Greetings,

Albany Med is a regional leader in innovative and comprehensive heart care and we are committed to the heart health of your patients. We will periodically share information with you regarding the latest news, advancements, and innovative heart care treatments Albany Med has to offer.

With Albany Med’s recent affiliations with Columbia Memorial Health and Saratoga Hospital, I am proud to say that residents in Columbia, Greene and Saratoga counties now have improved access to life-saving heart care.

In this communication, we focus on restrictive and infiltrative cardiomyopathies, with particular emphasis on cardiac amyloidosis. These disorders, once thought to occur rarely in clinical practice, are gaining increased attention as newer imaging modalities facilitate more accurate diagnosis. Moreover, the emergence of FDA-approved treatments offer hope that the clinical course of these disorders, once thought mostly intractable and untreatable, can be modified through clinical treatment.

I hope you find this information helpful as you seek out the best cardiac care for your patients.

Best Regards,

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What is Restrictive and Infiltrative Cardiomyopathy? And How Are They Related?

The term cardiomyopathy describes disorders that arise principally from the myocardium itself, rarely the endocardium. In humans with cardiomyopathy, the disease mechanisms that cause changes in myocardial structure, functional impairment, myocyte loss, and/or associated scar formation are numerous. They include inherited genetic disorders, as well as local and systemic infiltrative and inflammatory diseases. Cardiomyopathies are classified on a phenotypic basis — dilated, hypertrophic, and restrictive. By far, the latter is the least often seen in adult clinical practice in western societies.

Let’s briefly discuss nomenclature. “Restriction” refers to a disturbance of normal ventricular filling. “Restrictive physiology” occurs when a disease process causes ventricular stiffening with resultant diastolic dysfunction. Restrictive physiology can be induced by various pathophysiological means including myocyte loss, scarring of the myocardium or endocardium, and/or deposition of abnormal matter in myocardial cells or interstitial spaces. Patients with “restrictive cardiomyopathy” will, almost by definition, display “restrictive physiology,” characterized by stiff ventricles which fill only under higher-than-normal diastolic pressures. Consequently, there is enlargement of the atria and pulmonary and peripheral congestion. In the more advanced stages of restrictive physiology, ventricular stiffening progresses to the point where end-diastolic volume is compromised, causing stroke volume and cardiac output to fall and leading to organ dysfunction or even death, despite a normal or above-normal ejection fraction.

“Infiltrative cardiomyopathy” refers to disease entities in which abnormal matter is deposited or accumulates within the heart — either within the myocytes themselves or in the interstitial spaces. What material is deposited within the heart depends on the underlying primary systemic (or local) disease process. Infiltrative cardiomyopathy can be caused by genetic errors of metabolism such as Fabry disease, Gaucher disease and Hurler syndrome. Sarcoidosis, an inflammatory disorder, is classified among the infiltrative cardiomyopathies, as well. Additionally, infiltrative cardiomyopathy may also be caused by deposition of normally-occurring human proteins that circulate through the body. Amyloidosis caused by AL disease (deposition of immunoglobulin light chains) and ATTR disease (deposition of transthyretin) are examples. This deposition of abnormal matter often leads to thickening of the walls of the heart which can be observed by imaging studies. Furthermore, excessive deposition of these various substances may lead to myocyte death and scar formation, a process also detectable by imaging modalities. Clinically, endomyocardial biopsy can confirm this pathologic deposition and permit biochemical characterization of the abnormal matter. While there is no pathognomonic clinical presentation in infiltrative cardiomyopathy, in advanced stages, restrictive physiology is commonly observed.

What’s the relationship between “restrictive cardiomyopathy” and “infiltrative cardiomyopathy”? While we often discuss these entities together, and they have significant clinical overlap, the terms should not be considered synonyms. It is certainly common for restrictive cardiomyopathies to be caused by infiltrative disorders such as amyloidosis. However, there are other causes of restriction that are not infiltrative, such as idiopathic (familial) restrictive cardiomyopathy and scleroderma heart syndrome. Moreover, patients with infiltrative cardiomyopathy, especially when diagnosed early in the disease process, may not display restrictive physiology. To further confuse matters, cardiac sarcoidosis, usually classified as an infiltrative cardiomyopathy, may present with a phenotype more akin to dilated than to restrictive cardiomyopathy. Furthermore, remembering that common things happen commonly, a patient with restrictive or infiltrative cardiomyopathy may present with a clinical picture attributable to more common pathology such as atherosclerotic or hypertensive heart disease. Finally, for patients with infiltrative cardiomyopathy caused by systemic and/or genetic conditions, the extra-cardiac features may dominate the clinical presentation.

