Having a Heavy Heart
Approaches to Infiltrative Cardiomyopathy

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Forward
Information about a real patient is presented in stages (boldface type) to expert clinicians (Drs. Neal K. Lakdawala and Jacob P. Laubach) who respond to the information, sharing his or her reasoning with the reader (regular type). A discussion by the authors follows.

A 63-year-old man with previous combat-related Agent Orange exposure and no healthcare contact for 40 years presented to his primary care physician with dyspnea on exertion, orthopnea, and bilateral lower extremity edema. Electrocardiography reportedly showed sinus rhythm, and transthoracic echocardiography demonstrated moderate left ventricular hypertrophy with normal systolic function. New onset heart failure with preserved ejection fraction, attributed to hypertensive heart disease, was diagnosed, and he was begun on diuretics with an initial modest improvement in his symptoms. He presented to our hospital 1 month later with worsening heart failure symptoms and inadequate outpatient response to escalating doses of oral furosemide.

The patient reported dyspnea with minimal activity, severe orthopnea, nightly paroxysmal nocturnal dyspnea, and worsening lower extremity edema. There was a history of abdominal distension, although he found that his arms were thinner and his eyes appeared more sunken-in. On examination he was cachectic with a pulse of 85 beats per minute, blood pressure of 82/70 mm Hg, and respiratory rate of 28 breaths per minute with labored breathing. His skin was cool to touch. A diminished single first heart sound, persistently split second sound with a prominent pulmonary component, and S3 gallop were present. Jugular venous pressure was estimated at 18 cm H₂O. The remainder of the examination was notable for dullness to percussion at the lung bases, ascites, tender hepatomegaly, and marked abdominal venous pressure with associated ascites and edema. Signs and symptoms (orthopnea and paroxysmal nocturnal dyspnea) of left heart failure are also present. Meta-analyses have shown the presence of a S3 gallop, increased jugular venous pressure, and positive abdominal reflux to be predictive of increased left ventricular filling pressure. However, the absence of pulmonary rales is not helpful in ruling out left-sided heart failure, as chronic pulmonary venous congestion leads to pulmonary lymphatic adaptation, which limits the development of alveolar edema and associated rales. The persistently split second sound with a prominent pulmonary component suggests elevated pulmonary arterial pressures with delayed right ventricular emptying.

The physical examination in decompensated heart failure is critical to triaging the severity of the patient’s condition and selecting appropriate medical therapy. Several findings in this patient are concerning. First is the degree of respiratory impairment with increased work of breathing, and urgent management of the patient’s respiratory status should be a top priority. Additionally, the patient’s skin temperature was described as cool, suggesting a low cardiac output state. This is supported by the finding of a low pulse pressure proportion (by convention <25%), which suggests impairment in cardiac output (≤ 2.1 L/min/m²). Given the constellation of biventricular congestion and diminished cardiac output, positive inotropic therapies are typically needed to augment diuresis.

Although the patient had been provisionally diagnosed with hypertensive heart disease, it is notable that there are no criteria for left ventricular hypertrophy present on ECG. The finding of low QRS voltages in the limb leads with normal
voltages in the precordial leads is suggestive of an infiltrative process, including cardiac amyloid.

The case to this point presents an important diagnostic dilemma. A previously healthy man was initially found to have mild clinical heart failure and increased left ventricular (LV) thickness with preserved systolic function on echocardiography. When presented with such a patient, infiltrative heart disease should be considered alongside common hypertensive heart disease. In this assessment, findings incongruent with hypertensive heart disease in the patient’s evaluation should be reviewed. Infiltrative disease is suggested by the severity of heart failure out of proportion to the reported TTE results and increased LV thickness on TTE with diminished QRS amplitude on ECG. Other clinical features and ECG/TTE findings that should instigate further evaluation are detailed in the Table.2–8

The physical examination findings in this patient are supported by the laboratory findings. Whereas passive hepatic congestion typically manifests as cholestatic transaminits, the finding of hepatocellular transaminits suggests ischemic hepatitis from diminished cardiac output. Elevation in serum lactate, as is seen here, is a late finding providing evidence of systemic hypoperfusion. The elevated total protein and low albumin suggest an increased level of a circulating monoclonal protein (paraproteinemia). The bicytopenia and suspected paraproteinemia provide evidence for an underlying hematologic disorder, although anemia from abnormal iron handling9 and thrombocytopenia from splenomegaly and sequestration could be alternative explanations in a patient with heart failure.

