Risk Stratification in Cardiac Amyloidosis: Novel Approaches

Arnt V. Kristen,[1,6] F. Joachim Meyer,[1] Jolanta B. Perz,[2] Stefan O. Schonland,[2] Michael Hundemer,[2] Ute Hegenbart,[2] Reinhard Singer,[3] Philipp A. Schnabel,[4] Falk-Udo Sack,[5] Hartmut Goldschmidt,[2] Hugo A. Katus,[1] and Thomas J. Dengler[1]

Amyloidosis is a term for diseases with extracellular deposition of insoluble beta-fibrillar proteins in different organs. The heart is primarily involved in more than half of patients with immunoglobulin light-chain amyloidosis or hereditary amyloidosis and associated with poor prognosis. Different traditional diagnostic tools that have been described for risk stratification lack of sufficient sensitivity and specificity for patient survival. Until November 2004 in 50 consecutive patients with light chain amyloidosis and 15 patients with hereditary amyloidosis electrocardiography, echocardiography, Holter monitoring, cardiopulmonary exercise test, lung function testing, tilt-test, and laboratory investigations have been performed at our department. Cardiac amyloidosis was found in 32 patients. Interventricular septum (14.3±0.5 mm vs. 12.3±0.7 mm, $P<0.05$), plasma NT-proBNP (7154±2122 ng/l vs. 380±113 ng/l; $P<0.01$), cardiac Troponin T (0.105±0.030 vs. 0.019±0.010 μg/l; $P<0.05$) were increased in patients with cardiac amyloidosis as compared to patients light chain amyloidosis but no cardiac involvement. Maximal inspiratory (Pi_{max}) and expiratory (Pe_{max}) mouth pressure were decreased with CA compared to controls. Correlation of NT-proBNP and interventricular septum thickness (r=0.53, $P=0.029$) as well as and Pi_{max} (r=0.72, $P<0.01$) or Pe_{max} (r=0.69; $P<0.01$) was noticed. A correlation of grade of arrhythmias in Holter monitoring and syncopes was not observed.Cardiac involvement of amyloid disease carries a poor prognosis and is not well characterized by classic heart failure determinants. Heart transplantation based on novel risk markers including NT-proBNP might be a suitable therapeutic approach for patients with manifest cardiac amyloidosis, but will require alternative patient selection and listing criteria.

Keywords: Amyloidosis, Heart transplantation, Risk stratification, Diastolic heart failure.

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Amyloidosis is a term for diseases with extracellular deposition of pathologic insoluble beta-fibrillar proteins in different organs. So far, several proteins are known to result in amyloid deposition. However, the heart is primarily involved in immunoglobulin light chain amyloidosis (AL) or hereditary amyloidosis (HA), especially transthyretin amyloidosis (ATTR), where specific point mutations of the transthyretin gene and age seem to have an important impact on the pattern and extent of organ involvement. The heart is involved in more than half of patients with AL at diagnosis. The extent of cardiac involvement is the most important determinant of clinical outcome (*1–3*). In general, manifest cardiac amyloidosis (CA) is associated with a poor prognosis and survival for AL with CA is about 6 months without any therapy. Clinical symptoms of CA are similar in different types of amyloidosis and depend on the extent of amyloid deposition. Initially, cardiac amyloid infiltration results in diastolic dysfunction (limitation in exertion, peripheral edema, ascites, dyspnoea, hypotonia), but sustained systolic left ventricular function, and/or arrhythmias (palpitations, syncopes) due to amyloid infiltration in the conduction system. In advanced CA with massive ventricular thickening due to massive amyloid infiltration, even systolic function is attenuated. According to the present data, about 30-50% of the patients with CA die from sudden cardiac death (*4*). However, the exact correlate of death is still unknown because definition of sudden cardiac death summarizes diverse events, such as ventricular tachyarrhythmias, cardiac bradyarrhythmias, and/or even electromechanical dissociation, each of them requiring a different therapeutic approach.