KEY POINTS:

- Restrictive cardiomyopathies are those entities of the heart muscle or endocardium that impair ventricular filling, leading to elevated cardiac filling pressures, atrial enlargement, pulmonary and systemic congestion, arrhythmias, and, ultimately, reduced cardiac output, organ dysfunction and even death.
- Restrictive cardiomyopathy can be caused by infiltrative disorders or non-infiltrative disorders.
- Infiltrative cardiomyopathies are those entities that result from the deposition or accumulation of abnormal matter in the heart. This matter may include byproducts of errors of metabolism, sarcoid granulomas, or normally occurring (eg, immunoglobulin light chains) or mutant (eg, mutant transthyretin) human proteins. Scarring of the heart often results as infiltrative cardiomyopathy progresses.
- The clinical presentation in infiltrative cardiomyopathy varies with the underlying disease, the stage of cardiac involvement, and the amount of extra-cardiac involvement. In the latter stages of cardiac involvement, restrictive physiology would be a common but not universal presentation.
Cardiac Amyloidosis: Increasing Prevalence and New Treatments

Amyloidosis occurs when wild-type or mutant proteins, circulating systemically at normal or above-normal levels, become misfolded and are deposited as insoluble fibrils in various body tissues, including the heart. Various proteins are known to constitute the amyloid fibrils in human disease. Some are rare, such as the acute phase reactant serum amyloid A protein, which is known to cause amyloidosis in the context of chronic inflammatory diseases, and beta-2-microglobulin, which is deposited in patients on hemodialysis for many years. By far, the 2 most common forms of cardiac amyloidosis seen in the modern practice of adult cardiovascular medicine are AL (amyloidosis caused by deposition of immunoglobulin light chains) and ATTR (amyloidosis caused by the deposition of human transthyretin).

Transthyretin is produced predominantly by the liver and serves to transport retinol and thyroxine. Deposition of wild-type (wt) transthyretin in the heart causes amyloidosis. Using older nomenclature, ATTR-wt was once called senile cardiac amyloidosis. The deposition of this biochemically normal transthyretin leads to infiltrative cardiomyopathy, and frequently, restrictive physiology. Why certain individuals are susceptible to deposition of this normal protein is unclear. This tends to be disease of older age, with a striking male predominance.

In mutant ATTR, the liver produces biochemically abnormal transthyretin, which is deposited most often in the heart and/or nervous system, leading to familial cardiac amyloidosis and/or familial amyloid polyneuropathy. Familial ATTR is known to be a genetic disorder, caused by mutations of the TTR gene. Single point mutations are known to be disease-causing. Certain mutations cluster along racial, ethnic and geographic lines. Commercial laboratories offer DNA testing of the TTR gene for patients with known or suspected ATTR.

It was previously thought that amyloidosis was a rare condition, but recent data would suggest otherwise. At Albany Med, we are seeing ~1 new confirmed case each month. It is likely that amyloidosis was grossly underdiagnosed in the past. Improvements in imaging modalities and other technical advances also contribute to the increasing “prevalence” of this disorder. With the aging of the population, more patients are at risk for certain forms of amyloidosis, especially ATTR-wt. Finally, the emergence of treatment options for this once untreatable condition may have attracted increased physician attention more so than in the past.

