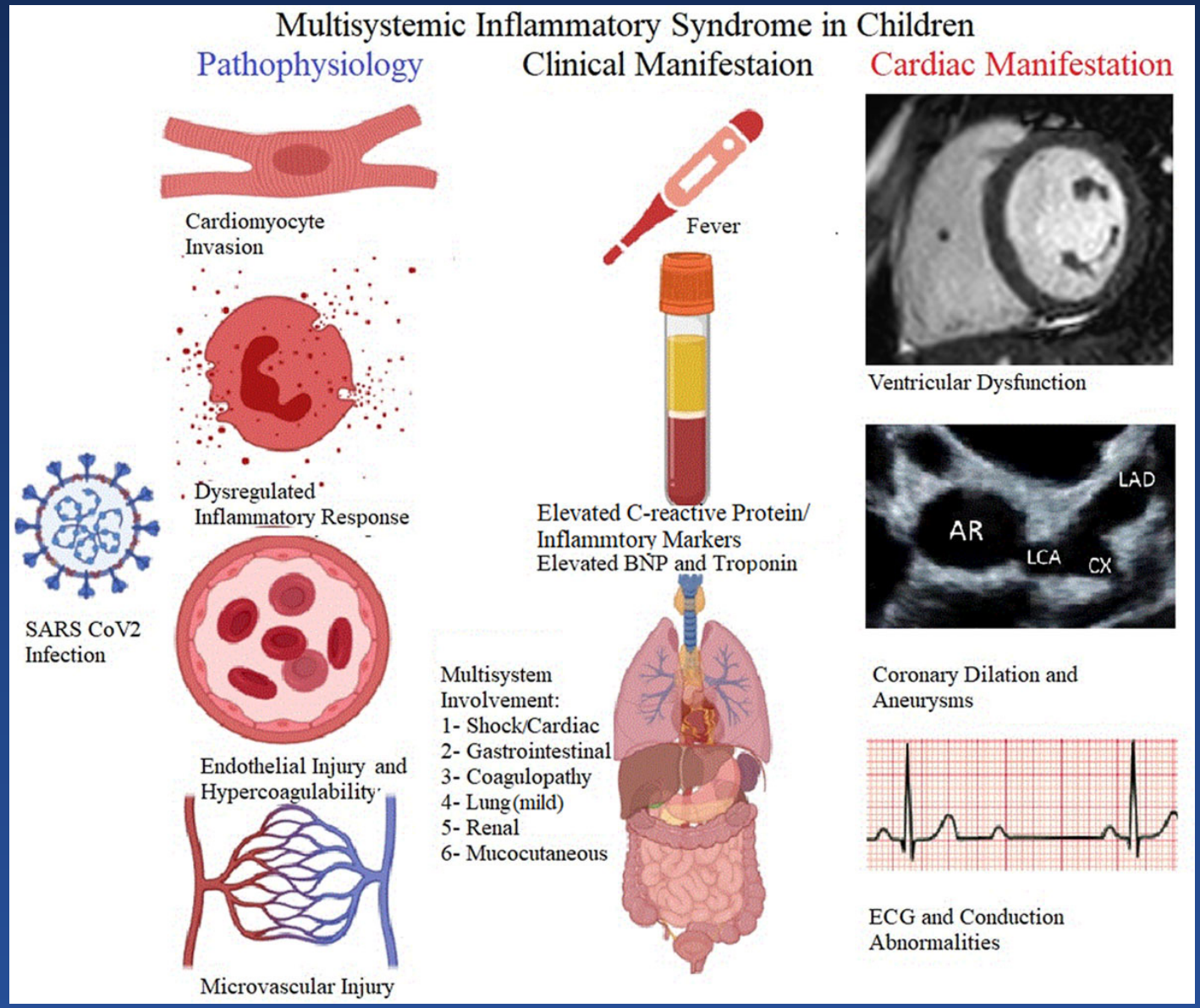
    +
- No alternative plausible diagnoses

    +
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

Clinical presentation and findings

- Fever is seen in all children
- Important clinical findings are
  - Shock (upto 76% of children)
  - Myocardial dysfunction – upto 56-60% patients
  - Arrhythmias (51-90%)
  - Acute respiratory failure (28-52%)

Feldstein, Leora R et al. "Multisystem Inflammatory Syndrome in U.S. Children and Adolescents." The New England journal of medicine vol. 383,4 (2020): 334-346. doi:10.1056/NEJMoa2021680



- *Tarek Alsaied. Circulation. Review of Cardiac Involvement in Multisystem Inflammatory Syndrome in Children, Volume: 143, Issue: 1, Pages: 78-88, DOI: (10.1161/CIRCULATIONAHA.120.049836*

Cardiac Imaging findings

- Echo
  - Depressed LV function – 31-58%
  - Coronary artery dilation – 8-38%
  - Pericardial effusion and mitral regurgitation
- CXR
  - Normal mostly
  - Small pleural effusion
  - Patchy and focal consolidation and atelectasis
- Chest CT
  - Normal
  - Few have nodular ground-glass opacification

Elevated cardiac markers (lab)

- Troponin elevated – 50-90%
- BNP/NT proBNP – 73-90%

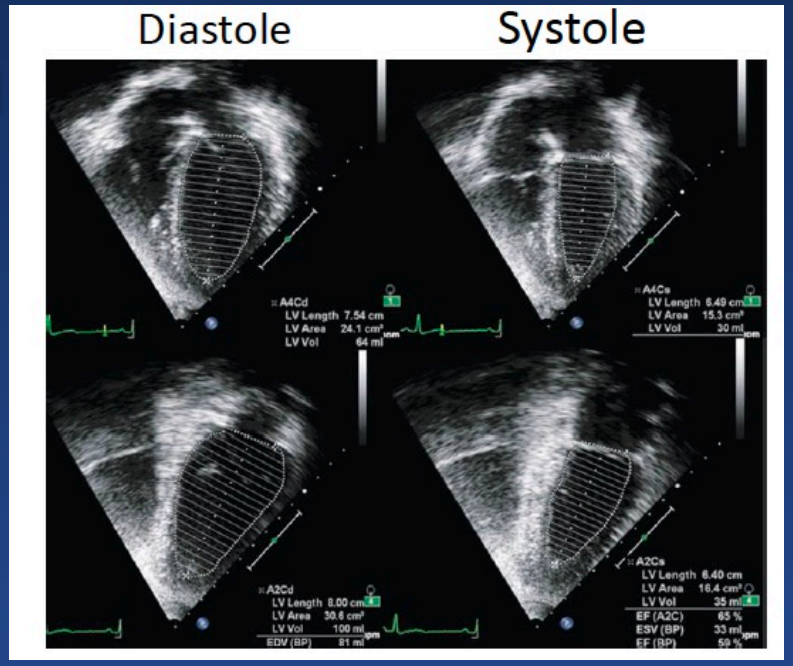
- Cardiac involvement is the key in the differentiation between MIS-C from severe acute COVID-19.
- Can lead to shock and multi-organ failure
- Much remains unknown regarding
  - Epidemiology
  - Pathogenesis
  - Long-term outcomes