Previously, potential curative therapeutic approaches for AL using high-dose melphalan chemotherapy with autologous stem cell support (*5, 6*) as well as ATTR using orthotopic

[1] Department of Cardiology, Angiology, and Respiratory Medicine, University Hospital Heidelberg, Heidelberg, Germany.
[2] Department of Hematology and Oncology, University Hospital Heidelberg, Heidelberg, Germany.
[3] Department of Surgery, University Hospital Heidelberg, Heidelberg, Germany.
[4] Department of Pathology, University Hospital Heidelberg, Heidelberg, Germany.
[5] Department of Cardiac Surgery, University Hospital Heidelberg, Heidelberg, Germany.
[6] Address correspondence to: Dr. Arnt V. Kristen, Department of Cardiology, Angiology, and Respiratory Medicine, University Hospital Heidelberg, Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany.
E-mail: Arnt_Kristen@med.uni-heidelberg.de.
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liver transplantation (OLT) have been described eliminating the sources of amyloid production (*8*). Recently, alternative therapies have been described using nutritional (*9, 10*) or gene therapeutic (*11*) approaches because the use of liver transplantation has given rise to several problems.

Manifest CA is associated with high therapy-related mortality, such as arrhythmias or cardiac decompensations during chemotherapy for AL or perioperative in the OLT for ATTR. Therefore, these therapies are not feasible in patients with manifest CA. Prior orthotopic heart transplantation followed by the curative therapy might represent a suitable approach to improve the prognosis of these patients. Identification of patients who are at high risk of cardiac-related mortality presents a major challenge.

Diagnostic Tools for Risk Stratification in Cardiac Amyloidosis

According to the different pathophysiologies of the amyloid diseases diverse rationales for heart transplantation and standards on risk stratification in AL and HA are needed. The following questions have to be answered: 1. Which patient is at high risk for fatal cardiac events during chemotherapy or orthotopic liver transplantation? 2. Which patient qualifies for a curative therapeutic approach if they had no CA?

Currently available diagnostic tools include the following, but have consistently failed to identify high risk patients reliably.

Clinical Signs

In early stages of CA, impairment of left ventricular filling (diastolic dysfunction) occurs because of left ventricular stiffness due to massive amyloid infiltration. Increased atrial filling pressures are needed to maintain left ventricular filling volume. Systolic left ventricular function is sustained in these early stages of CA, but also decreased in advanced organ involvement. Clinical signs are mainly of right-sided heart failure (raised jugular venous pulse, right-sided third heart sound, peripheral edema and hepatomegaly) or those associated with a low cardiac output, including orthostatic hypotension. Patients with symptomatic heart failure due to amyloid deposition (dyspnoe, peripheral edema) have a poorer survival (*12, 13*). Additionally, exertional syncopes are relevant predictors for sudden cardiac death in AL (*14*).

Laboratory Tests

Recently, serum levels of cardiac troponins (cTNT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have been described to provide potent prognostic information in patients with AL (*14, 15*). Brain natriuretic peptides are predominantly synthesized in the left ventricle and have been shown to be sensitive and effective for diagnosis of ventricular dysfunction (*16*), prognosis of left ventricular heart failure (*17*), and after myocardial infarction (*18–20*). CTNT is a high specific and sensitive marker of cardiac injury (*21, 22*). Their high concentration in myocardium, high release ratio, and prolonged elevation after injury allows detection of even subtle myocyte damage (*14*).

Electrocardiography

Evidence for CA in electrocardiography includes low voltage, bundle branch block, atrioventricular block, and/or pseudoinfarction pattern. These electrocardiographic abnormalities per se, however, have unsatisfactory sensitivity and/or specificity (*23*), but in combination with histological proven amyloidosis specificity and sensitivity of ECG increases and may predate clinical congestive heart failure.

Echocardiography

Different studies demonstrated two-dimensional, M-mode, and doppler echocardiographic parameters, such as interventricular septum thickness, as independent predictors of survival (*13*). But diagnosis of CA based on these conventional techniques, increased interventricular septum thickness and "granular sparkling" at echocardiography, is often only possible once the disease has reached an advanced stage. However, these abnormalities have an unsatisfactory sensitivity and/or specificity (*23*). Therefore, in recent studies novel parameters, such as tissue doppler imaging and myocardial strain rate, have been investigated for earlier diagnosis of CA (*24, 25*). These new parameters might provide clinical tools in the assessment of cardiac amyloid deposition, but further investigations are needed to define the prognostic relevance of these parameters.