Virtually all organ systems can be involved in amyloidosis. Cardiac involvement is fairly common in ATTR and AL, with up to 50% of patients with AL being found to have cardiac involvement at some level. As an infiltrative cardiomyopathy, amyloidosis is frequently associated with restrictive physiology. Accordingly, a common presentation in patients with cardiac amyloidosis is “heart failure with preserved ejection fraction.” In fact, among patients with right- and left-sided heart failure with preserved EF and left ventricular hypertrophy (LVH) that is not explained by other conditions (e.g., uncontrolled hypertension or aortic stenosis), cardiac amyloidosis should be a serious consideration. This statement is especially true when left ventricular wall thickness measurements exceed 15 mm. Paroxysmal or persistent atrial fibrillation is another common presentation, being explained by the atrial dilation so common among patients with restriction. Orthostatic hypotension, conduction system disease, pericardial disease, stroke, syncope and sudden death are other common ways that patients will present. Of course, in patients with involvement of other organ systems (eg, renal, neurologic, digestive or hematologic), the extra-cardiac manifestation may dominate the clinical picture.

Diagnosis of cardiac amyloidosis starts with awareness of the entity and clinical suspicion. The presence of HFpEF plus LVH without another explanation for the LVH should certainly evoke concern for amyloidosis. Clinical history (including careful family history), physical exam, ECG (watch for low QRS voltage) and cardiac imaging (including echocardiographic strain imaging) will assist in establishing a diagnosis. Strain imaging is a newer echocardiographic technique.

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According to Dr. Mikhail (Misha) Torosoff, Professor of Medicine at Albany Medical College, “Myocardial strain evaluation is an advanced echo-cardiographic imaging technique for investigating left ventricular deformation during mechanical systole. Strain is assessed by measuring change in distance between individual myocardial points, speckles, during the cardiac cycle. Normal global longitudinal strain is -20% or less. Myocardial strain imaging has a particular role in evaluation of patients with increased left ventricular wall thickness, which may be due to an infiltrative disease, like amyloidosis. In cardiac amyloidosis, affected myocardial segments manifest decreased deformation which is reflected in less negative strain.”

As AL originates from a disorder of plasma cells, patients with cardiac AL will often have a circulating paraprotein, a plasmacytosis in the marrow, and/or amyloidosis demonstrable by biopsy of extra-cardiac tissue. Patients with ATTR will have no detectable paraprotein or plasma cell dyscrasia, unless they have a separate and unrelated condition such as monoclonal gammapathy of uncertain significance (MGUS), as rarely occurs. Technetium pyrophosphate scanning is a newer nuclear imaging modality that identifies the presence of ATTR, albeit with confidence, treatment is focused on biochemical characterization of the precursor protein and development of an accurate treatment plan.

When the biochemical analysis of amyloid material obtained by biopsy indicates ATTR, it is useful to characterize this as ATTR-wt versus mutant. ATTR-wt usually presents sporadically, in later life, and with a ~90% male predominance. Clues to mutant ATTR will come from the family history. Genetic testing can also be helpful for distinguishing the two. Genetic testing has its pitfalls, however, such as the known presence of TTR gene variants that are not disease-causing. In this regard, referral to a cardiomyopathy specialist with experience in these matters can be helpful.

Establishing a secure diagnosis of cardiac amyloidosis is crucial, not only for prognostication, but also allows for development of an accurate treatment plan. In the presence clinical and imaging findings typical of infiltrative cardiomyopathy, the demonstration of a paraprotein together with biopsy-proven amyloidosis detected in extra-cardiac tissue, is compelling for the diagnosis of cardiac AL. However, characterization of the amyloid precursor protein as light chain versus transthyretin (using advanced techniques such as laser microdissection) is advised before initiating therapy. In this way, one can avoid treating cardiac amyloidosis as AL when it is, in fact, ATTR, and vice versa. When cardiac amyloidosis is suspected and there is no apparent involvement of extra-cardiac organs or tissues, we prefer endomyocardial biopsy over “blind” organ/tissue biopsies such as fat pad biopsies. At Albany Med, we do heart biopsies at high volume with good results and low complication rates. Moreover, we enjoy a productive working relationship with our cardiac pathologists. Having a heart biopsy specimen in hand that shows amyloid protein deposition (via routine staining techniques) not only confirms the diagnosis of amyloidosis but also allows for biochemical characterization of the precursor protein and development of an accurate treatment plan.