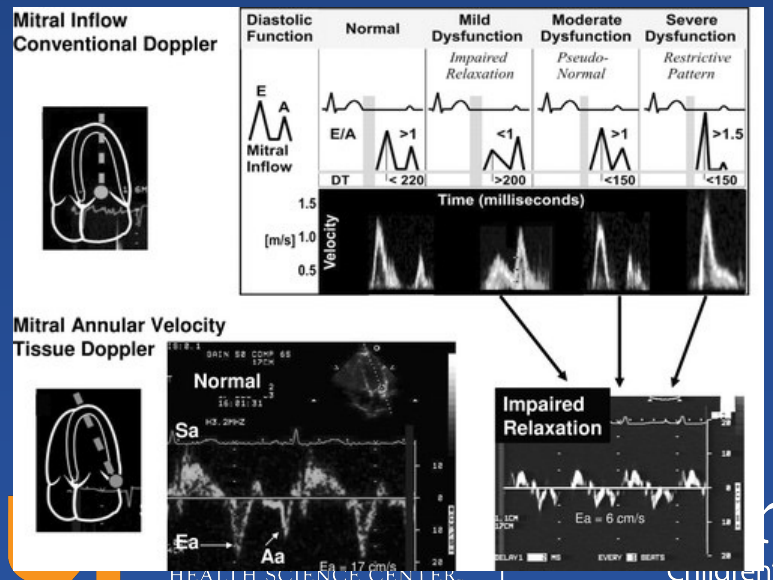
Role of echocardiography

- Echo plays critical role in
  - Early diagnosis
  - Management guidance – inpatient and outpatient
- Critical element in addition to clinical findings, serum labs

Parameters for echocardiogra

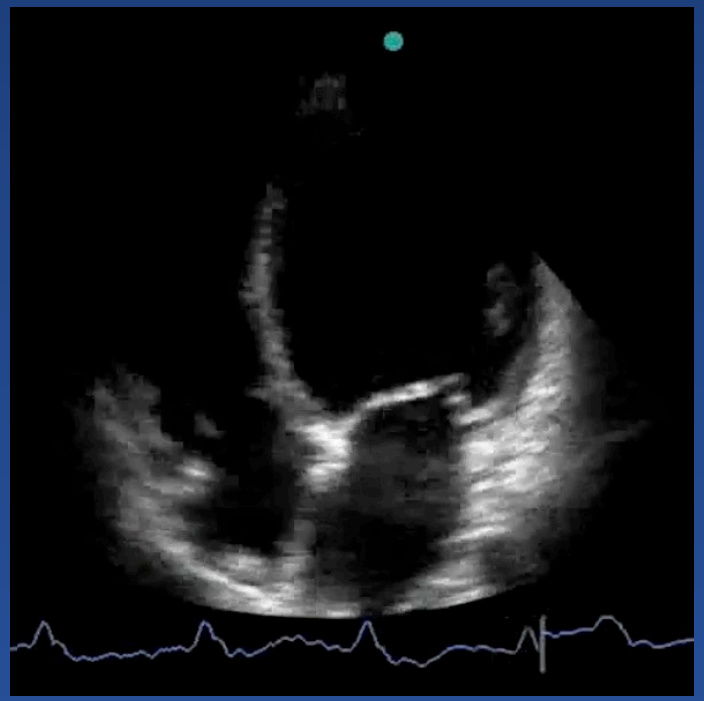
- Myriad of parameters
  - Assessment of systolic function
    - Ejection fraction
  - Diastolic function
    - Tissue doppler
  - Deformation indices
    - Ventricular strain
    - Left atrial strain
  - Coronary artery measurements