Holter Monitoring

Holter monitoring is easy to perform, inexpensive, and might help to assess prognosis even in asymptomatic patients with CA. It has been shown that complex ventricular arrhythmias were prognostic determinants for survival, but only the presence of couplets correlated with sudden cardiac death and has been an independent predictor of survival in multivariate analysis, while ventricular tachycardia has not been (*13*). However, even when accuracy of Holter analysis is carefully monitored there is a considerable day-to-day intrapatient variability. Confounding to ability of this diagnostic tool the significance of arrhythmia on Holter monitoring unaccompanied patient by symptoms is as uncertain in CA as in virtually all heart diseases.

Cardiopulmonary Exercise Testing

More recently, exercise capacity indices have been found to be useful in assessing prognosis in patients with CA, independently of echocardiography (*26*). Reduction of maximal oxygen consumption occurred which is accompanied by a slight decrease of respiratory efficiency, as a marker of failure of cardiopulmonary interaction. Even syncopes due to exertion might be discovered.

Endomyocardial Biopsy

Gold standard for diagnosis of any organ involvement in amyloidosis is congo red staining of biopsies. But, especially in CA, endomyocardial biopsies are associated with high risk of ventricular perforation. Therefore, in patients with histologically proven amyloidosis of any extra-cardiac organ and abnormalities in electrocardiography (low voltage, pseudoinfarction pattern) or echocardiography (speckled-appearing myocardium, increased myocardial thickness) myocardial involvement my safely be assumed, obviating the need for endomyocardial biopsy (*27*).

Scintigraphy

Recently scintigraphic verification of ATTR with the bone scanning agent technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) has been described

in HA (*28*). Tracer retention correlates well with clinical symptoms of cardiomyopathy or arrhythmias. Therefore, ^{99m}Tc-DPD scintigraphy is proposed as a simple and valuable diagnostic aid to evaluate the severity of hereditary amyloidosis (amyloid deposition in the whole body and in the heart) and the risk of concomitant heart problems even in follow-up investigations.

Taken together, these tools (electrocardiography, echocardiography, cardiopulmonary exercise testing, and Holter monitoring) should be combined to achieve a better assessment of the prognostic impact of heart involvement in patients with AL or HA.

RESULTS

Until November 2004, 50 consecutive patients with AL and 15 patients with HA have been investigated at Department of Cardiology, Angiology, and Respiratory Medicine at the University of Heidelberg, Germany. In the following only data of patients with AL are presented. Patients with hereditary amyloidosis were too few for meaningful analysis. CA was found in 32 patients with AL. Other involved organs in AL were kidney (50%), gut/rectum (30%), (autonomous) nervous system (20%), lung (10%), skin (6%), tongue (4%), and others (10%). 5 patients (10%) with AL had more than three organs involved, three organs were affected in 12 (24%) patients, two organs in 19 (38%) patients, and only one organ in 14 (28%) patients.

According to the guidelines of amyloidosis management (*29*), CA amyloidosis was ascertainable by myocardial biopsy (21 patients) or due to histological proof of amyloid in organs combined with abnormal ECG or echocardiography (11 patients). These abnormalities were diastolic dysfunction (7 patients), pseudo-infarction pattern (3 patients), or low voltage (1 patient). Mean interventricular septum thickness in patients with CA was increased in comparison to patients without CA (14.3±0.5 mm vs. 12.3±0.7 mm, $P<0.05$). As a marker of left ventricular strain, diastolic stiffness and prognosis NT-proBNP were measured (*14, 30*). Mean NT-proBNP plasma levels were increased to 7154±2111 ng/l compared to patients without CA (380±113 ng/1; $p < 0.01$). *Plasma cardiac troponin T as a marker of myocardial damage and prognosis (15)* was significantly increased in patients with CA compared to patients without CA (0.105±0.03 vs. 0.019±0.010 μg/l; $P<0.05$). 28 of the patients with CA were above the prognostic cut-off value for NT-proBNP of 332 ng/l (*30*), 10 were above the cut-off value of cardiac troponin T (0.035 μg/l). A significant correlation between NT-proBNP and interventricular septum thickness was observed (r=0.53, $P=0.029$). Maximal inspiratory (Pi_{max}) and expiratory (Pe_{max}) mouth pressure was decreased in male (Fig. 1A) and female (Fig. 1B) patients with CA compared to control subjects matched for age, sex, and weight recruited from the hospital community. An inverse correlation between NT-proBNP and Pi_{max} (r=0.72, $P<0.01$; Figure 2) or Pe_{max} (r=0.69; $P<0.01$) was noticed.

