Utilizing Echocardiography: Differentiating Amyloidosis from Hypertrophic Cardiomyopathy and Systemic Hypertension

Background

In 1834, a German botanist, Mattias Scleiden, described the waxy starch in plants as “amylon”. It wasn’t until 1854, when Rudolph Virchow coined the word “amyloid” which he used to describe “tissue deposits that stained like cellulose when exposed to iodine”.[1] Amyloidosis (amyloid) (seen in Figures 1, 4, and 7), is considered an infiltrative disease in which there are deposits of amyloid fibrils in extracellular space of a variety of tissues, such as: heart, kidney, liver, peripheral and autonomic nervous systems, and the GI tract.[1] In cardiac involvement, amyloid proteins deposit between the cardiac myocytes, resulting in increased wall thickness, as seen by 2D.[2] Different types of amyloid include AL (light chain) amyloid, which is considered primary amyloid, TTR amyloid which is split into TTR wild type and TTR familial, and AA amyloid which is considered secondary amyloid. It is a relatively rare disease with an incidence of 5.1-12.8 per million person-years and only 1,275-3,200 new cases being diagnosed in the United States annually.[1] Echocardiography is a great screening mechanism that can assess and decipher if the heart is affected by amyloid or if the findings are caused by amyloid mimickers such as hypertrophic cardiomyopathy (HCM) and systemic hypertension (HTN).[3]

Hypertrophic cardiomyopathy (seen in Figures 2, 5, and 8), occurs when there is hypertrophy of the left ventricle (LV), which happens in the absence of an underlying cause.[4] HCM is an autosomal dominant genetic disease that alters the contraction function of the cardiac sarcomere. In turn, that leads to myocardial hypertrophy as well as fibrosis. There are five typical distribution patterns of HCM which include: asymmetrical septal hypertrophy (ASH) (increased septal thickness), concentric hypertrophy (all walls are thick), free wall hypertrophy, mid-ventricular hypertrophy, and apical hypertrophy. The hypertrophy is usually asymmetric instead of concentric - but it can vary.[2,4]

Systemic hypertension (seen in Figures 3 and 6) can be categorized into either primary (essential) hypertension or secondary hypertension. Primary HTN is idiopathic, meaning there is not a definitive cause. Secondary HTN occurs when the patient has underlying issues that contribute to HTN.The guidelines for systemic hypertension are a systolic blood pressure greater than or equal to 140 mmHg and a diastolic blood pressure greater than or equal to 90 mmHg.[2] A patient with HTN may show signs of increased wall thickness which may be mistaken for amyloid. The increased thickness of the LV wall is caused by the extensive exposure to increased systemic resistance. An increased amount of pressure may also cause the left atrium (LA) to be enlarged - as also seen in amyloid and HCM.[5]

Clinical Presentation

Clinical presentation may vary for each patient depending on the progression of the disease. For instance, fatigue levels and edema may vary depending on the severity and stage of the disease process.

	Amyloid	HCM	HTN
Weight loss	✓		
Fatigue	✓	✓	✓
Peripheral Edema	✓	✓	✓
Arthropathy	✓		
Cardiomyopathy	✓	✓	
Glossomegaly	✓		
Carpal Tunnel	✓		
Congestive Heart Failure	✓		
Peripheral Neuropathy	✓		
Angina		✓	✓
Asymptomatic		✓	✓
Dyspnea		✓	✓
Syncope		✓	✓
Arrhythmias			✓
Stroke			✓

Table 1: A comparison of clinical presentation typically found with each specific disease.[1,2,5,8,9,11]

Echocardiographic Findings

When Amyloid, HCM and HTN first present, the heart often has a preserved ejection fraction with any degree of diastolic dysfunction. As they progress, the diastolic function may decline. In the later stages of these diseases, systolic function will begin to deteriorate leading to systolic dysfunction. This can lead to an overall decrease in function and a decrease in cardiac output. In order to help determine between the various pathologies, echocardiography is considered the gold standard. Tables 2 and 3 (below) show the specific 2D and Doppler findings for each disease and how the appearance may mimic each other (depending on the stage and distribution of the disease).

2D Findings	Amyloid	HCM	HTN
Increased Wall Thickness	✓	✓	✓
Sparkling appearance of the myocardium	✓		
Thickened Valves	✓	✓	
Pericardial Effusion	✓		
Pleural Effusion	✓		
Atrial Enlargement	✓	✓	✓
Regional Wall Motion Abnormalities			✓
Increased Cardiac Mass		✓	✓
Left Ventricular Systolic Dysfunction	✓	✓	✓

Table 2: Typical 2D findings of Amyloid, HCM and HTN[2,4,5]

Doppler	Amyloid	HCM	HTN
Diastolic Dysfunction	✓	✓	✓
Left Ventricular Outflow Tract Obstruction*		✓	
Decreased Mitral Annular Velocity	✓	✓	✓

Table 3: Comparison of Doppler findings consistent with Amyloid, HCM and HTN.[2,4,6,7]
*Apical HCM is not associating with having left ventricular outflow tract obstructions.