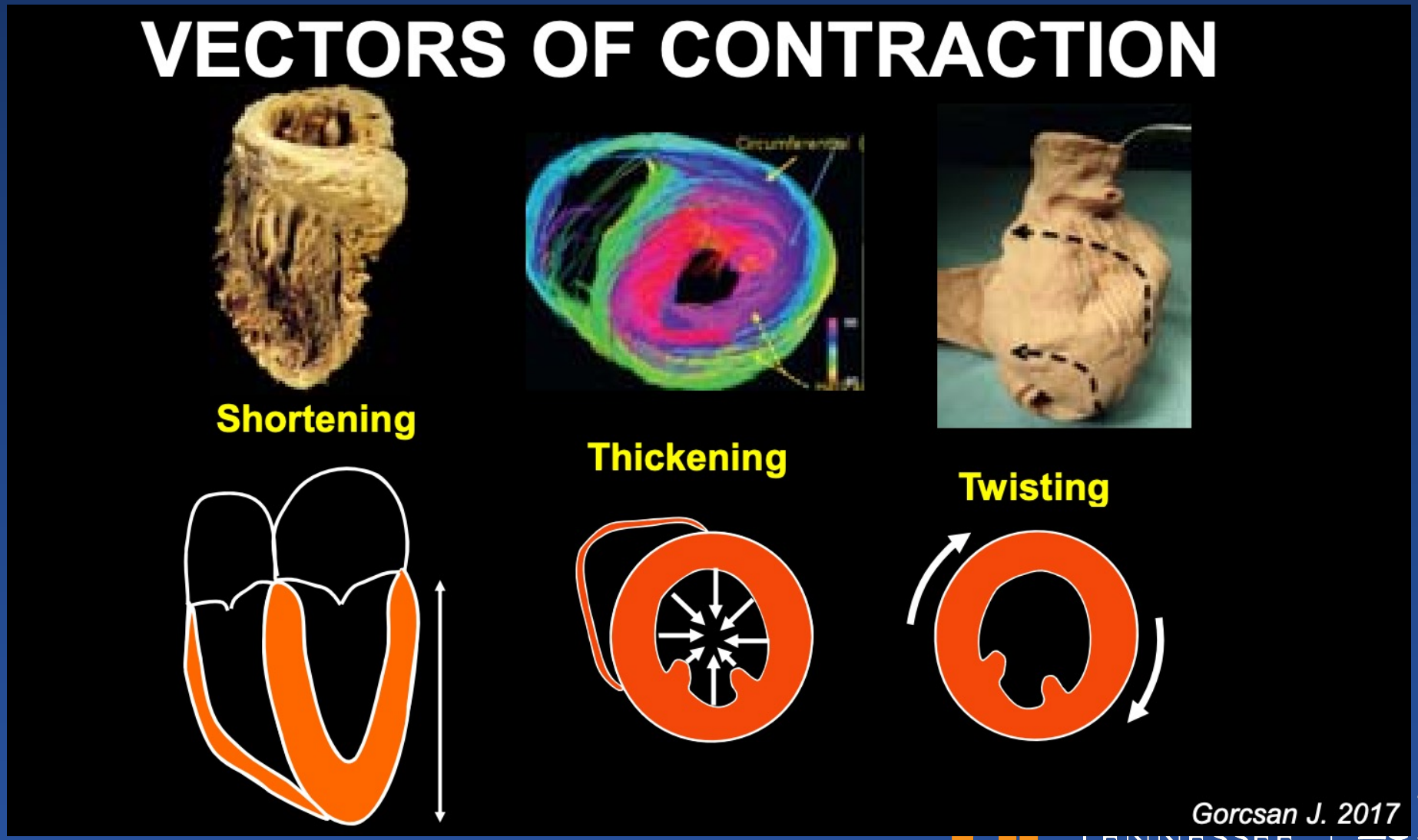
Systolic function analysis

Abnormal

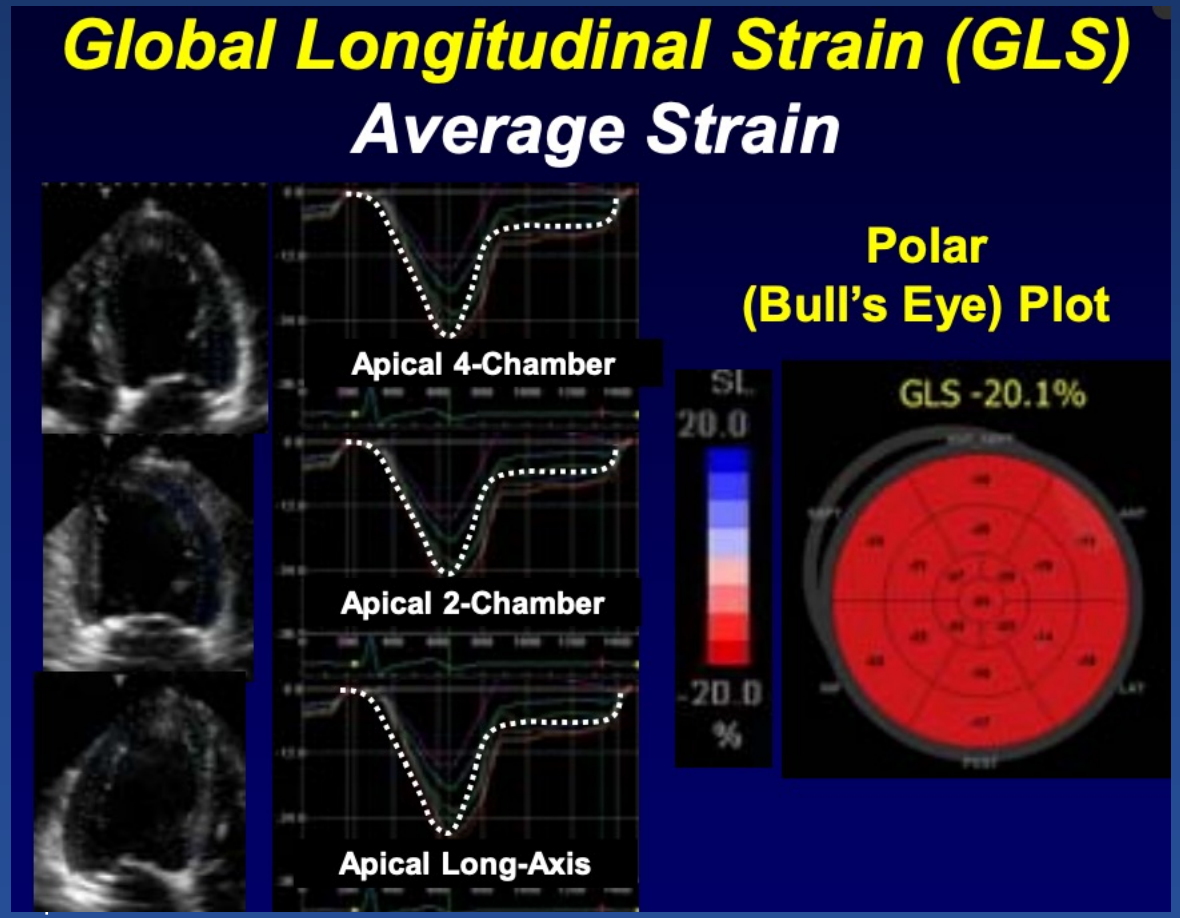


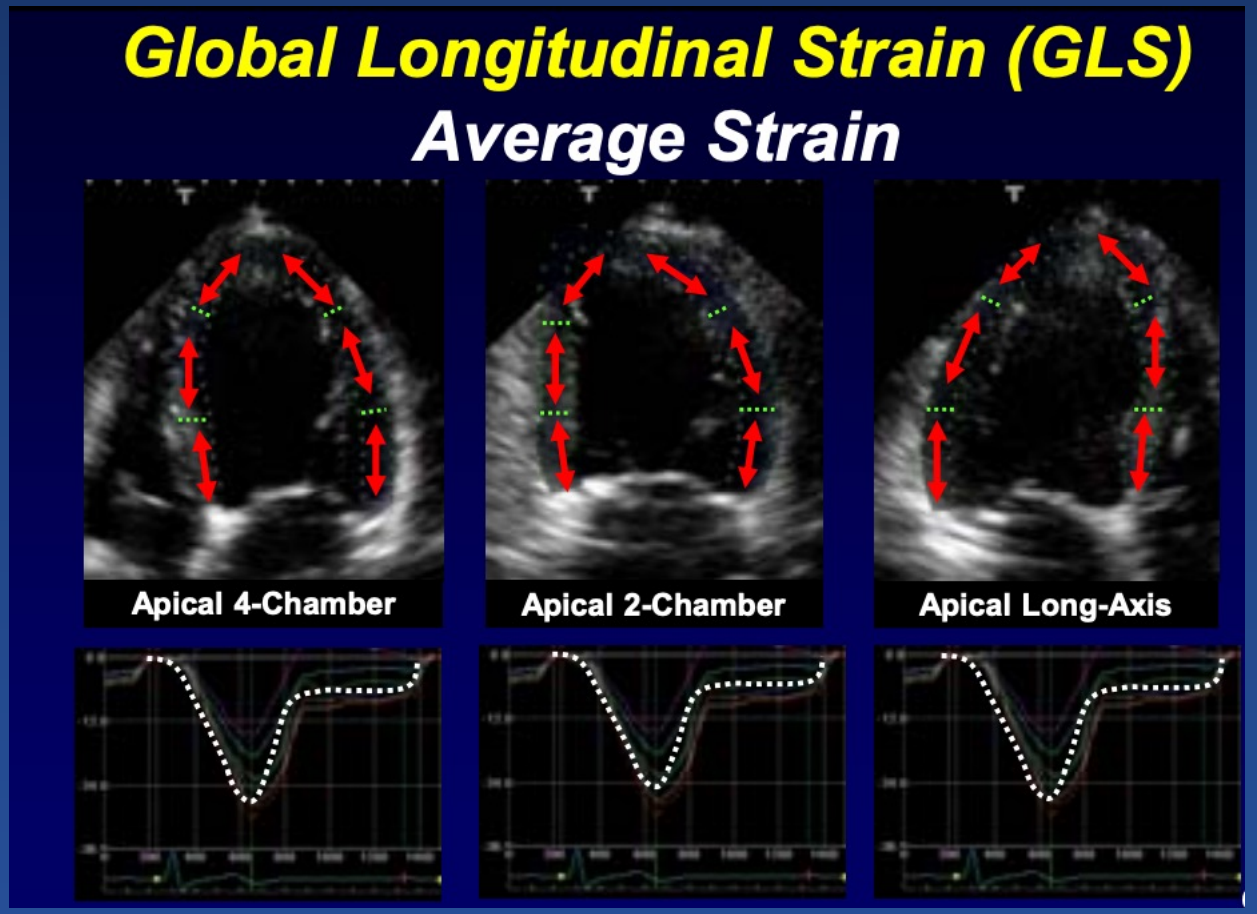
Normal

Myocardial strain



Global Longitudinal Strain





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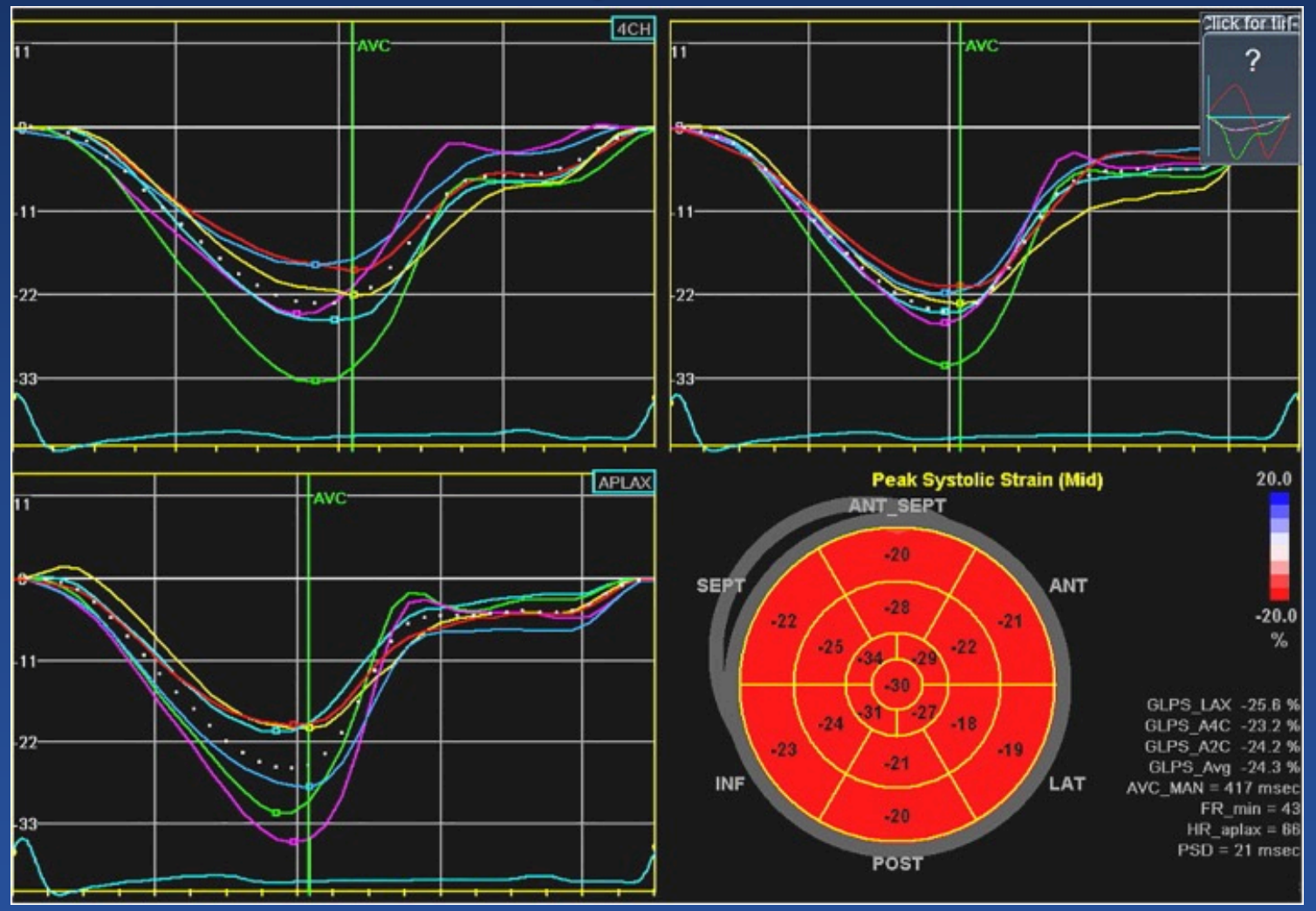
Vector normal strain parameter



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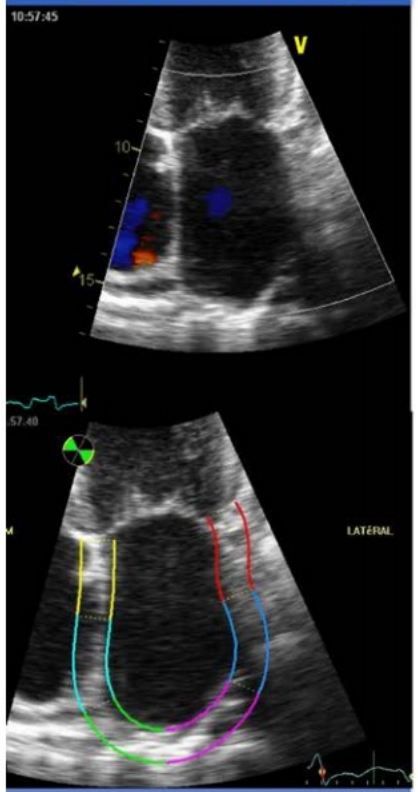
Left atrial strain measurement

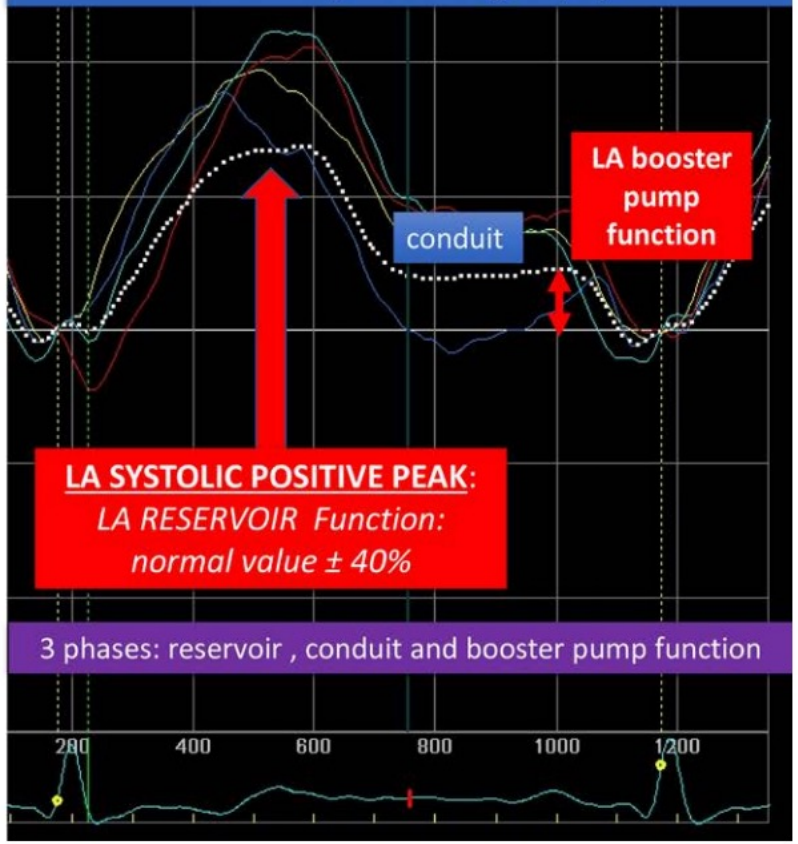