After initial stabilization of the patient, echocardiography is the next important step toward identifying an etiology.

Patient presentation (continued): Transthoracic echocardiography demonstrated severe concentric biventricular hypertrophy with end diastolic interventricular septal thickness of 1.9 cm and left ventricular posterior wall thickness of 1.7 cm (Figure 2A and 2B; Movie I in the online-only Data Supplement). The left ventricular cavity size was small, and the systolic function was moderately reduced with a left ventricular ejection fraction of 40%.

Measures of diastolic filling were consistent with restrictive diastolic filling (at least grade 3 diastolic dysfunction), with E dominant mitral inflow, short E velocity deceleration time (110 ms), peak mitral E velocity 101.0 cm/sec, and E/E' (averaged from tissue Doppler at the lateral mitral annulus and inferoseptum) >13 (Figure 2C). Right ventricular hypertrophy was seen, and the right ventricular function was reduced. Both right and left atria were severely enlarged. There was diffuse thickening of all 4 valves (Figure 2A). The estimated pulmonary artery systolic pressure was 37 mm Hg plus right atrial pressure (estimated at 15–20 mm Hg based on IVC appearance). There were moderate pleural effusions.

Dr Neal K. Lakdawala: The echocardiogram demonstrates moderate systolic dysfunction in the setting of severe biventricular hypertrophy and restrictive diastolic filling. Biatral enlargement is also seen, which is a common feature of restrictive processes and results from reduced ventricular compliance. The findings are suggestive of an infiltrative cardiomyopathy, including cardiac amyloid. The differential diagnosis based on this echocardiogram includes hypertrophic cardiomyopathy, hypertensive heart disease, infiltrative cardiomyopathy including amyloidosis, storage diseases such as Danon and Fabry diseases, and others.8 Including biventricular hypertrophy, valvular thickening, and abnormalities of diastolic filling, the classic appearance of the myocardium
<table>
<thead>
<tr>
<th>Differential Diagnosis and Differentiating Features of Diseases With Increased Left Ventricular Wall Thickness*†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Presentation</strong></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>AL amyloid</td>
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<tr>
<td>Senile (WT TTR) amyloid</td>
</tr>
<tr>
<td>Mutant TTR amyloid</td>
</tr>
<tr>
<td>Fabry disease</td>
</tr>
<tr>
<td>Danon disease</td>
</tr>
<tr>
<td>Friedrich ataxia</td>
</tr>
<tr>
<td>PRKAG2-related cardiomyopathy</td>
</tr>
</tbody>
</table>

*Compiled from select references.2–8
†Mucopolysaccharidosis, familial nontransthyretin amyloid, cardiac oxalosis, Pompe disease, glycogen storage disease IV, and mitochondrial disease (eg, MELAS) are exceedingly rare causes of increased LV wall thickness.
‡Good Positive predictive value, poor negative predictive value.
§Good positive and negative predictive value.

99mTc-DPD-SPECT/CT indicates 99mTc-diphosphono-propanodicarboxylic acid single photon emission computed tomography; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MR, magnetic resonance; RV, right ventricle; TTR, transthyretin; and WT, wild type.
on echocardiography in patients with cardiac amyloidosis has
been described as speckled. However, most echocardiogra-
phy machines now use harmonic imaging, which makes this
finding nonspecific. Disabling harmonic imaging on most
machines is simple and can be undertaken for obtaining se-
veral select images to help support the diagnosis.
This degree of echocardiographic hypertrophy, without
increased voltages, points to cardiac amyloid. It is notable
that several storage cardiomyopathies are associated with
increased QRS voltages (eg, Danon and Fabry diseases).8

**Patient presentation (continued):** Given the initial and
ongoing instability of the patient, central access was
obtained and the patient was transferred to an intensive
care unit for closer monitoring. The patient was begun on
intravenous diuretic with dopamine infusion at an initial
dose of 2 μg/kg/min. Measurement of intracardiac filling
pressures with a pulmonary artery catheter demonstrated
a mean right atrial pressure of 21 mm Hg, a pulmonary
artery pressure of 59/36 (mean 45) mm Hg, and pulmonary
artery wedge occlusion pressure of 38 mm Hg (Figure 3).
The cardiac output by Fick calculation was 3.2 L/min,
with a cardiac index of 1.7 L/min/m². Systemic vascular
resistance was 1313 dyn-s-cm⁻², and pulmonary vascular
resistance was 2.2 Woods units.

