In The Name Of God
The Role of Heart transplantation in cardiac amyloidosis

M. beheshti monfared, MD
Cardiac Surgeon
Shahid Beheshti University of Medical Sciences
In a system that lacks sufficient organs to meet demand, offering heart transplantation for cardiac amyloidosis has been hypothesized by some to be a poor allocation of a limited resource.
Amyloidosis is a disease characterized by deposition of insoluble protein fibrils in tissues, which leads to toxic effects and progressive organ dysfunction. Amyloid fibrils in cardiac amyloidosis are most frequently derived from immunoglobulin light chains (AL) or transthyretin (ATTR).
ATTR amyloidosis occurs from deposition of misfolded transthyretin protein, in either a wild-type form or associated with inherited mutations.
Cardiac Amyloidosis in a restrictive cardiomyopathy with thick ventricular walls and small cavity, getting progressively smaller as disease develops.
An analysis of UNOS database showed that patients with restrictive cardiomyopathy (which likely includes those with amyloidosis) had a higher risk of death while awaiting transplantation than patients with ischemic or dilated cardiomyopathy.
While routine pharmacologic therapies for heart failure are rarely effective, chemotherapy can prolong life in AL amyloidosis.
Nevertheless, cardiac involvement makes the prognosis worse in all types of the disease, and advanced heart failure therapies are increasingly considered.

a) LVAD

b) Heart Or combine heart / liver / kidney transplantation
LVAD

Although small ventricular cavity precludes patients from receiving long-term left ventricular assist devices, transplantation still remains an option.
One challenge in treating cardiac amyloidosis is that biventricular restrictive physiology frequently leads to intolerance of traditional guideline-directed medical therapies for heart failure. No cardiac medications or implantable devices have been shown to improve mortality for patients with amyloid cardiomyopathy.
Heart transplantation is 1 option for treating amyloid cardiomyopathy, but its use has been controversial due to early reports of poor post-transplantation outcomes.
Several types of systemic amyloidosis can involve the heart and are described by the fibril type. The main fibril types are light chain (AL) and transthyretin (ATTR). In AL amyloidosis abnormal plasma cells produce inappropriate quantities of light-chain protein.

In ATTR amyloidosis, amyloid deposits in the heart as a result of inherited genetic mutations (familial type), or as genotypically normal proteins in a wild-type disease (ATTRwt), also known as senile amyloidosis.
Since the prognosis for AL amyloidosis is often determined by the degree of cardiac involvement, a concept of heart transplant followed by autologous stem cell transplantation in select patients with advanced cardiac AL amyloidosis has been suggested.
Although this approach may lead to higher response rates and improved overall survival in select patients, there is a significant treatment-related mortality.
1. **Induction chemotherapy**: to minimize the burden or to eliminate plasma cells in the bone marrow producing light chains.

2. **Heart transplant**: to create cardiovascular stability for high-dose chemotherapy. The interval between step 1 and step 2 is typically about 6 months.
3. High-dose melphalan conditioning chemotherapy followed by autologous hematopoietic stem cell transplant (bone marrow transplant):

The interval between step 2 and step 3 is also about 6 months.

The objective is to replete bone marrow with healthy hematopoietic tissue elements and minimize the production of amyloid protein, and hence delay further organ deposition and dysfunction.
AL amyloidosis most commonly affects multiple vital organs; common organ involvement includes the heart, kidneys, the gastrointestinal tract, liver, and nerves.
Vital organ involvement in ATTR amyloidosis is typically primarily limited to the heart (wild-type form) or the heart and peripheral nerves (hereditary variant forms). Amyloid fibril deposition in the myocardium can result in restrictive cardiomyopathy, arrhythmias, and conduction system disease.
Per current ISHLT guidelines, heart transplant in cardiac amyloidosis is a IIA indication. For AL amyloidosis, it is limited to selected cases in experienced centers with established collaborations between cardiovascular and hematology teams.
For ATTR amyloid, transplant also should be considered, but for familial cases, the collaboration between cardiology, hepatology, and neurology teams is recommended, because liver transplantation can be considered for familial cases.
In any case, especially in AL amyloidosis, severe extracardiac amyloid organ dysfunction is a contraindication to heart transplant. Amyloidosis of the stomach, intestines, liver, and kidneys is a sign of poor prognosis, while localized amyloid in the skin, bladder and ureters, larynx, or conjunctiva is less worrisome while considering cardiac transplantation.
Historically, cardiac transplant has been a treatment option since 1985 in the UK and since 1988 in the USA. The main issue has been concerns about long-term survival of patients with AL amyloidosis undergoing transplantation.
Dubrey et al. in a series of patients in the UK reported 1-year survival of 50% in 10 patients with AL amyloid undergoing heart transplantation. Five-year survival was only 20%. Amyloid reoccurrence in the allograft was found in 4 out of the 6 patients who survived greater than 3 months.
Kpodonu et al. examined data from the United Network for Organ Sharing (UNOS) from 1987 to 2002 to compare the survival of patients with amyloidosis undergoing transplantation versus the rest of the transplant recipients.

