Hidden in Plain Sight: Cardiac Amyloidosis as a Cause of Heart Failure

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Heart failure (HF) remains the second highest cause of hospital admissions in patients over the age of 65, after septicemia.  

6.5 million people are living with HF in the United States, and this number is expected to rise by 46% by 2030.  

The annual cost of HF in the United States is estimated at $30.7 billion.  

Approximately 23% of Medicare patients with a diagnosis of HF were readmitted within 30 days.  

*American Heart Association (AHA) estimate. †Cost estimates include both direct and indirect costs for treatment and care of patients with HF. Direct costs were estimated to be 68% of total HF costs. Direct costs were estimated using the 2004-2008 Medical Expenditure Panel Survey (MEPS). Indirect costs were estimated based upon per capita work loss and home productivity loss costs, which were attributable to HF based upon estimates from the 2001-2008 MEPS data and a negative bimodal model for annual days of work missed and annual days in bed attributable to illness or injury as a function of HF or other comorbid conditions.*  

HF can be classified by its impact on cardiac ejection fraction

### HF Classification Definitions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Classification Criteria</th>
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<tr>
<td>HF with reduced ejection fraction (HFrEF)</td>
<td>When left ventricular ejection fraction is less than 40%</td>
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<tr>
<td>HF with preserved ejection fraction (HFpEF)</td>
<td>When left ventricular ejection fraction is greater than 50%</td>
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The prevalence of HF characterized as HFpEF appears to be increasing. Currently, HFpEF is present in approximately half of HF hospitalizations.

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There May Be Underlying Causes of Heart Failure

Common causes of/risk factors for heart failure may include but are not limited to:

- Hypertension
- Cardiomyopathy, such as hypertrophic cardiac myopathy (HCM)
- Aging
- Diabetes
- Atrial fibrillation (as a trigger)
- Other, such as cardiac amyloidosis

Most HF patients are in the aging population. Patients over 65 with HF present with 6.5 comorbidities on average. This may complicate presentation, disease course, and treatment.

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1. There May Be Underlying Causes of Heart Failure

2. Most HF patients are in the aging population. Patients over 65 with HF present with 6.5 comorbidities on average. This may complicate presentation, disease course, and treatment.

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*Up to 80% of patients affected by HF are in the aging population. Aging population is defined as patients 65 years and older.

Cardiac amyloidosis (CA) is a rare, fatal, and underdiagnosed group of diseases that lead to HF\textsuperscript{1-3}

- CA is an infiltrative cardiomyopathy that occurs due to extracellular deposition of misfolded proteins, known as amyloid fibrils\textsuperscript{4,5}
- CA typically presents as HFP EF, eventually progressing to HFrEF\textsuperscript{6}

### Main types of CA\textsuperscript{7-9}

**Cardiac Amyloidosis**

- Light-chain amyloidosis (AL)
- Transthyretin amyloid cardiomyopathy (ATTR-CM)

**Others include:**
- Serum amyloid A
- Apolipoprotein A1
- Immunoglobulin heavy chain
- Atrial natriuretic peptide (ANP)

### Subtypes of ATTR-CM

- Wild-type ATTR (ATTRwt)
- Hereditary ATTR (hATTR)

AL and ATTR-CM account for ~95% of all CA diagnoses.\textsuperscript{7,8}

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Pathophysiology of ATTR-CM

Prevalence of ATTR-CM is unknown, but it is believed to be significantly underdiagnosed.

Your health system may be underdiagnosing ATTR-CM

50% of patients with HF have HFpEF

In 2 studies of older patients with HFpEF, ATTRwt deposits were identified in the hearts of 13%-17% of patients.

Proper diagnosis and management of a rare disease requires flexibility, personalization, and coordination through a multidisciplinary treatment approach.\(^4,\,6\) Missed, delayed, and incorrect diagnosis of rare diseases may lead to an inefficient use of resources\(^1\)

**Challenges for Diagnosis**
Primary care providers (PCPs) are often first to see patients with rare conditions. PCPs may lack the knowledge and confirmatory tests when addressing overlapping patient symptoms, making proper diagnosis of rare conditions difficult\(^2\).

**Suboptimal Disease Management**
Failure to recognize the correct diagnosis may result in prescription of inappropriate medications and not receiving disease-appropriate medications\(^1,\,3\).

**Frequent Care Points**
The average patient with a rare disease requires more than 9 health services, which includes hospitalizations, over a 2-year period\(^4\). Hospitalizations remain a main driver of direct and indirect health care costs\(^5\).