In Holter monitoring of AL patients Lown <IIIa was found in six (reduced heart rate variability in 3/ sustained heart rate variability in 3 patients), Lown IIIa in 18 (12/6), Lown IVa in 16 (11/5), and Lown IVb 7 (5/2) patients. Nine patients with CA (28%) had a history of syncopes, eight of them had no CA. However, a significant correlation between Holter monitoring and the occurrence of syncopes were not observed. Sudden cardiac death caused loss of patients with CA in about 15%, but the specific pathological correlative is not clear so far. Therefore cardioverter defibrillator (ICD) was implanted to prevent sudden cardiac death in patients with AL and CA to get information about arrhythmias and causes of death in these patients. Eight patients with AL re-

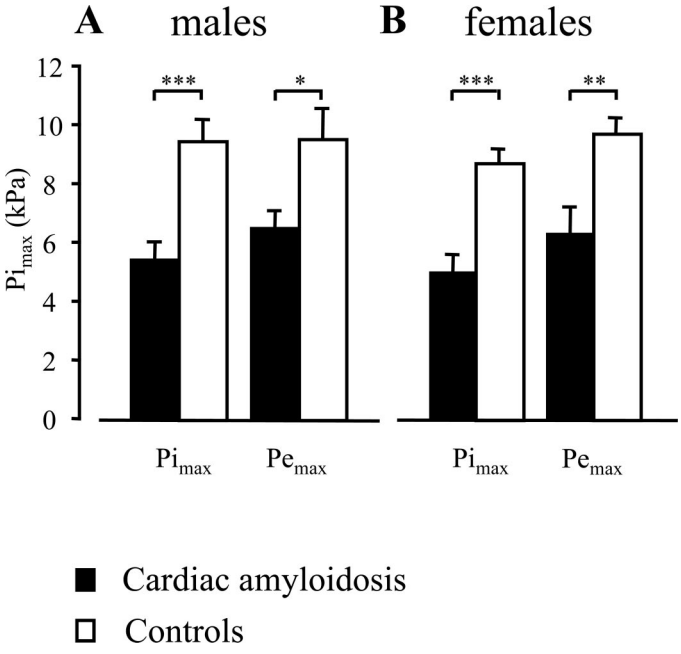

FIGURE 1. Maximal inspiratory (Pi_{max}) and expiratory (Pe_{max}) mouth occlusion pressure in males (A; n=14) and females (B; n=12) with cardiac light chain amyloidosis and healthy, age-matched controls (males n=14, females n=15). *$P<0.05$; **$P<0.01$; ***$P<0.001$ compared to controls.

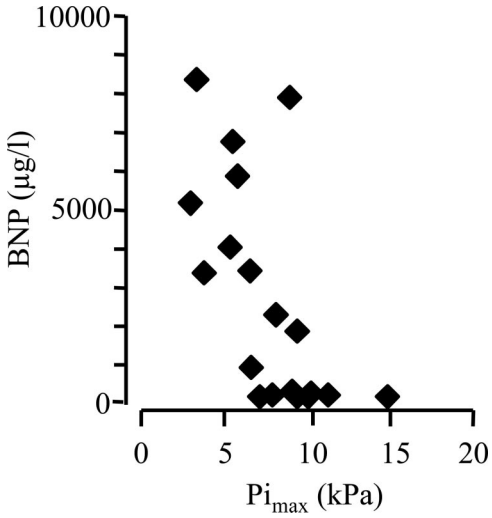

FIGURE 2. Correlation of maximal inspiratory (Pi_{max}) mouth occlusion pressure and brain natriuretic peptide (NT-proBNP) in males (n=18) patients with amyloid light chain amyloidosis (r=0.53, $P=0.029$).

ceived an ICD: Patient 1 (A. M.) died after 46 days of electromechanical dissociation (EMD), patient 2 (J. F.) after 54 days of EMD, and patient 3 (E. W.) after 350 days of sepsis after successful cardiac transplantation at day 170. During follow-up of 18 months five further patients out of 50 died due to undefined causes. Two further heart transplantations have been performed successfully at our centre in patients with CA.

