Cardiac function in hereditary transthyretin amyloidosis
- An echocardiographic study

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Akademisk avhandling

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Abstract

**Background:** Hereditary transthyretin amyloidosis (ATTR) is a lethal disease in which misfolded transthyretin (TTR) proteins accumulate as insoluble aggregates in tissues throughout the body. A common mutation is the exchange of valine to methionine at place 30 (TTR V30M), a form endemically found in the northern parts of Sweden. The main treatment option for ATTR amyloidosis is liver transplantation as the procedure halts production of mutated transthyretin. The disease is associated with marked phenotypic diversity ranging from predominant cardiac complications to pure neuropathy. Two different types of fibril composition – one in which both fragmented and full-length TTR are present (type A) and one consisting of only full-length TTR (type B) have been suggested to account for some phenotypic differences. Cardiac amyloidosis is associated with increased myocardial thickness and the disease could easily be mistaken for other entities characterised by myocardial thickening, such as sarcomeric hypertrophic cardiomyopathy (HCM). The aims in this thesis were to investigate echocardiographic characteristics in Swedish ATTR amyloidosis patients, and to identify markers aiding in differentiating ATTR heart disease from HCM. Another objective was to examine the impact of fibril composition and sex on the phenotypic variation in amyloid heart disease.

**Methods:** A total of 122 ATTR amyloidosis patients that had undergone thorough echocardiographic examinations were included in the studies. Analyses of ventricular geometry as well as assessment of systolic and diastolic function were performed, using both conventional echocardiographic methods and speckle tracking technique. ECG analysis was conducted in study I, allowing measurement of QRS voltage. In study I and study II ATTR patients were compared to patients with HCM. In addition, 30 healthy controls were added to study II.

**Results:** When parameters from ECG and echocardiography were investigated, the results revealed that the combination of QRS voltage <30 mm (<3 mV) and an interventricular/posterior wall thickness quotient <1.6 could differentiate cardiac ATTR amyloidosis from HCM. Differences in degree of right ventricular involvement were also demonstrated between HCM and ATTR amyloidosis, where ATTR patients displayed a right ventricular apical sparing pattern whereas the inverse pattern was found in HCM. Analysis of fibril composition revealed increased LV wall thickness in type A patients compared to type B, but in addition type A women displayed both lower myocardial thickness and more preserved systolic function as compared to type A males. When cardiac geometry and function were evaluated pre and post liver transplantation in type A and B patients, significant deterioration was detected in type A but not in type B patients after liver transplantation.

**Conclusions:** Increasing awareness of typical cardiac amyloidotic signs by echocardiography is important to reduce the risk of delayed diagnosis. Our classification model based on ECG and echocardiography could aid in differentiating ATTR amyloidosis from HCM. Furthermore, the apical sparing pattern found in the right ventricle may pose another clue for amyloid heart disease, although it requires to be studied further. Furthermore, we disclosed that type A fibrils, male sex and increasing age were important determinants of increased myocardial thickness. As type A fibril patients displayed rapid cardiac deterioration after liver transplantation other treatment options should probably be sought for this group of patients.

**Keywords**

Amyloid, echocardiography, ECG, HCM, fibril type, strain, ATTR, cardiomyopathy, speckle tracking