*Dr Neal K. Lakdawala:* Appropriate clinical stabilization
of the patient is underway. The elevated left- and right-sided
filling pressures and depressed cardiac output measured by
the pulmonary artery catheter are consistent with our clin-
ical assessment. Among patients with advanced heart failure,
there is a 70% to 80% concordance between elevated right
atrial pressure (≥10 mm Hg) and elevated pulmonary artery
wedge occlusion pressure (≥22 mm Hg).10,11 During the bed-
side evaluation it is important to be mindful of causes of
elevated right atrial pressure in the absence of high left-sided
filling pressures, such as pulmonary arterial hypertension. The
elevated right ventricular end diastolic pressures are sug-
gestive of a restrictive cardiomyopathy but are relatively nonspe-
cific. Other hemodynamic findings characteristic of restriction
can be obtained using simultaneous left and right ventricular
pressure recordings, and include pulmonary hypertension, an
early ventricular diastolic dip-and-plateau (square root sign),
and near-equilibration of diastolic pressures, although the
diastolic left ventricular pressure is frequently slightly higher
than the right ventricular diastolic pressure.12 Additionally, in
patients with restrictive cardiomyopathy, there is often simul-
taneous decrease of LV and right ventricular pressure during
inspiration, referred to as ventricular concordance. This latter
finding contrasts with the changes in pressure with respira-
tory variation seen in constrictive pericarditis, wherein pres-
ures are discordant (ie, right ventricular pressure increases on
inspiration and the LV pressure decreases).13

Before sending this patient to the cardiac catheterization
laboratory, two important questions should be considered a
priori. First, does this patient require invasive hemodynamic
support with intra-aortic balloon pump or percutaneous ven-
tricular assist device? The placement of these hemodynamic
support devices is increasingly recognized as an important
short-term bridge for hemodynamic support in patients with
cardiogenic shock while recovery or more definitive therapies
can be pursued.14 Studies of these devices to date support their
role in augmenting hemodynamics in patients with cardiogenic
shock compared with intra-aortic balloon pump, but have not
yet shown an effect on mortality.15–17 perhaps owing to the
small number of patients studied or the heterogenous popula-
tion of patients with cardiogenic shock enrolled. Additionally,
it is important to consider that surgical VAD placement may be
impossible in some patients with cardiac amyloid or other infil-
trative diseases as a result of insufficient chamber dimensions
to accommodate the device’s inflow conduit. Nonetheless,
in patients in whom inadequate perfusion is observed, these
devices deserve consideration where available.

In this patient, a trial of inotropic support is reasonable
before pursuing invasive mechanical circulatory support.
Studies have not shown a long-term mortality benefit with
inotropic therapy, and indeed these therapies may increase
mortality.18 Among patients with acute heart failure and renal
dysfunction, a recent study found that neither low-dose dopa-
mine nor nesiritide improved renal function or adequacy of
diuresis.19 Patients in cardiogenic shock, as presented here,
were excluded from this trial, and inotropic therapy remains
commonly used in this setting to support hemodynamics, assist
diuresis, and temporize to further therapy such as mechanical
support, or transplantation. The use of inotropes is limited by
the provocation of dysrhythmia or ischemia.