DISCUSSION

In general, survival of manifest CA is about 6 months without therapy. This commits the physician to start therapy as early as possible, patients with manifest CA, however, have an increased risk for therapy-related mortality due to cardiac decompensation or ventricular arrhythmias. Therefore, precise and expedient risk stratification is required for institution of adequate therapy. High-dose chemotherapy with melphalan and autologous stem cell support is a potentially curative approach achieving complete responses in about 60% of patients (*5*). In patients with cardiac amyloid deposition this curative therapeutic approach is largely inappropriate due to excessive treatment-related mortality. In these instances, prior orthotopic heart transplantation followed by the curative chemotherapy with stem cell support is suitable and might increase the prognosis of these patients.

Rationale for Heart Transplantation in Immunoglobulin Light-chain Amyloidosis

The rationale for heart transplantation in AL is the existence of a potential curative therapy approach which is not feasible in patients with diminished cardiac function due to amyloid deposition because of a high therapy-related mortality. After heart transplantation with improved cardiac function high-dose chemotherapy with melphalan and autologous stem cell support should cause significant loss of cardiac-related mortality during chemotherapy and therefore increasing overall survival of these patients. So far, only two case reports using this promising therapeutic regimen have been described (*31–33*).

Rationale for Cardiac Transplantation in Hereditary Amyloidosis

More than 99% of transthyretin is synthesized in the liver and secreted into the circulation, less than 1% is produced in the choroid plexus. Therefore, OLT is a curative approach for HA as it removes the source of pathogenetic amyloid proteins. However, this procedure presents an unacceptably high risk for patients with manifest cardiac involvement and diminished cardiac function. After heart transplantation, subsequent OLT will be considerably better tolerated. Even in cases of still relatively well preserved cardiac function, heart transplantation will ultimately not be avoidable as long-term follow-up studies of patients with HA suggest progression of cardiac deterioration even after OLT.

Patient Selection and Risk Stratification

As curative therapy for amyloidosis requires enormous resources and needs to be instituted early if the curable approach should be obtained risk stratification has to performed carefully. Exact parameters predicting risk for therapy-related complications are often unclear, because real cause of death is still not defined. Some parameters for risk-stratification have been described so far (*13, 34*). Recently, we found a correlation between NT-proBNP and Pi_{max} and Pe_{max} mouth pressure in patients with AL reflecting cardiopulmonary interaction (unpublished data). Pi_{max} is an independent risk predictor in patients with diminished systolic left heart failure (*17, 35*). Recently a decrease of Pi_{max} in diastolic dysfunction has been described, too (*36*). Disturbed cardio-pulmonary interaction might make a contribution to risk stratification of patients with AL and CA. Half of the patients with manifest CA die from cardiac complications, most of them from sudden cardiac death, but the precise clinical correlate is still not understood. Aiming at prevention of sudden cardiac death ICDs were implanted in patients with ventricular arrhythmias (Lown≥IVa) and manifest CA (NYHA≥III). According to our experience of 14 patients and a report of 10 patients in the literature (*37*) an ICD itself might not have the expected benefit for survival as EMD occurred in two patients. Therefore, patients with AL and CA might really profit by early heart transplantation followed by high-dose chemotherapy and autologous stem cell support. This regimen might be promising for a selected collective of patients tolerating high-dose chemotherapy and stem cell transplantation after cardiac limitation from amyloid disease has been removed by transplantation (*31–33*).

At the moment, existence of amyloidosis is a relative contraindication for heart transplantation, because AL is considered as a (semi)malignant disease. According to current data based on optimized therapy regimens achieving complete remission in more than 60% of the patients this contraindication may not be maintainable in such generality. Furthermore, high-urgency criteria for heart transplantation including especially the requirement for intravenous catecholamine therapy do not make sense because of pathophysiology of amyloid cardiomyopathy. Due to the limited availability of donors this therapeutic approach is not realisable for all patients with AL and minor CA. Some parameters for risk-stratification and patient selection have been described so far (*13, 15, 30*). We found additional parameters in AL reflecting cardio-pulmonary interaction that might improve risk stratification of patients with AL and CA. Evaluation of these risk-factors in patients with HA and CA should ideally be performed as a multicenter approach because of limited number of patients at each centre.

Concerning heart transplantation in cardiac amyloidosis, physicians and storing organizations contributors have to come to specific arrangements for a selected collective of patients with CA to find an adequate solution for all patients with congestive heart failure due to AL or other pathophysiology.

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