Zoom on the left atrium in apical 2 and 4 chambers views



Semi-automatic contouring of the left atrial borders for speckle tracking

Parametric imaging for checking the quality of the tracking

Display of the left atrial deformation over a cardiac cycle, starting in this example at the QRS (following the settings made for the left ventricular speckle tracking analysis)



3 phases: reservoir , conduit and booster pump function

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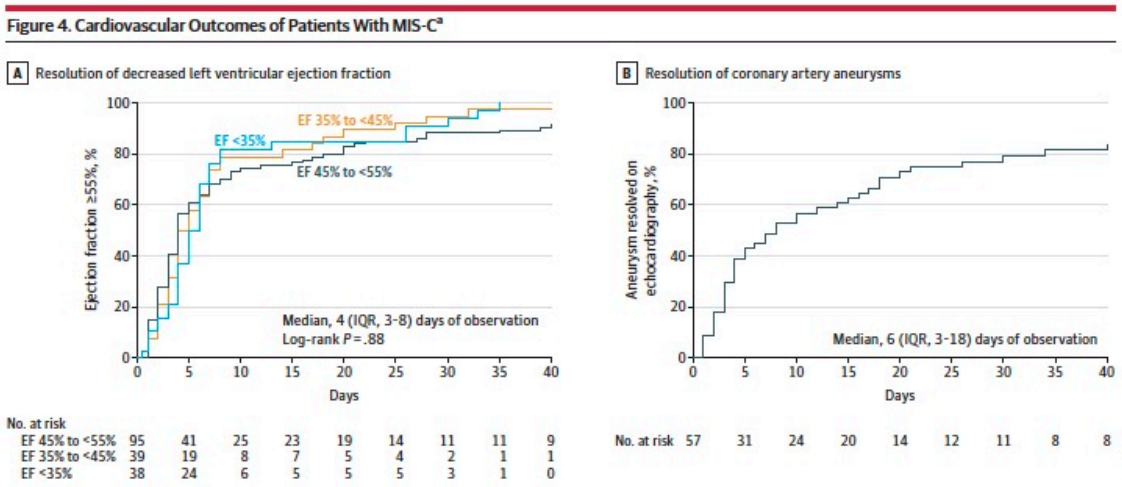
Cardiovascular findings in MIS-C