The second consideration is whether endomyocardial
biopsy (EMB) is indicated at this stage. In the most recent
American Heart Association Scientific Statement regarding

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**Figure 2.** Transthoracic echocardiographic (A) parasternal long-axis and (B) short-axis views demonstrate right ventricular thickening,
severe left ventricular thickening, a speckled appearance to the left ventricle, and left atrial enlargement (Movie I in the online-only Data
Supplement). End diastolic interventricular septal and posterior wall thickness was 1.9 cm 1.7 cm, respectively. There was grade III dia-
stolic dysfunction, evidenced here by E dominant mitral inflow and rapid mitral valve E deceleration time of 110 ms (C).
the indications for EMB, heart failure associated with unexplained restrictive cardiomyopathy was given a class IIa (level of evidence C) recommendation. Indeed, there are circumstances in which EMB is required to establish the diagnosis. However, before undertaking this procedure, it must be recalled that if there is clinical suspicion for cardiac amyloid, as there is here, fat pad aspirate is an easy, safe, first-line diagnostic procedure. Rectal biopsy is an alternative if fat pad is unrevealing. Furthermore, advanced imaging can help elucidate an etiology of cardiac amyloidosis. For example, in addition to the echocardiographic features above, myocardial strain and strain rate imaging may help differentiate cardiac amyloidosis from hypertrophic cardiomyopathy. In cardiac amyloidosis, there is greater restriction of basal compared with apical motion, and indeed mean left ventricular basal strain has been shown to be an independent predictor of cardiac and all-cause mortality. Cardiac MRI can demonstrate global subendocardial late gadolinium enhancement and associated abnormal myocardial and blood-pool gadolinium kinetics. Finally, nuclear scintigraphy is emerging as a novel method for detecting visceral amyloid using 99mTc-DPD. This method appears to be highly sensitive for detecting transthyretin cardiac amyloid, but is only positive in 30% of patients with light chain (AL) amyloid. Thus, EMB biopsy should be considered when there is clinical suspicion but histological confirmation from noncardiac tissue is lacking, concomitant paraproteinemias confuses the diagnosis of possible systemic amyloid, when there is suspicion of senile cardiac amyloid (generally confined to the heart), or before undertaking orthotopic heart transplant. Overall, there are limited data on safety of EMB specifically in cardiac amyloid, but overall the reported rate of complications of EMB is low. In a prospective study of patients with unexplained cardiomyopathy, the rate of biopsy procedure-related complications—including cardiac tamponade, ventricular arrhythmia, heart block, and damage to the tricuspid valve—was reported at 3.3% and the rate of vascular access complications at 2.7%, although the rate of the latter is likely to be lower in the era of ultrasound-guided sheath insertion.

**Patient presentation (continued):** Serum protein electrophoresis revealed an IgM lambda monoclonal protein at 20.8% of total protein (1.60 g/dL) with markedly elevated serum free lambda (λ) light chains and decreased kappa (κ):lambda light chain ratio (free κ:λ ratio of 0.02). Fat pad and bone marrow biopsies were obtained. The fat
Dr Jacob P. Laubach: These findings support a diagnosis of Waldenstrom macroglobulinemia with secondary light chain amyloidosis involving the myocardium. Systemic amyloidosis is a heterogeneous disorder characterized by extracellular deposition of 8 to 10 nm fibrils derived from a range of low-molecular-weight proteins circulating in plasma. AL amyloidosis can occur as a primary disorder or secondary to a hematologic malignancy such as multiple myeloma or Waldenstrom macroglobulinemia, as in the patient described, wherein there is production of an amyloidogenic light chain. The Institutes of Medicine have concluded that there is evidence to suggest that exposure to Agent Orange is a risk factor for the development of AL amyloidosis.26

Dr Neal K. Lakdawala: At this point, several management considerations become relevant. First, certain medications are classically contraindicated in patients with cardiac amyloid. One is digoxin, which experimental studies suggest can directly bind myocardial fibers and lead to elevated (and toxic) local myocardial drug concentrations even in the absence of elevated systemic levels. Additionally, systemic amyloid can infiltrate various sensory, motor, and autonomic nerves, the latter leading to autonomic dysfunction. Accordingly, angiotensin receptor enzyme inhibitors are generally avoided, because these drugs blunt an important axis for blood pressure control, and in the presence of preexisting autonomic dysfunction and diminished vascular tone can lead to profound hypotension. Nondihydropyridine calcium channel blockers are poorly tolerated because of their negative inotropic effect. Patients with amyloidosis are suspected to be at higher risk of cardiac thromboembolic disease, even in the absence of atrial arrhythmia. This is likely a result of diminished contractility of the atrium attributable to infiltration with amyloid fibrils. Hence, even in the absence of documented atrial fibrillation, anticoagulation is often considered, particularly if there is a history of cerebrovascular events.