Proper diagnosis and management of a rare disease requires flexibility, personalization, and coordination through a multidisciplinary treatment approach.\(^4,\,6\)

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A sample patient affected by wild-type ATTR (ATTRwt) who presents to the clinic for evaluation and treatment*

**Chief Complaint**
A 68-year-old Caucasian male reports **dyspnea on exertion** that has been getting progressively worse over the last 3 years. He thought he was just “slowing down.”

**Past Medical History**: History of atrial fibrillation, 4 years ago  
**Past Surgical History**: Carpal tunnel release, about 10 years ago; left knee total replacement, 4 years ago  
**Medications**: Daily vitamin, baby aspirin  
**Allergies**: No known drug allergies  
**Review of Systems**: No headaches, reports no chest pain, notes some weakness in his hands bilaterally, no change in sleeping, normal stooling and voiding  
**Vitals**: BMI 31, mildly hypotensive, heart rate of 75

During the clinical encounter, various signs and symptoms can raise suspicion for ATTR-CM, many of which are signs of HF.¹

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¹Representative case for illustrative purposes only.

Confirming Suspicion of ATTR-CM: Invasive Techniques\textsuperscript{1-3}

Cardiac Tissue Biopsy

- Document the extent of amyloid infiltration
- Provide definitive etiologic classification of the amyloidogenic protein
- Achieve a definitive classification to help rule out AL amyloidosis

Reprinted with permission from Ruberg FL and Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation. 2012;126(10):1286-1300. https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.111.078915. Published by American Heart Association.\textsuperscript{3}

ASNC Practice Points highlight the importance of PYP cardiac imaging in diagnosing ATTR-CM noninvasively for select patients\(^1\)

Nuclear scintigraphy is a highly sensitive diagnostic imaging technique that displays increased cardiac uptake of a radiotracer, indicating the presence of ATTR\(^2,3\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Myocardial uptake absent</td>
</tr>
<tr>
<td>1</td>
<td>Myocardial uptake &lt; rib</td>
</tr>
<tr>
<td>2</td>
<td>Myocardial uptake = rib</td>
</tr>
<tr>
<td>3</td>
<td>Myocardial uptake &gt; rib</td>
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</table>

Both planar and SPECT imaging should be reviewed and interpreted using visual and quantitative approaches, irrespective of the timing acquisition. SPECT imaging is necessary for studies that show planar myocardial uptake because it can help differentiate myocardial uptake from blood pool or overlying bone uptake.

A diagnostic algorithm that provides an invasive and noninvasive diagnostic approach\(^1\)

**Heightened Clinical Suspicion for Cardiac Amyloid**
Older adult with clinical, biomarker, ECG, echocardiogram, and/or MRI imaging suggestive of cardiac amyloidosis

**Diagnostic Counseling**
Patient-centered counseling on diagnostic process, which may include further blood testing, nuclear imaging, genetic testing, and potential endomyocardial biopsy

**Testing for AL Cardiac Amyloidosis**
Presence of monoclonal protein by free light-chain assay and serum/urine immunofixation?

- **Biopsy**
  - **Congo Red Positive**
    - **Tissue Typing**
      - Immunohistochemistry & Mass Spectrometry (AL vs TTR vs Other)
    - Unlikely AL Cardiac Amyloidosis
  - **Congo Red Negative**
    - Unlikely AL Cardiac Amyloidosis

- **\(^{99m}\text{Tc-PYP Scan}**
  - **Negative**
    - Unlikely ATTR Cardiac Amyloidosis\(^*\)
  - **Positive**
    - ATTR Cardiac Amyloidosis
      - **TTR Genotyping**
        - hATTR
        - ATTRwt

\(^*\)If clinical suspicion remains for cardiac amyloidosis despite negative \(^{99m}\text{Tc-PYP scan}, biopsy may be considered to evaluate for other types of infiltrative cardiomyopathy (eg, AA).

Suspecting and diagnosing ATTR-CM allows patients and HCPs to choose an appropriate management plan

MOA of current and investigational pharmacological agents to address the underlying protein misfolding disorder

<table>
<thead>
<tr>
<th>TTR Stabilizers</th>
<th>TTR Silencers</th>
<th>Fibril Disruptors</th>
</tr>
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<tr>
<td>Stabilize the TTR protein, which slows breakdown and formation of fibrils</td>
<td>Target the liver to prevent the production of the TTR protein</td>
<td>Break up ATTR amyloid fibrils that have been deposited</td>
</tr>
</tbody>
</table>

Another option in select patients may include heart or heart/liver transplantation

A multidisciplinary approach includes a variety of specialists across the care continuum to differentiate, diagnose, and manage ATTR-CM.

