Imaging cardiac amyloidosis: Patient page

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Amyloidosis is a disease that develops when abnormally folded proteins collect together to form amyloid fibrils, which deposit in various organs and cause organ damage. Amyloidosis in the heart can be identified by using various imaging tests. This patient page provides an overview of imaging in cardiac amyloidosis.

Key Words: PET • SPECT • cardiomyopathy • amyloid heart disease • echo • MRI

AMYLOIDOSIS

What is Amyloidosis?

Amyloidosis is a disease that develops when abnormally folded proteins (misfolded) collect together to form amyloid fibrils, which deposit in various organs and cause organ damage. Normal circulating proteins occasionally misfold, but the body's protective mechanisms can get rid of these misfolded proteins and recycle the protein components. When this process fails, or when an excess of circulating misfolded proteins overwhelms the process, amyloidosis can result.

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What is Cardiac Amyloidosis?

Cardiac amyloidosis is caused by the deposition of amyloid fibrils between the heart muscle cells. The two most common types of protein fibrils depositing in the heart are light chain (AL) and transthyretin (ATTR) proteins. While light chain amyloidosis results from an excess of abnormal light chain proteins produced by cancerous plasma cells in the bone marrow, transthyretin amyloidosis may result from misfolding healthy TTR proteins produced by the liver, as in wild type amyloidosis of aging. Alternatively, a genetic mutation of the TTR gene can result in altered TTR protein that aggregates and causes hereditary ATTR amyloidosis. Whatever the cause, a build-up of amyloid fibrils in the heart may keep the heart muscle from relaxing between heart beats, causing high pressure in the heart chambers and blood vessels. Eventually, the heart may not be able to squeeze blood adequately to supply oxygen to the body.

What are the Symptoms of Cardiac Amyloidosis?

Amyloidosis usually is suspected in people with any of the following: swollen tongue; easy bruising, especially around the eyes; heart symptoms (listed below); tingling in the hands or feet; lightheadedness; and

swelling in the feet from kidney problems. People with hereditary ATTR may experience tingling and postural changes in blood pressure without heart symptoms. Due to the variety of symptoms, a definitive unifying diagnosis of amyloidosis is challenging and often delayed. Amyloidosis in the heart or cardiac amyloidosis typically causes fluid build-up in the heart and body, causing difficulty in breathing, swelling of the feet, discomfort at rest or with exercise in the jaw or chest, heart rhythm abnormalities, changes in blood pressure with posture, lightheadedness, or loss of consciousness.

How is Amyloidosis Diagnosed?

When your doctor suspects you might have amyloidosis, he or she may perform blood and urine tests [serum protein electrophoresis, urine protein levels, urine protein electrophoresis, free light chain assay, troponin (T, I, or high sensitivity), brain natriuretic peptide, BNP, or NT-proBNP]. A pathologist usually confirms the diagnosis by examining affected cells or tissues (fat cells from belly fat, bone marrow, or heart muscle) through a biopsy. If ATTR amyloidosis is diagnosed, genetic testing may also be performed.

IMAGING CARDIAC AMYLOIDOSIS

If you have symptoms of cardiac amyloidosis, your doctor may order imaging tests for the heart, such as echocardiography (ultrasound of the heart), magnetic resonance imaging (MRI of the heart), and radionuclide imaging [single photon emission computed tomography (SPECT) or positron emission tomography (PET) scan of the heart and whole body].

ECHOCARDIOGRAPHY (HEART ULTRASOUND OR ECHO TEST)

What is Echo?

In this test, sound waves are used to take moving pictures of the heart, enabling better study of the structure and function of the heart.

How is an Echo Test Done?

You are asked to lie down on your left side for this test. Small metal sticky pads are placed on your chest to monitor your heart rhythm during the procedure. A small amount of gel material (may be lukewarm or cool) is placed on the left side of your chest and heart pictures are taken using a wand (ultrasound probe) on the left side of your chest. You may be asked to hold your breath briefly for some of the pictures. The gel is cleaned after the test is completed. No special preparation is needed for this test and you can eat and drink at normal times. This test does not hurt, has no side effects, and is completed in about 30 minutes.