An echocardiography comparison (seen below) of the apical four chamber views of each pathology. Notice the 2D similarities and differences as listed in Table 2.
*LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; LVH = left ventricular hypertrophy

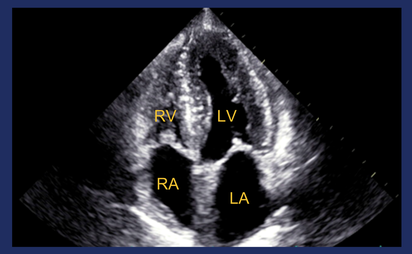


Figure 1: Amyloid: shows the speckled or ground glass appearance and increased wall thickness of a typical case. Atrial enlargement and thickened valves can be visualized in this example.

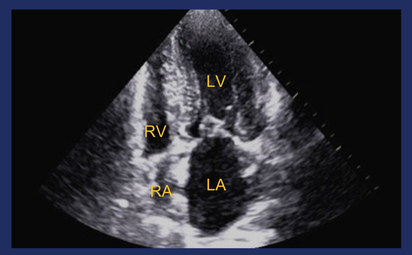


Figure 2: HCM: Shows the increased wall thickness of the LV as well as left atrial enlargement. In response to the LVH, the LV mass will increase. In this image there is also a thick mitral valve as seen between the LA and LV.

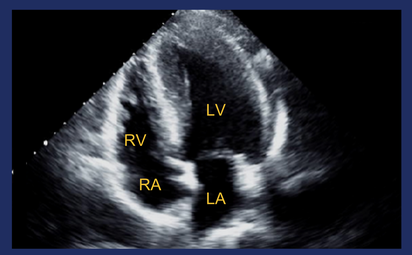


Figure 3: HTN: Shows the increased wall thickness of the LV as a result of prolonged exposure to increased afterload. As a response to LVH, LV mass will increase as well. The LA compared to the RA appears to be enlarged.

Strain

Strain is a speckle tracking technique used to visualize the way the cardiac muscle contracts longitudinally and circumferentially. The type of strain used in Figures 7 and 8 is LV GLS (global longitudinal strain). Amyloid may be difficult to differentiate from mimickers such as HCM and HTN; strain is able to depict the functional capabilities between these diseases. Typical strain values for a normal functioning heart fall around a value more negative than -18; whereas cardiac amyloid patients will present with strain values that are less negative than -12%.[6] This means that in a heart with amyloid, there will be less movement detected each heartbeat. The characteristic appearance of a cardiac amyloid strain pattern is apical sparing. This means that there is a noticeable preservation in contraction of the apical segments and a decrease in contraction of the basal and mid segments.[3] As for HCM, the strain pattern will show regional systolic myocardial impairment that is dependent on the distribution pattern[4] and HTN may show concentrically decreased longitudinal strain values.[7] Strain is a fairly new technology for cardiac sonographers. Due to this, hypertension is not a routine indication for echocardiographers to perform strain. It is more likely performed in patients with amyolid and HCM. However, as strain becomes more prevalent, sonographers and cardiologists may find it beneficial to be used in other pathologies as well.

ECG Tracings

An Electrocardiogram (ECG) may be the first indication of the amyloid disease process. An ECG is an exam of the heart’s electrical signals. It is a quick and painless test that is administered via 12 electrode patches and leads (wires) that are placed on the chest and limbs. The wires are attached to a device that reads the electrical signals produced with each cardiac cycle. An ECG is a noninvasive exam that can diagnose common heart issues such as arrhythmias (abnormal heart rhythms), waveform patterns indicating a current or previous heart attack, and can evaluate how well medications and pacemakers are controlling the heart conditions. These findings on an ECG may be an indication for an echocardiogram.

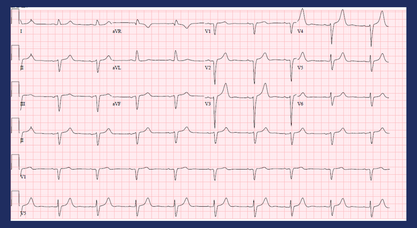


Figure 4: Amyloid
Low voltage in limb leads is a characteristic finding

Pseudoinfarct in chest leads[6,10]

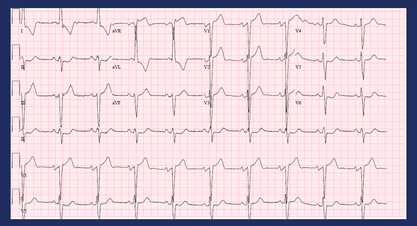


Figure 5: HCM
High voltage QRS

Repolarization abnormalities: ST-segment depression, T-wave inversion[9]

T-wave inversions in the inferolateral leads specifically for apical LV hypertrophy[9]

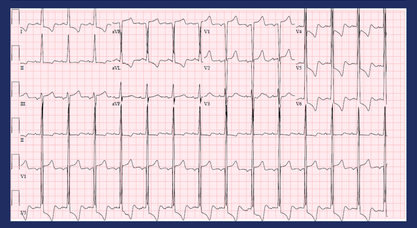


Figure 6: HTN
High voltage QRS

LA enlargement seen via a P-wave duration of 0.04 seconds with a depth of 1mm[5]

Strain Tracings

The strain bullseye is similar to a radar map. The lighter the color the less the myocardium is contracting in that segment of the heart. In the strain diagram, the conical LV is displayed in a 2D collapsed image. There are 3 rings, demonstrating the levels of the LV (base, mid, and apex) and the center, which is the apical cap. Each level is further subdivided into segments: base 6, mid 6, apex 4, apical cap 1. Including the apical cap, in total there are 17 segments.