JAMA | Original Investigation

Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19

Leora R. Feldstein, PhD; Mark W. Tenforde, MD; Kevin G. Friedman, MD; Margaret Newhams, MPH; Erica Billig Rose, PhD; Heda Dapul, MD; Vijaya L. Soma, MD; Aline B. Maddux, MD; Peter M. Mourani, MD; Cindy Bowens, MD; Mia Maamari, MD; Mark W. Hall, MD; Becky J. Riggs, MD; John S. Giuliano Jr, MD; Aalok R. Singh, MD; Simon Li, MD; Michele Kong, MD; Jennifer E. Schuster, MD; Gwenn E. McLaughlin, MD; Stephanie P. Schwartz, MD; Tracie C. Walker, MD; Laura L. Loftis, MD; Charlotte V. Hobbs, MD; Natasha B. Halasa, MD; Sule Doymaz, MD; Christopher J. Babbitt, MD; Janet R. Hume, MD; Shira J. Gertz, MD; Katherine Irby, MD; Katharine N. Clouser, MD; Natalie Z. Cvijanovich, MD; Tamara T. Bradford, MD; Lincoln S. Smith, MD; Sabrina M. Heidemann, MD; Sheemon P. Zackai, MD; Kari Wellnitz, MD; Ryan A. Nofziger, MD; Steven M. Horwitz, MD; Ryan W. Carroll, MD; Courtney M. Rowan, MD; Keiko M. Tarquinio, MD; Elizabeth H. Mack, MD; Julie C. Fitzgerald, MD; Bria M. Coates, MD; Ashley M. Jackson, MPH; Cameron C. Young; Mary Beth F. Son, MD; Manish M. Patel, MD; Jane W. Newburger, MD; Adrienne G. Randolph, MD; for the Overcoming COVID-19 Investigators



- 1116 COVID-19 patients
  - 539 MIS-C diagnosis
- 56% cardiovascular involvement
  - 34% - reduced EF
    - Mild – 55%
    - Moderate – 22.7%
    - Severe – 22.1%
  - 91% had normal EF by 30 days
  - 99.4% had normal EF by 90 days
  - 1 patient normal by 142 days
- 13% - coronary aneurysms

Echo parameters

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CJC Open ■ (2021) 1–8

Original Article

Detailed Assessment of Left Ventricular Function in Multisystem Inflammatory Syndrome in Children, Using Strain Analysis

Ryan Kobayashi, MD, MS,[a,b] Audrey Dionne, MD,[a,b] Alessandra Ferraro, MD,[a,b] David Harrild, MD, PhD,[a,b] Jane Newburger, MD, MPH,[a,b] Christina VanderPluym, MD,[a,b] Kim Gauvreau, ScD,[a,b] Mary Beth Son, MD,[b,c] Pui Lee, MD,[b,c] Annette Baker, RN, MSN, PNP,[a,b] Sarah de Ferranti, MD, MPH,[a,b] and Kevin G. Friedman, MD[a,b]

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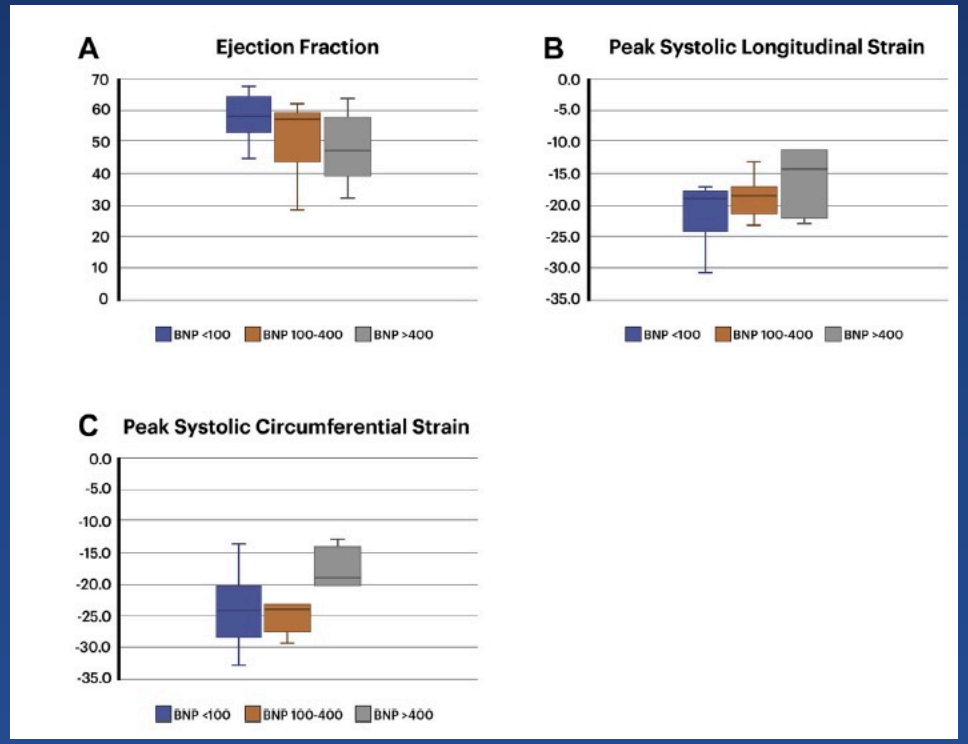

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COVID-19-Related Multisystem Inflammatory Syndrome in Children Affects Left Ventricular Function and Global Strain Compared with Kawasaki Disease

Gaitonde M, Ziebell D, Kelleman MS, Cox DE, Lipinski J, Border WL, Sachdeva R. COVID-19-Related Multisystem Inflammatory Syndrome in Children Affects Left Ventricular Function and Global Strain Compared with Kawasaki Disease. J Am Soc Echocardiogr. 2020 Oct;33(10):1285-1287. doi: 10.1016/j.echo.2020.07.019. Epub 2020 Jul 31. PMID: 33010854; PMCID: PMC7832547.

SF (2D), %	25.3 (22.1 to 29.1)	32.1 (29.0 to 33.6)	**.01**
LVEF (biplane Simpson), %	42.5 (39.6 to 56.8)	58.4 (56.8 to 64.3)	**.03**

Two-chamber peak systolic strain, %	−12.7 (−15.8 to −11.2)	−18.3 (−21.2 to −17.4)	**<.01**
Three-chamber peak systolic strain, %	−15.2 (−16.8 to −11)	−17.8 (−23.8 to −15.8)	**.05**
GLS, %	−14.0 (−18.9 to −11.4)	−19.3 (−20.1 to −18.3)	**.02**

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Differences in findings for KD and MIS-C

- Unlike patients with KD, the majority of those with MIS-C had significantly reduced left ventricular function at presentation.
- Even though LVEF and GCS normalized by days 7 to 9 of illness in most patients, abnormalities in GLS persisted.
- Correlations of abnormal LVEF and GLS with cardiac inflammatory biomarkers, such as CRP and troponin, highlight the presence of myocarditis in patients with MIS-C.