Drs Neal K. Lakdawala and Jacob P. Laubach: Definitive management of patients with primary or secondary AL cardiac amyloid with myocardial involvement is challenging, because these patients often experience multisystem disease, either as sequelae of systemic amyloid (eg, renal dysfunction from light chain nephropathy) or cardiac dysfunction (eg, cardiorenal syndrome). In general, if patients are not yet prohibitively decompensated from a cardiac perspective, chemotherapy can be considered. Systemic chemotherapy, although not indicated in other forms of amyloidosis, is the mainstay of treatment for AL amyloidosis and is administered with the goal of decreasing production of amyloidogenic light chain. High-dose myeloablative chemotherapy and autologous stem cell transplantation can be considered in primary AL amyloid.27,28 However, patient selection is important, particularly with significant myocardial involvement, which is associated with high transplant-related morbidity and mortality. Chemotherapy regimens used in patients with secondary AL amyloidosis should have proven efficacy against the underlying malignancy, whether it be multiple myeloma, Waldenstrom macroglobulinemia, or other hematopoietic neoplasm. In this patient, treatment strategies aimed at underlying Waldenstrom macroglobulinemia could be considered.

Patient presentation (continued): Despite ongoing diuretic and inotropic support, the patient remained critically ill. He was deemed too unstable to undergo chemotherapy, with a Karnofsky Performance Score of 20. Mechanical circulatory support as a bridge to sequential cardiac transplantation and stem cell transplant was considered. However, when the prognosis and anticipated forthcoming clinical course was presented to the patient, he chose to focus care on comfort care and expired peacefully shortly thereafter.

Drs Neal K. Lakdawala and Jacob P. Laubach: As illustrated here, the prognosis for individuals with severe organ amyloidosis...
Cardiac amyloid is an uncommon, albeit increasingly recognized, cause of heart failure. Systemic amyloidosis generally results from dystrophic deposition of misfolded protein precursors, including free light chains (AL amyloidosis), amyloidogenic mutant transthyretin (ATTR), and wild-type senile transthyretin, arising from heterogenous underlying conditions.\(^2,22\) Amyloid deposition leads to abnormalities of myocardial structure and function, either through infiltration of the myocardium causing a restrictive cardiomyopathy, and, in the case of AL amyloidosis, through direct myocardial toxicity. Differentiating the types of cardiac amyloidosis is essential to guiding treatment and prognosis. Common amyloid features include the finding of apple-green birefringence under polarized light when stained with Congo red, as well as a distinctive green color when stained with sulfated Alcian blue. Multiple organ systems—including cardiac, neural, renal, and hepatic—can be affected, although the pattern of organ involvement varies with the cause of amyloidosis.

Primary AL amyloidosis results from dysregulated production of either mutant immunoglobulin kappa or lambda light chain by a clonal population of bone marrow plasma cells. Likewise, AL amyloidosis may be related to dysregulated production of either mutant kappa or lambda light chain, in the setting of a B-cell malignancy such as multiple myeloma, Waldenstrom macroglobulinemia (as in the patient described), or other non-Hodgkin lymphoma. When these amyloid-forming light chains deposit systemically, organ toxicity arises, including neuropathy (peripheral or autonomic), nephropathy (including light chain nephropathy), hepatopathy, and cardiomyopathy.

Cardiomyopathy manifests most commonly as a restrictive cardiomyopathy, wherein fibril infiltration causes increased ventricular mass and wall thickness and abnormal myocardial relaxation. Unlike other causes of amyloidosis, light chain amyloidosis results in direct myocardial toxicity. In experimental studies, when adult rat cardiomyocytes were exposed to free light chains from purified urine of patients with AL amyloid, a decrease in fractional cardiomyocyte shortening was seen.\(^29\)