What Can the Echo Test Reveal About Cardiac Amyloidosis?

The echo can provide images of the size and function of the four chambers of the heart: right atrium, right ventricle, left atrium, and left ventricle. The atria are the upper chambers and the ventricles are the lower chambers of the heart. The echo pictures can reveal an increase in wall thickness of the left and right ventricles (lower chambers of the heart), increase in brightness of the signal from the heart (see Figure 1A), increase in

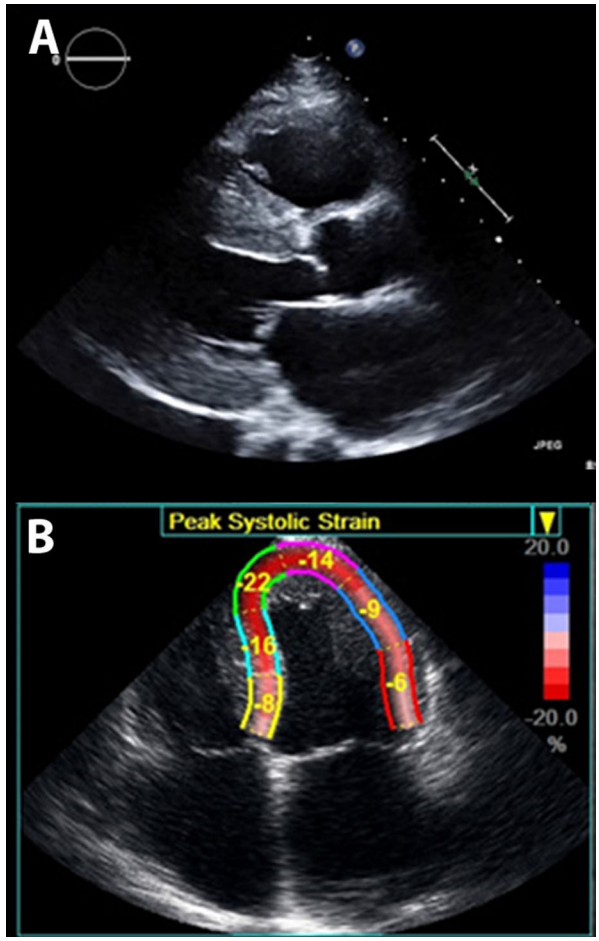

Figure 1. Echocardiogram in cardiac amyloidosis. Panel **A** shows increased wall thickness of the left ventricle and the bright and sparkly myocardium. Panel **B** shows that the function of the heart measured as peak systolic strain is better preserved at the apex compared to the base (− 22 vs – 8, − 14 vs − 6). These two features as well as relaxation abnormalities (not shown) are commonly seen in cardiac amyloidosis.

overall heart weight, abnormal relaxation of the heart muscle (tissue Doppler imaging), abnormal contraction of the heart muscle (reduced ejection fraction), or thickening of the heart valves. An advanced echo test called longitudinal strain imaging can identify a typical pattern of contraction in the heart muscle, where, on the left side, the tip contracts better than the base of the heart. Abnormal strain is an early marker of amyloidosis and can identify amyloid deposits before there are obvious increases in wall thickness or heart weight (see Figure 1B). The atria commonly increase in size and decrease in function, with increased thickness of the wall between the atria. These features can be imaged with echo. Decrease in atrial function can sometimes result in irregular heart rhythms or blood clot formation. In addition, fluid build-up around the heart (pericardial effusion) occasionally can be seen in amyloidosis. All of the above are indirect features of cardiac amyloidosis, and your doctors have to separate these findings from other heart conditions, such as hypertrophic cardiomyopathy or high blood pressure related heart muscle thickening. With echo imaging, amyloid deposits cannot be discovered right away. Your doctor may sometimes repeat the echo test to check your heart size and function and monitor changes after treatment.

CARDIAC MAGNETIC RESONANCE IMAGING (HEART MRI, OR CMR)

What is an MRI?