Gaitonde M, Ziebell D, Kelleman MS, Cox DE, Lipinski J, Border WL, Sachdeva R. COVID-19-Related Multisystem Inflammatory Syndrome in Children Affects Left Ventricular Function and Global Strain Compared with Kawasaki Disease. J Am Soc Echocardiogr. 2020 Oct;33(10):1285-1287. doi: 10.1016/j.echo.2020.07.019. Epub 2020 Jul 31. PMID: 33010854; PMCID: PMC7832547.

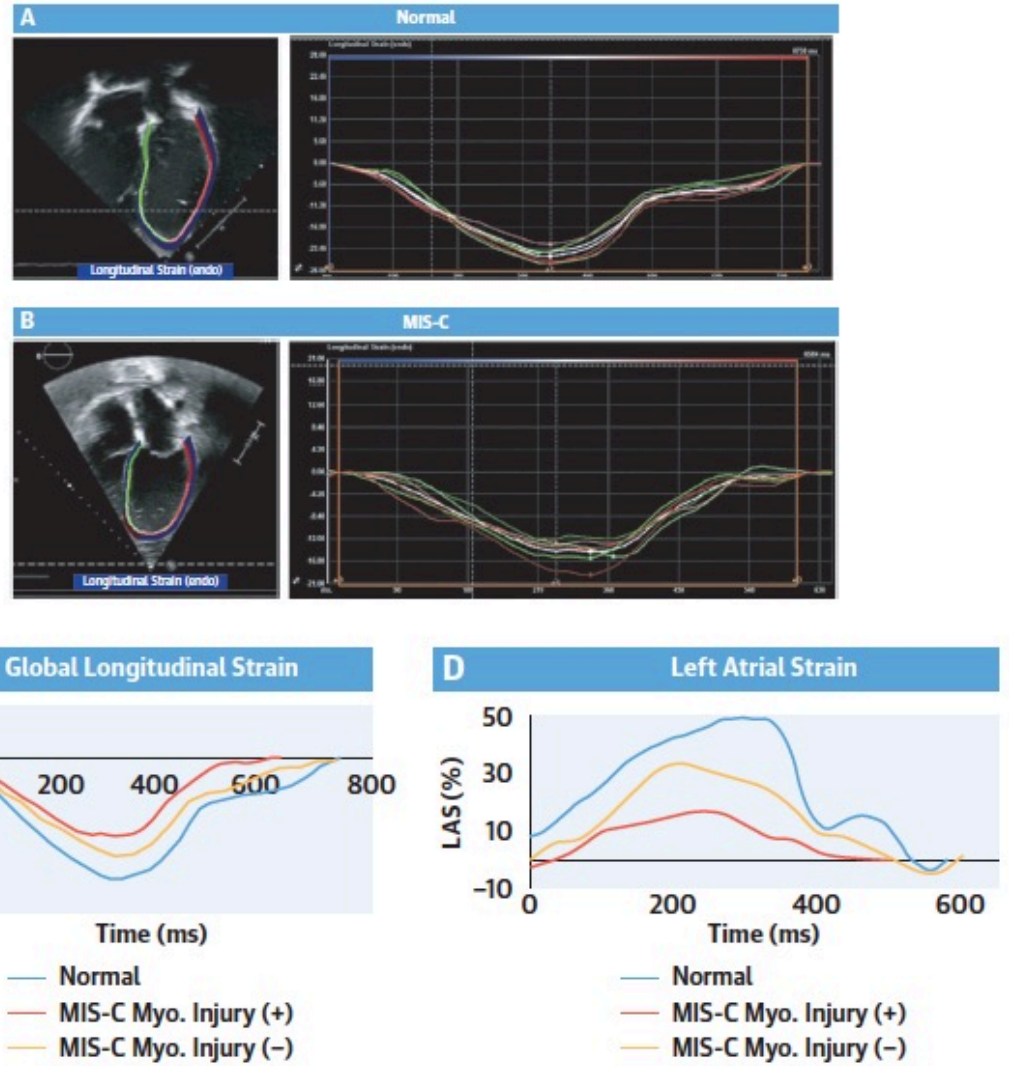
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 17, 2020

PUBLISHED BY ELSEVIER

Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States

Daisuke Matsubara, MD, PhD, Hunter L. Kauffman, BS, Yan Wang, RDMS, Renzo Calderon-Anyosa, MD, MSc, Sumekala Nadaraj, MD, Matthew D. Elias, MD, Travus J. White, MD, Deborah L. Torowicz, CRNP, Putri Yubbu, MBBS, Therese M. Giglia, MD, Alexa N. Hogarty, MD, Joseph W. Rossano, MD, Michael D. Quartermain, MD, Anirban Banerjee, MD

FIGURE 3 Strain Curves



Strain curves in a normal **(A)** and multisystem inflammatory syndrome in children (MIS-C) patient during acute phase **(B)** for global longitudinal strain (GLS). **(C)** GLS curves and **(D)** left atrial strain (LAS) curves for normal, myocardial injury (+), and injury (–) in MIS-C patients. All MIS-C patients show decreased GLS and LAS compared with normal patients. In addition, myocardial injury (+) patients are worse than injury (–) patients. myo. = myocardial.