Aggressive treatment of AL amyloidosis has been shown to improve prognosis.\(^30\) In patients with primary AL amyloidosis, melphalan and prednisone was for many years the standard approach, but regimens incorporating the proteasome inhibitor bortezomib are now more widely used based on higher levels of hematologic response. Moreover, bortezomib therapy has been associated with improved surrogate cardiac measures, including LV wall thickness, N-terminal brain natriuretic peptide, and New York Heart Association functional class.\(^31\) There are data for the use of the immunomodulatory agents lenalidomide and pomalidomide as well. Treatment options remain limited by advanced organ dysfunction or poor functional class. In these patients, sequential orthotrophic heart transplant followed by stem cell transplantation has shown clinical promise,\(^32-34\) although prognosis remains guarded and organ availability in most areas is a limitation. Overall, early and rapid referral of patients to an experienced center is crucial to assuring optimal outcomes.

Amyloidosis from mutant amyloidogenic transthyretin (ATTR) arises from mutations in the tissue transthyretin (TTR) gene, which cause production of misfolded TTR in hepatocytes, and causes neuropathy and cardiomyopathy.\(^35\) Interestingly, hepatic accumulation is minimal, and hepatic failure is uncommon. Nonetheless, liver transplant is the definitive treatment in ATTR. Inheritance of ATTR is autosomal dominant with variable expression but high penetrance. The prognosis is considerably more favorable than AL amyloidosis. Although >70 mutations have been implicated in ATTR, 1 of the most common mutations is a substitution of isoleucine for valine at position 122 (V122I).\(^36\) V122I heterozygosity occurs in ≈4% of blacks\(^37\) and can result in late-onset cardiomyopathy in both men and women. Differentiating this from hypertensive heart disease in this population relies on recognition of clinical clues as illustrated in the case presentation.

Unlike mutant transthyretin, amyloidosis attributable to wild-type transthyretin—senile systemic amyloidosis—occurs as a result of aberrant deposition of normal transthyretin in the myocardium, and occurs almost exclusively in elderly men. This course is more slowly progressive, and the prognosis more favorable than AL amyloidosis: median...
survival from the onset of heart failure is 7.5 years versus 15 months in patients with AL amyloidosis, for an identical degree of left ventricular thickening. Extra-cardiac involvement in senile systemic amyloidosis is rare, and hence EMB is often required. However, fibril infiltration may be patchy reducing the sensitivity of EMB. Additionally, the finding of transthyretin fibrils on EMB occurs in a number of patients without clinical amyloidosis as a benign consequence of aging, reducing the specificity of EMB. Ruling out underlying AL amyloidosis is essential. Care should be undertaken here, too, because 3% to 5% of these elderly patients will have an incidentally found monoclonal gammopathy of unknown significance, with paraproteinemia which is unrelated to cardiac amyloidosis. In these patients biopsy or advanced imaging modalities are key to making this distinction.

Diagnostic approaches to suspected cardiac amyloid were illustrated in the case presentation above. Differentiation of various types of amyloidosis is critical to determining treatment options and prognosis. In assessing for AL amyloidosis, the most common form of amyloid, serum, or urine electrophoresis with immunofixation as well as serum-free light chain assay should be performed. A bone marrow evaluation that includes an aspirate, core biopsy, cytogenetics, and congo red staining is suggested as well. The sensitivity of bone marrow Congo red staining is limited, and thus, if negative, biopsy of the abdominal fat pad, rectum, or organ in which there is suspected amyloid involvement should be pursued. Amyloid subtyping by mass spectrometry proteomic analysis can be considered in selected patients where there is uncertainty regarding the specific amyloid type. Advanced imaging has promise to play an increasingly important role in facilitating the diagnosis. Overall, a number of diagnostic algorithms have been proposed. A modification of these algorithms is presented (Figure 7).

In conclusion, cardiac amyloidosis is a heterogeneous group of clinical conditions manifesting as heart failure with important overlapping and differentiating features. Early interspecialty collaboration is essential for prompt diagnosis and effective management.

Disclosures

None.

References


Key Words: amyloid □ cardiomyopathies
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**Movie Legend**

**Movie 1.** Transthoracic echocardiographic parasternal long axis views demonstrating right ventricular thickening and hyokinesis, severe left ventricular thickening and hyokinesis, a speckled appearance to the left ventricle, and significant left atrial enlargement. Best viewed with Windows Media Player.