This is a test that can take moving pictures of the heart based on its water content. A small plastic tube may be placed in your blood vessel (vein) to inject gadolinium, a dye used to improve MRI pictures. Also, small metal sticky pads may be placed on your chest to monitor your heart rhythm during the test.

How is a Heart MRI Test Done?

An MRI camera is used to take pictures of the heart. Although the MRI test does not hurt, it can be noisy, and a head set is provided to minimize the noise. You will be asked to lie still and flat on your back for this test. You may be asked to hold your breath briefly for some of the pictures. The MRI takes about 45 minutes to complete. Most people can take this test, but if you are claustrophobic you may need medicine to reduce anxiety. People with pacemakers or metallic objects in their bodies may not undergo MRI. Good kidney function is necessary to receive gadolinium, and people with allergy to gadolinium may not receive it. You may be asked to fast for 4 hours before this test.

What Can an MRI Test Show in Cardiac Amyloidosis?

MRI images are typically better quality than echo images and can show most of the same features, including thickened walls of the heart, large atria, and small fluid around the heart and lungs (see Figure 2A). As with the echo test, the MRI test does not directly image the amyloid fibrils, though it can show indirect features of amyloidosis in the heart. When cardiac amyloidosis is present, the MRI may show a bright signal in the heart muscle (ventricles and atria) after injection of gadolinium [late gadolinium enhancement (LGE)]. LGE may involve the entire thickness or only part of the thickness of the heart muscle (see Figure 2B), and LGE in the atrial walls is a typical feature of cardiac amyloidosis. MRI is especially successful at studying atrial function Also, amyloidosis expands the space between the heart muscle cells [extracellular volume

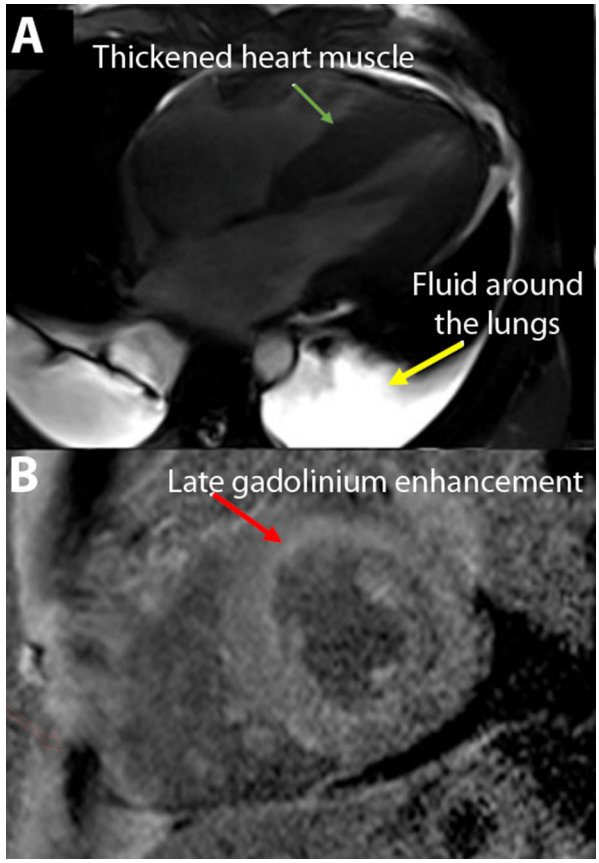

Figure 2. MRI of the heart in cardiac amyloidosis. Panel **A** shows increased wall thickness of the left ventricle (green arrow) and fluid around the lungs (yellow arrow). Panel **B** shows diffuse late gadolinium enhancement (gray color, red arrow) of the entire left ventricle (normal appearance on these images should be black). These features are commonly seen in cardiac amyloidosis.

(ECV)], and this can be measured with an MRI. In healthy hearts, the ECV is about 0.25; with amyloidosis, this level can increase to 0.40 or higher. LGE and ECV may be helpful in identifying early amyloid deposits in the heart before wall thickness starts to increase. Early studies suggest that ECV may identify changes in the heart after treatment.

RADIONUCLIDE IMAGING

What is Radionuclide Imaging?