Functional parameters

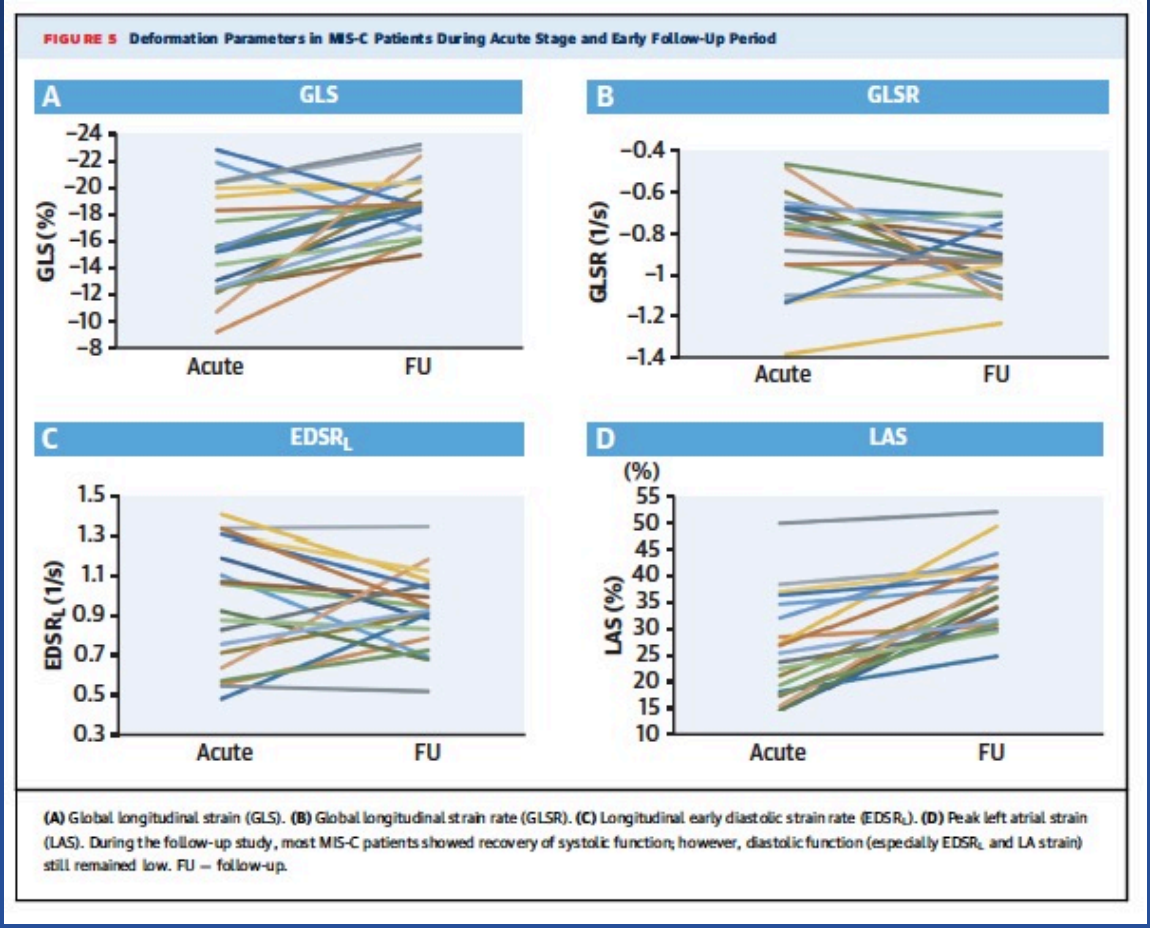


FIGURE 5 Deformation Parameters in MIS-C Patients During Acute Stage and Early Follow-Up Period

(A) Global longitudinal strain (GLS). (B) Global longitudinal strain rate (GLSR). (C) Longitudinal early diastolic strain rate (EDSR$_L$). (D) Peak left atrial strain (LAS). During the follow-up study, most MIS-C patients showed recovery of systolic function; however, diastolic function (especially EDSR$_L$ and LA strain) still remained low. FU = follow-up.

TABLE 9 Results of Correlation Coefficients Between Functional Parameters and Biomarkers

	BNP		Troponin I	
	R^2 Value	p Value	R^2 Value	p Value
GLS	0.26	0.0098	0.23	0.01
GLSR	0.12	0.09	0.12	0.09
EDSR$_L$	−0.02	0.50	−0.01	0.67
GCS	0.14	0.06	0.14	0.06
GCSR	0.17	0.04	0.18	0.03
EDSR$_C$	−0.14	0.07	−0.12	0.09
LAS	−0.38	0.001	−0.31	0.003
RVFWLS	0.29	0.01	0.46	<0.001

BNP = brain natriuretic peptide; other abbreviations as in Table 4.

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Goal

- Develop machine learning and deep learning tools to identify pediatric cardiac dysfunction and coronary changes associated with MIS-C from echocardiogram.

Proposal for AI based tools

- Curate a pediatric cardiac imaging dataset (from local and global open data sources) and develop feature engineering tools specifically for echo.

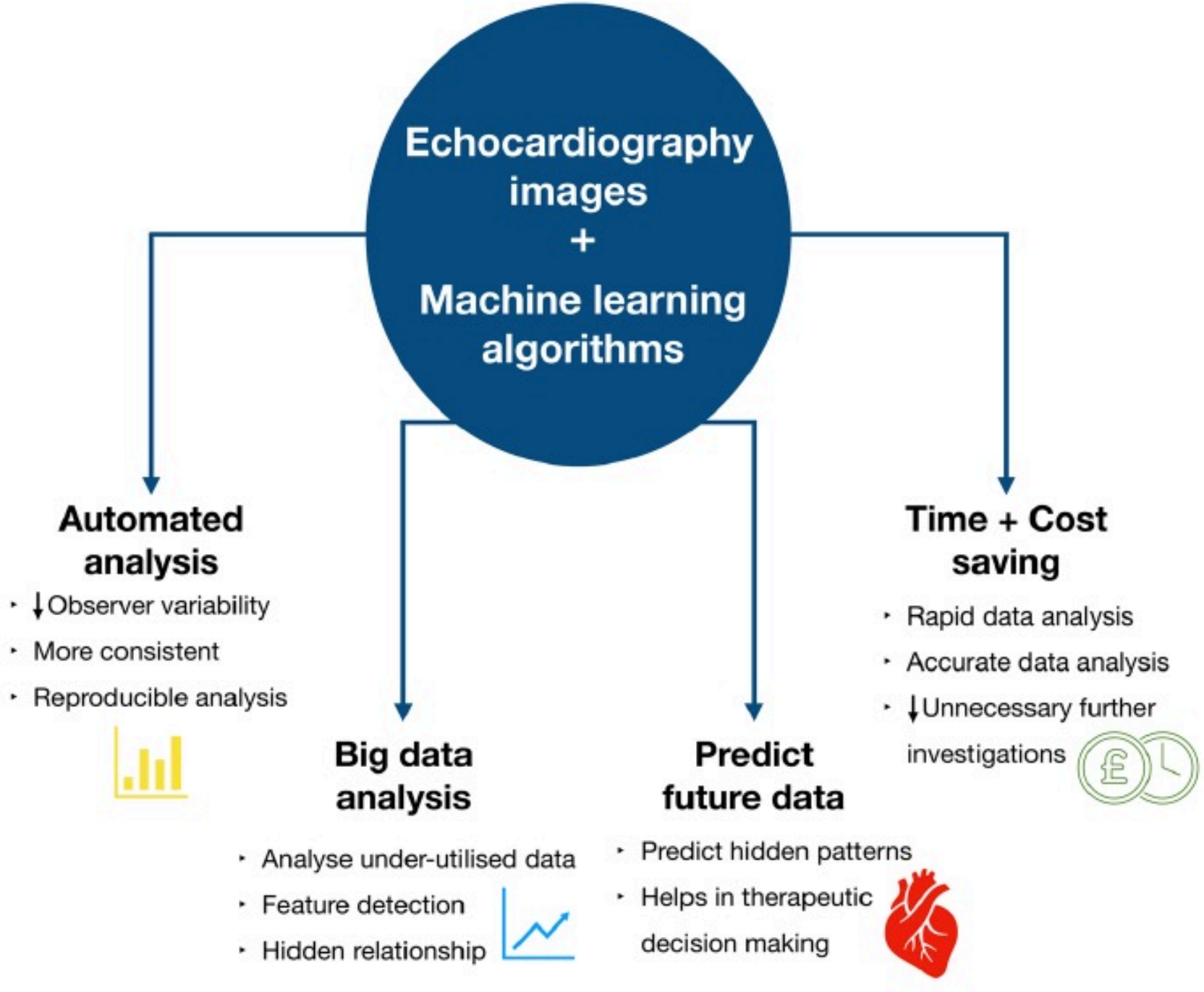
- Develop an echo-based AI tool for automated quantitative annotation
  - Measure ejection fraction
  - Deformation parameters
  - Volume of the ventricles
  - Coronary artery dimensions
    - Coronary artery dilations or aneurysms of echo with active learning (feed back loop from experts)

- Develop a tool that can perform differentiation of MIS-C from other similar syndromes.
- Validate the tool with a locally pool sourced dataset for robust clinically translatable AI tools.
- Eventually, this pipeline will accelerate clinical workflow and improve the consistency/accuracy of MIS-C diagnosis.

But why do this?

- Identify long term outcomes
- Use AI for
  - **Classification of Shock-like syndrome**
  - **Prediction of outcomes**
  - **Utilization of several parameters for accurate and consistent diagnosis**

Advantages of machine learning assisted echo interpretation



Datasets

- Echocardiogram images for patients and controls with corresponding annotations (points/contours) that help identify the region of interest required to calculate metrics
  - Ex: cardiac output, ejection fraction, stroke volume, volume of ventricle, strain, coronary artery size, morphology of dilation, origin, etc.
  - These values with cardiologist confirmed values will be used as ground truth for AI training and validation of methods.