**Primary Care Physician**
- Recognize the clinical presentation and signs and symptoms of ATTR-CM
- Refer to cardiologist for further evaluation

**Hematologist**
- Recognize the diagnostic workup for ATTR-CM in patients referred with abnormal monoclonal protein
- Evaluate patients with abnormal monoclonal protein

**Gastroenterologist**
- Recognize clinical presentation of common gastrointestinal symptoms that may be present in patients with ATTR-CM

**Orthopedist**
- Recognize the noncardiac orthopedic clinical clues that may be present in patients with ATTR-CM (e.g., carpal tunnel syndrome, hip/knee arthroplasty, biceps tendon rupture, lumbar spinal stenosis)

**Genetic Counselor**
- Provide counseling to patients and families about genetic testing and screening

**Neurologist**
- Awareness of the noncardiac neurologic clinical clues that may be present in patients with ATTR-CM (e.g., autonomic neuropathy, orthostatic hypotension, peripheral neuropathy, and peripheral sensory motor dysfunction)

**Cardiologist**
- Recognize the clinical presentation and clinical clues of ATTR-CM
- Integrate PYP testing into the diagnostic algorithm for patients with suspected ATTR-CM after ruling out AL

**Nuclear Cardiologist, Nuclear Medicine Specialist, or Radiologist**
- Recognize proper PYP cardiac imaging procedure
- Standardize testing protocols and reporting

**Neurologist**
- Awareness of the noncardiac neurologic clinical clues that may be present in patients with ATTR-CM (e.g., autonomic neuropathy, orthostatic hypotension, peripheral neuropathy, and peripheral sensory motor dysfunction)
Health systems may drive awareness, diagnosis, and management of ATTR-CM to advance health outcomes and quality of life for patients

Disease Burden and Unmet Need
Increase awareness of ATTR-CM as an underdiagnosed and fatal cause of HF

Suspicion and Diagnosis
Improve suspicion and diagnosis of ATTR-CM in a systemic manner within the organization

Management
Drive action by encouraging systemic ATTR-CM management to advance heart failure outcomes and quality measures
Rare Causes of Heart Failure: Can AI Technology Help?

Can we build systems where providers have AI support to detect these diseases?

**Input**
- Diagnostic codes
- Structured data from ECG, echocardiogram
- Laboratory values
- ECG voltage tracing
- Echocardiogram images

**Algorithm**
- Decision tree
- Logistic regression
- Random forest
- Convolutional neural network (“deep learning”)

**Output**
- Probability of ATTR
- Probability of AL
- Joint probability of all cardiac amyloid
- Probability of HCM
- Probability of PAH

**Decisions**
- Follow-up diagnostic testing (eg, PYP, serum free light chains)
- Markers of cardiac risk (eg, NT-proBNP, TnI)

HCM, hypertrophic cardiomyopathy; PAH, pulmonary arterial hypertension; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TnI, cardiac troponin I.

Challenges with introducing automated systems

Input
• Is the input (e.g., chest x-ray, echocardiogram) ordered frequently at an early treatable stage?
• Are the inputs consistent across institutions?
• Are there APIs to pull data (cost)?
• Can we access data without disrupting clinical workflow?

Algorithm
• How high of a positive predictive value do we need?
• How computationally demanding is preprocessing the data and deploying the model?
• Will models trained in one system generalize to another?

Output
• How should the results be presented?
• Does the provider need to see the “evidence” behind the recommendation?

Decisions
• Who will see the result?
• Do they have the expertise to make follow-up decisions?
• Can remote assistance be deployed to facilitate follow-up testing, prior authorizations?
• How to avoid adding to provider burnout generated by more pop-ups?
Upcoming!

Live Forum – March 26, 2020, in San Diego, CA

Rare Causes of Heart Failure: Can AI Technology Help?
An ATTR-CM Case Study

Rahul Deo, MD, PhD, cardiologist and data analytics expert from Brigham and Women’s Hospital (a Harvard-affiliated Partners HealthCare hospital), will review transthyretin amyloid cardiomyopathy (ATTR-CM), a rare, fatal, and underdiagnosed disease that can lead to heart failure. Patients affected by ATTR-CM often go years without a diagnosis and may cycle through multiple physicians and health systems. Artificial intelligence (AI) may lead to new approaches to identify at-risk patients. Dr Deo will discuss how AI may be employed to help systems identify patients affected by rare diseases, like ATTR-CM. Following this discussion, attendees will participate in a Q&A session where Dr Deo will facilitate a discussion regarding potential approaches to leveraging technology to detect rare diseases within their health care systems.

Featuring:

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