These tests use small and safe amount of radioactive dye (radiotracers) to take pictures of the heart. Two types of radionuclide imaging tests are used for amyloidosis: SPECT with radiotracers such as ^{99m}technetium pyrophosphate (PYP scan in the US), or (DPD or HMDP scan in Europe) and amyloid PET scan with one of several amyloid binding radiotracers (see below).

What is a PYP Scan?

The most commonly used radionuclide imaging test for TTR cardiac amyloidosis is the PYP scan, performed on a SPECT scanner.

How is a PYP Scan Performed?

A small plastic tube is placed in a blood vessel to inject a small and safe amount of ^{99m}Tc-PYP. Images of the heart are taken about 1-3 hours after injection of ^{99m}Tc-PYP. This test does not hurt. You will have to lie still and flat on your back for 15 minutes. Sometimes after completing the heart picture, images of the whole body may be taken for 20 minutes. The total time for this test is 2-4 hours. No special preparation is needed and you can eat and drink at your normal times.

What Can a PYP Scan Show About Cardiac Amyloidosis?

In people without cardiac amyloidosis, the scan is negative, meaning the heart does not appear on the ^{99m}Tc-PYP scan, while in those with ATTR amyloidosis, the scan is positive, meaning the heart lights up on the ^{99m}Tc-PYP scan. In cardiac ATTR amyloidosis, the scan is strongly positive: the heart is as bright as the ribs (Grade 2), and the heart is brighter than the ribs and bones are faintly seen (Grade 3), as shown in the Figures 3A and 3B. Your doctors also can compare the brightness of the heart with the right lung; a ratio of > 1.5 indicates the presence of cardiac ATTR amyloidosis. However, in people with AL cardiac amyloidosis, the scan may be entirely normal (Grade 0) or faintly abnormal (Grade 1), with a heart to lung ratio of < 1.5. If amyloidosis of the heart is suspected based on symptoms, echo, or MRI tests, further testing of the blood, urine, and bone marrow may be necessary to identify AL amyloidosis.

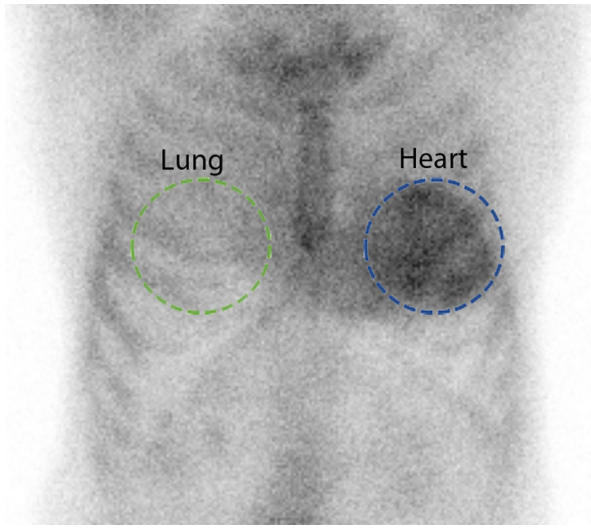

Figure 3. ^{99m}Tc-PYP amyloid heart scan in ATTR cardiac amyloidosis. This figure shows uptake of ^{99m}Tc-PYP scan by the heart (blue dotted oval) suggesting cardiac ATTR amyloidosis. Normal expected appearance is shown in the green dotted oval.

What is an Amyloid PET Scan?

This is an advanced test that uses one of several PET amyloid tracers (^{18}F-florbetapir, ^{18}F-florbetaben, ^{11}C-pittsburgh B compound, and other tracers). Currently, these tracers are FDA approved for imaging amyloid but not cardiac amyloidosis in the brain. These radiotracers have been shown in multiple research studies to image both AL and ATTR cardiac amyloidosis.

The advantage of this test is that it can directly image both AL and ATTR amyloid deposits in the heart, and it is the only imaging test that can reveal AL amyloidosis in the heart as well as in the whole body. But the test is not widely available, and it is not yet FDA approved for imaging the heart.

How is an Amyloid PET Scan Performed?