When a diagnosis of AL is established with confidence, treatment is focused on suppression of the plasma cell clone that is producing the monoclonal precursor protein in unchecked quantities. A lengthy discussion of treatment of AL is beyond the scope of this review. In brief, in AL patients well enough for treatment, suppression of the plasma cell clone can be achieved with chemotherapeutic approaches, with or without autologous stem cell transplantation. However, cardiac involvement with amyloidosis is a major barrier to successful stem cell transplantation. For a few select patients who have cardiac AL disease, but without significant involvement of extra-cardiac organs and without multiple myeloma, heart transplantation followed by stem cell transplantation is an option in a few experienced centers worldwide.

Absence cardiac involvement, treatment of AL can be very effective. With the onset of cardiac involvement, especially with advanced cardiac disease such as full-blown restrictive physiology, treatment options become limited. This highlights the importance of prompt and definitive recognition of cardiac involvement in patients with AL. Having said that, it can be difficult to distinguish garden variety HFpEF from early-stage AL or ATTR, especially in the absence of LVH, restriction or evidence of a plasma cell dyscrasia. Once again, referral to a cardiomyopathy specialist with experience in these matters can be helpful.

Treatment of cardiac ATTR is about to undergo a revolution. Newer drugs undergoing testing, some soon coming to market, are known to stabilize circulating transthyretin tetramers, such that tissue (heart and nervous system) deposition is blunted. While amyloid protein deposited in tissue was once thought to be insoluble, methods for leeching amyloid protein from affected tissues are now being explored. Finally, for a very few select patients with the mutant form of cardiac ATTR, combined liver and heart transplant offers the hope of long term survival. Liver replacement corrects the production of mutant transthyretin, whereas heart transplant is a viable long term solution for the consequences of restrictive-infiltrative manifestations in the heart.
Ralph N. was a 77-year-old man who had a long-standing plasma cell dyscrasia, characterized as monoclonal gammopathy of uncertain significance (MGUS), since at least 2012. He had renal insufficiency, but no known cardiac disease in the past. He denied a heart murmur and had no evidence of cardiomyopathy or sudden cardiac death in blood relatives. He felt well until the fall of 2017 when he developed, fairly abruptly, symptoms of fatigue, breathlessness and swelling. He was referred to a local cardiologist and underwent a number of diagnostic tests:

- A cardiac MRI showed normal LV EF with diffuse LVH, but no evidence of scarring.
- An echocardiogram showed marked atrial dilation, mitral and aortic valve thickening, LVH, normal LV EF, and diastolic dysfunction. There was no mention of systolic anterior motion of the mitral valve or an LV outflow tract gradient.
- A stress test revealed diminished exercise tolerance and ventricular arrhythmia, but no evidence of ischemia. He underwent coronary angiography showing no obstructive coronary disease. His LV end diastolic pressure was 27 mmHg.
- A Holter monitor showed ventricular tachycardia. A single chamber ICD was implanted for, as stated in the procedure note “a patient with non-sustained V-tach and hypertrophic cardiomyopathy.”
- In summary, he was believed to have hypertrophic cardiomyopathy (HCM). His medical treatment included sotalol and diuretics. He underwent repeated thoracenteses on a monthly basis for recurrent pleural effusions. He also underwent carpal tunnel surgery.

In the Spring of 2018, as his disease rapidly progressed despite treatment, he moved north to live closer to family. His diagnosis of HCM and its treatment plan were carried forward by his new doctors. The patient continued to accumulate pleural fluid with repeated therapeutic thoracenteses. When referred to a distant tertiary care center in October 2018 for a second opinion regarding HCM he was told that he most likely did not have HCM. He was seen by an Albany Med oncologist in November 2018 who suspected that the patient’s plasma cell dyscrasia had progressed to multiple myeloma with systemic amyloidosis. Evaluation revealed elevated serum free kappa and lambda light chain levels, and a plasmacytosis (29%) in the bone marrow. He was referred to Albany Med’s Heart Failure Clinic for evaluation and management of suspected cardiac amyloidosis.