1-year survival of patients with amyloidosis was significantly reduced (74.6% versus 81.6%; p< 0.03) compared to non-amyloid patients. The absolute disparity was even greater for 5-year survival (54.0 versus 63.8%) adding to the concerns of the suitability of heart transplantation in this patient population.
Given that AL amyloidosis is a systemic disease, patients with severe heart failure require a thorough assessment to determine eligibility for heart transplantation. Several groups have outlined the evaluation process which excludes patients with significant extracardiac amyloid involvement from heart transplant candidacy.
A multidisciplinary approach is required with specialists from hematology, gastroenterology, pathology, and nephrology often needing to evaluate transplant candidacy. A bone marrow biopsy is performed to exclude concomitant multiple myeloma.
Upper and lower gastrointestinal endoscopies with biopsies is performed to exclude amyloid deposition, which if extensive may be a contraindication for heart transplantation.
If patients have persistent abnormalities of liver function tests, liver biopsy is warranted. Those patients with renal dysfunction or significant proteinuria will require a kidney biopsy to exclude amyloid nephropathy. In some patients, combined heart/kidney transplantation may be an option.
Patients with extensive neuropathy which restricts mobility would likely not be able to rehabilitate sufficiently after transplant. Those with renal involvement may potentially be candidates for combined heart–kidney transplantation.
priority on the transplant wait-list?

there is some thought that patients with amyloidosis should receive whereas others have concerns regarding long-term survival of amyloid patients and not believe they should undergo heart transplantation at all. This is part of an on-going active debate regarding the heart transplant allocation system in USA.
The improvement in survival was further demonstrated by an analysis of the UNOS database by Davis et al. Although the database does not differentiate between types of amyloidosis and does not indicate the presence of adjuvant therapy such as stem cell transplantation, heart transplant survival for amyloid cardiomyopathy was statistically better from 2008 to 2013 compared to 1987 to 2007.
Because in transthyretin amyloid, the source of the abnormal protein is almost entirely in the liver, the liver transplantation has emerged as a treatment option aiming to replace mutant protein producing liver with the organ producing wild-type protein.
Combined heart/liver transplantation was also explored. In fact, the most common indication for combined heart and liver transplantation is amyloidosis (30%). It is important to understand that all discussions of liver or combine heart–liver transplantation pertain to familial type of ATTR only.
A total of 52 patients (42 men and 10 women) received liver and heart transplantation between September 1991 and December 2012, 11 of those received heart before the liver, one patient heart after liver, and two had liver, heart, and kidney. Of the 52 combined liver/heart transplant patients 32 (62%) were alive at a follow-up of median time of 4.5 years.
The survival analysis comparing patients with the same type of mutation with liver-only or combined liver/heart transplantation did not show statistical difference in outcomes. However, numerically, patients with combined transplant did better from 3 years on after surgery. There was no statistical difference in survival observed with simultaneous versus sequential transplantation.
The review of UNOS database on combined heart–liver transplantation reported 97 cases (26 of which were related to amyloidosis) between 1987 and 2010 and showed excellent survival rates for patients with combined transplantation. In the absence of subgroup analysis, it is unclear if the results can be extrapolated to the amyloid patients.
Isolated heart transplantation in transthyretin amyloidosis (ATTR)

In cases of severe cardiac amyloid disease and limited extracardiac involvement, isolated heart transplant may be a good option. TTR amyloidosis is predominantly disease of the elderly, and progression is usually slow—may be too slow to significantly damage the transplanted heart.
Several case reports of success with this strategy were published.

Similarly to AL amyloid, a 5-year survival of 65% or better is feasible.
Outcomes in Patients With Cardiac Amyloidosis Undergoing Heart Transplantation

Christopher D. Barrett MD, Kevin M. Alexander MD, Hongyu Zhao MD, Francois Haddad MD, Paul Cheng MD, PhD, Ronglih Liao PhD, Matthew T. Wheeler MD, Michaela Liedtke MD, Stanley Schrier MD, Sally Arai MD, Dana Weisshaar MD, Ronald M. Witteles MD.
Despite initial concerns about poor outcomes in patients with amyloidosis who are undergoing heart transplantation, multiple amyloid centers have continued pursuing this therapy with promising results.
Methods

This study examined all patients seen between 2004 and 2017, either at the Stanford University Medical Center or the Kaiser Permanente Santa Clara Medical Center, who were diagnosed with cardiac amyloidosis and ultimately underwent heart transplantation.

This study examined pre-transplantation characteristics and post-transplantation outcomes in this group compared with the overall transplantation population at our center.
Results

During the study period, 31 patients (13 with light chain amyloidosis and 18 with transthyretin [ATTR] amyloidosis) underwent heart transplantation. Patients with ATTR amyloidosis were older, were more likely to be male, had worse baseline renal function, and had longer waitlist times compared with both patients with light chain amyloidosis and the overall transplantation population.
Results

Post-transplantation, there were no differences in post-operative bleeding, renal failure, infection, rejection, or malignancy.
Results

There was no significant difference in mortality between patients who underwent heart transplantation for amyloid cardiomyopathy and patients who underwent heart transplantation for all other indications.
Take Home Message

In carefully selected patients with cardiac amyloidosis, heart transplantation can be an effective therapeutic option with outcomes similar to those transplanted for other causes of heart failure.
AL amyloidosis patients require considerable multidisciplinary collaboration and expertise in both solid organ and bone marrow transplantation, which requires specialized transplant centers.

In ATTR amyloidosis, heart transplant and heart/liver transplant could potentially be curative.

For those patients requiring heart and liver transplantation, a referral to a center offering dual transplantation is required.