A small plastic tube is placed in a blood vessel to inject a small and safe amount of amyloid PET radiotracer. Then, images of the heart are taken, usually

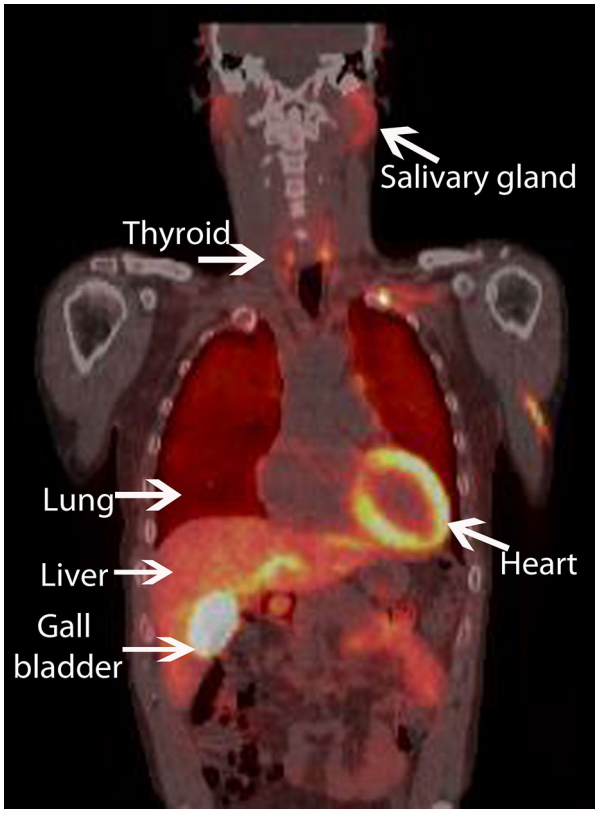

Figure 4. ^{18}F-florbetapir amyloid PET/CT scan in AL amyloidosis. This figure illustrating an uptake of ^{18}F-florbetapir by the heart, salivary glands, thyroid gland, and lungs consistent with AL amyloid deposition in these organs. The appearance in the liver and gall bladder is expected elimination of ^{18}F-florbetapir.

starting with the time of injection of the radiotracer. This test does not hurt. You will have to lie still and flat on your back for 60 minutes for these pictures. Sometimes after completing the heart picture, images of the whole body may be taken for 15 minutes. The total time for this test from start to finish is between 1 and 1.5 hours. No special preparation is needed, and you can eat and drink at your normal times. Most people tolerate this test well.

What Can an Amyloid PET Scan Reveal About Cardiac Amyloidosis?

In people without cardiac amyloidosis, the scan is negative, meaning the heart is not seen on the PET scan, while in those with AL or ATTR amyloidosis, the scan is positive, meaning the heart walls light up on the PET scan (see Figure 4). As opposed to a heart biopsy, which tests a small sample of 1-2 mm tissue, an amyloid PET scan may show amyloid deposits in the entire heart, lungs, and in the rest of the body as well.

SUMMARY

Cardiac amyloidosis is caused by misfolded proteins depositing in the heart as amyloid fibrils. Amyloidosis can be challenging to diagnose because it can manifest with different symptoms. If a diagnosis of amyloidosis is suspected in the heart, your doctor may order urine and blood tests and a biopsy. Your doctor may also order an echo or MRI test. More specifically, your doctor may order a ^{99m}Tc-PYP scan if ATTR cardiac amyloidosis is suspected. A strongly positive ^{99m}Tc-PYP scan confirms ATTR cardiac amyloidosis, meaning a heart biopsy may not be needed. Since a weakly positive scan or a negative scan is possible with AL amyloidosis, your doctor may suggest further evaluation based on your symptoms to exclude it. Imaging tests of the heart not only help diagnose cardiac amyloidosis, but they also help trace the course of the disease and evaluate response to treatment. Most of the imaging tests show indirect evidence of amyloidosis, but an advanced test such as amyloid PET scan can directly measure amyloid in the heart and detect both AL and ATTR cardiac amyloidosis. This test, however, is not widely available and more research is needed to understand its use in diagnosing cardiac amyloidosis and following up on response to treatment.

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