When seen in the Heart Failure Clinic he complained of progressive fatigue, dyspnea, and overall declining quality of life. His physical exam revealed a large right pleural effusion and anasarca. An echocardiogram was highly compatible with amyloidosis; HCM was thought to be unlikely. Arrangements were made for thoracentesis and pleurodesis. He underwent right heart catheterization showing elevated cardiac filling pressures and low cardiac output. An endomyocardial biopsy was also performed demonstrating advanced cardiac amyloidosis. Chemotherapy with dexamethasone (40 mg daily) was begun. Unfortunately, his clinical compromise and renal dysfunction progressed almost daily. Ultimately there was a decision to abandon chemotherapy and put a palliative care plan in place. His ICD, implanted only 8 months earlier for the diagnosis of “HCM”, was inactivated.
Robert S. is a 69-year-old man with very little prior cardiac history until recently. Earlier in his life he was a very active individual, running marathon distances in his 30s and 40s, and still running regularly until recently. Upon initial history-taking he complained of progressive exercise intolerance over a 6-month period, but upon further questioning he acknowledged that it had been closer to 2 years since he last enjoyed what he would consider his normal level of endurance and fitness. He denied chest pain with exertion or at rest. He also denied syncope, pre-syncope, or palpitations. There was no history of heart murmur. His family history was unremarkable.

He sought a cardiology evaluation locally. An echocardiogram was performed, and he was noted to have concentric LVH, with report of interventricular septal dimension of 18 mm. There was evidence of right and left atrial enlargement with diastolic dysfunction. His LV EF was normal and no significant valve disease was noted. He subsequently underwent ECG-stress testing where he completed 9 minutes and 24 seconds on a Bruce Protocol. He had a mildly hypertensive response with brief runs of supraventricular tachycardia during the post-exercise recovery period. There was no evidence of cardiac ischemia. He was started on verapamil for treatment of his hypertension and exercise-induced arrhythmia. He was referred for a cardiac MRI which demonstrated concentric LVH with LV walls measuring up to 18 mm. Late gadolinium enhancement suggested significant cardiac scarring. He was referred to Albany Med’s Heart Failure Clinic for further evaluation.

Upon examination his blood pressure was 144/94 on verapamil. No heart murmurs were noted. There was no pulmonary or systemic congestion. His ECG revealed sinus rhythm with frequent PACs and low QRS voltage.

Reflecting on his history, examination, ECG and imaging data, the Heart Failure team opined that cardiac amyloidosis was the most likely diagnosis. Hypertrophic cardiomyopathy presenting with a concentric and symmetric phenotype could not be excluded but seemed less likely. His history of hypertension was more recent and mild, making hypertensive heart disease a less likely diagnosis. There was no valve lesion that could explain his LVH. While he was a trained athlete decades earlier, there was no case to be made for athletic heart syndrome at this time. Moreover, diastolic dysfunction is not observed in this syndrome. Finally, cardiac wall thickness measurements in the range of 18 mm would be highly unusual for hypertensive heart disease or athletic heart syndrome.

Blood and urine studies ordered in the Heart Failure Clinic revealed no evidence of a paraprotein. A repeat echocardiogram with strain imaging was performed which showed depressed LV average global longitudinal strain, compatible with amyloidosis. Other findings on echocardiography were similar to those reported by the referring cardiologist. Technetium pyrophosphate nuclear scanning was performed and a pattern compatible with ATTR was reported by the interpreting nuclear medicine physician. To facilitate a definitive diagnosis of cardiac amyloidosis and permit biochemical analysis of the amyloid protein, endomyocardial biopsy was performed. The biopsy confirmed amyloidosis on H&E staining and analysis of the amyloid protein at a referral laboratory revealed the amyloid material to be transthyretin. Lacking a family history indicative of familial amyloidosis or any other clinical suspicion for mutant ATTR, the patient declined genetic testing looking for mutations of the TTR gene. His final diagnosis was cardiac amyloidosis, transthyretin, wild type.

Figure 1. Technetium pyrophosphate scan, anterior view, from patient Robert S. Note the marked increase in tracer uptake in the heart [blue circle, region of interest 2 (roi2)] by comparison with the lungs and other surrounding tissues [white circle, region of interest 1 (roi1)].

Figure 2. Heart biopsy specimens from patient Robert S. showing extensive deposition of amyloid protein with hematoxylin and eosin staining (upper panel) and congo red staining (lower panel).