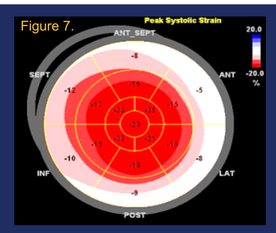
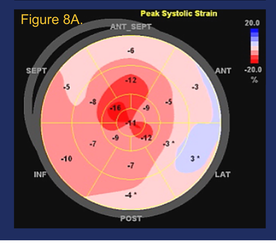


Figure 7. This strain bullseye represents amyloid. The basal segments are contracting the least because it is the lightest color. The mid segments, represented by light pink, indicate the heart is contracting better than the basal segments. The apex is represented by dark red because it is contracting the best. For amyloid this gives it the apical sparing appearance.



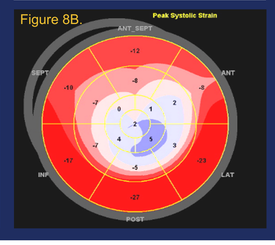


Figure 8. The strain bullseye pattern for HCM will demonstrate strain abnormalities dependent on the specific distribution pattern of hypertrophy. **A.** An asymmetrical septal hypertrophy case where the basal lateral and anterior walls indicate the least amount of longitudinal function whereas the basal inferior and most of the mid segments show better function. The red area of the mid/apical septum and anterior septum indicates stronger function. **B.** An apical HCM case indicating better GLS values in the basal segments and worse values in the apical region corresponding with the area of greatest hypertrophy.

Conclusion

Echocardiography is an important screening modality in differentiating amyloid from HCM and HTN. 2D findings such as sparkling appearance of the myocardium, presence of pericardial effusion, and pleural effusion, help to differ amyloid from its mimickers. Amyloid will present with low voltage QRS in contrast to HCM and HTN, which present with high voltage. Strain tracings help to visualize the different patterns that each pathology present with. Amyloid presents with a large apical sparring pattern. Depending on the distribution pattern of HCM, different segments of the heart may not function normally.

References

1. Baker KR, Rice L. The amyloidoses: clinical features, diagnosis and treatment. Methodist Debakey Cardiovasc J [Internet]. 2012 [cited 2020 Apr 26];8(3):3–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3487569/
2. Anderson B. A sonographer’s guide to the assessment of heart disease. 2016. 505 p.
3. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, et al. Echo parameters for differential diagnosis in cardiac amyloidosis: a head-to-head comparison of deformation and nondeformation parameters. Circ Cardiovasc Imaging [Internet]. 2017 Mar [cited 2020 Apr 30];10(3). Available from: https://www.ahajournals.org/doi/10.1161/CIRCIMAGING.116.005588
4. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res. [Internet]. 2017 Sep 15 [cited 2020 Apr 30];121(7):749–70. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5654557/
5. Vidt, MD DG, Prisant, MD M. Hypertensive heart disease . The Journal of Clinical Hypertension [Internet]. 2008 Oct 9 [cited 2020 Apr 30];7(4). Available from: https://onlinelibrary-wiley-com.ezp3.lib.umn.edu/doi/full/10.1111/j.1524-6175.2005.04119.x
6. Lang RM, Goldstein SA, Kronzon I, Khandheria B, Mor-Avi V, American Society of Echocardiography, editors. ASE’s comprehensive echocardiography. Second edition. Philadelphia, PA: Elsevier; 2015. 879 p.
7. Lee J-H, Park J-H. Role of echocardiography in clinical hypertension. Clin Hypertens [Internet]. 2015 Jun 17 [cited 2020 Apr 30];21. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4750785/
8. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. Clin Med (Lond) [Internet]. 2018 Apr 1 [cited 2020 Apr 30];18(Suppl 2):s30–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6334035/
9. Fuster V, Harrington RA, Narula J, Eapen ZJ, editors. Hurst’s the heart. Fourteenth edition. New York: McGraw-Hill Education [Internet]; 2017 [cited 2020 Apr. 30]; Available from: http://accessmedicine.mhmedical.com.mclibrary.idm.oclc.org/content.aspx?bookid=2046&sectionid=176567996.
10. Sanchorawala V. Light-chain (AL) amyloidosis: diagnosis and treatment. CJASN [Internet]. 2006 Nov 1[cited 2020 Apr 30];1(6):1331–41. Available from: https://cjasn.asnjournals.org/content/1/6/1331