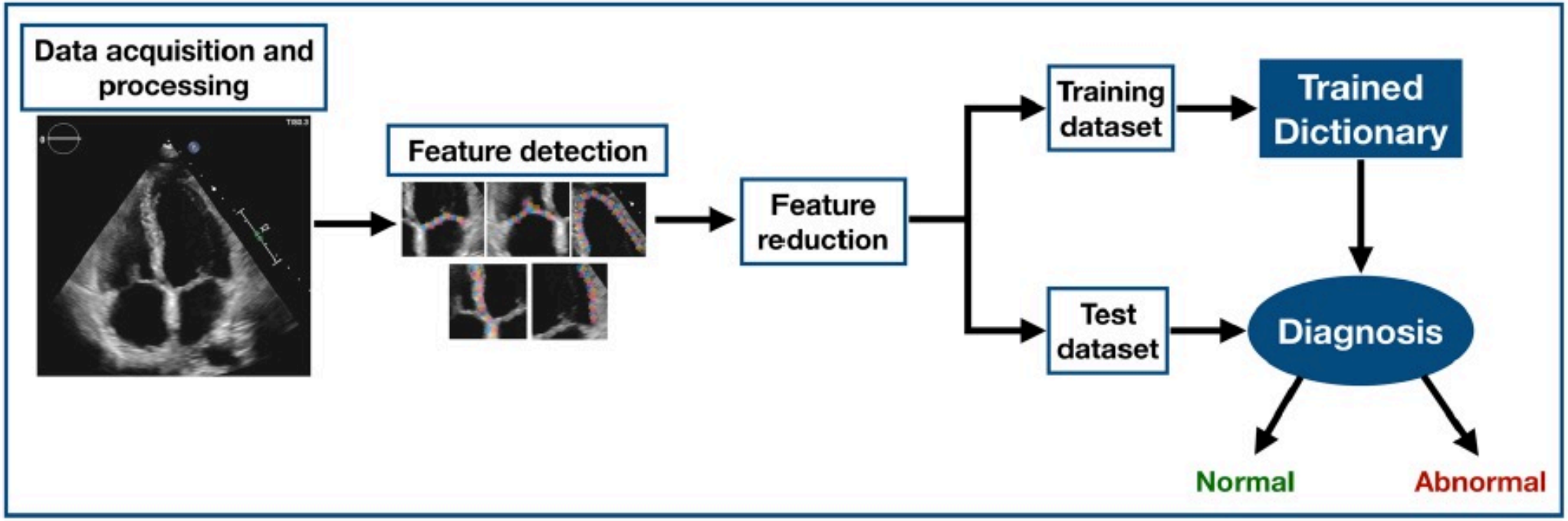
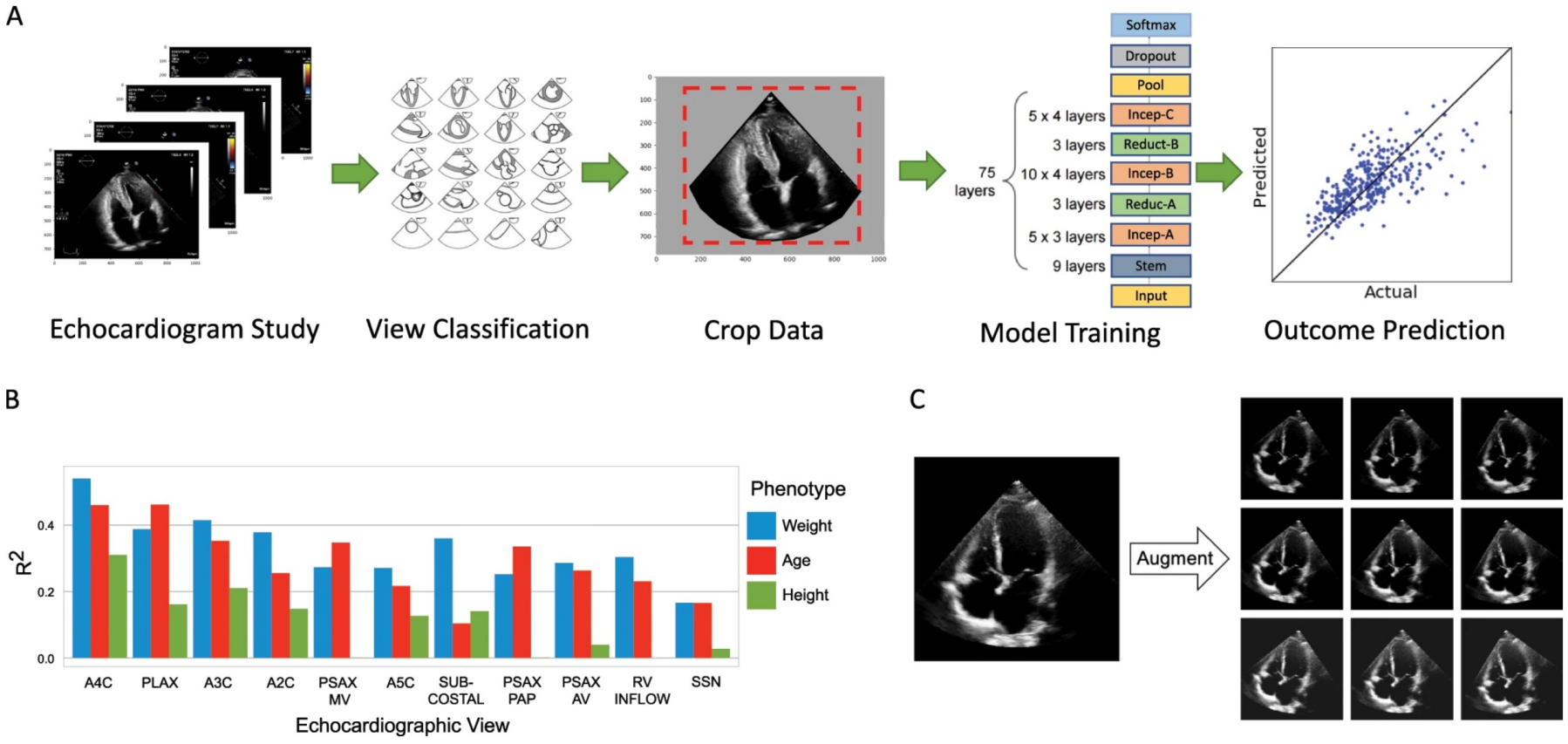


Figure 4
Diagram of an example of machine learning model process.

Fig. 1: EchoNet machine learning pipeline for outcome prediction.

From: Deep learning interpretation of echocardiograms



a EchoNet workflow for image selection, cleaning, and model training. **b** Comparison of model performance with different cardiac views as input. **c** Examples of data augmentation. The original frame is rotated (left to right) and its intensity is increase (top to bottom) as augmentations.

- In addition to echo-based metrics, following may increase the strength of the learning algorithm
  - Corresponding lab values
  - +/- pertinent clinical information such as physical exam findings, vitals, etc

- Controls
  - Patients with normal echo findings
    - Ex: Referral for evaluation of murmur
      - Chest pain
      - Palpitations
      - Dizziness or syncope
      - Equivalent referrals with normal cardiac anatomy findings

Sources of training data

- Normal echo data – needed for training datasets
- No pediatric publicly available datasets
  - Collaboration with institutions –
    - Help improve overall numbers
    - Increase heterogeneity – better train the machines

- Adult database – Stanford
  - https://echonet.github.io/dynamic/index.html
  - https://www.creatis.insa-lyon.fr/~bernard/research.html

Thank you!!!

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