CARDIO-PULMONARY FUNCTION IN FAMILIAL AMYLOIDOSIS WITH POLYNEUROPATHY
A clinical study of patients from northern Sweden

Akademisk avhandling som med vederbörligt tillstånd av rektorsämbetet vid Umeå Universitet för avläggande av medicine doktorsexamen kommer att offentligen förvaras i Medicinska klinikens föreläsningssal (9tr, sal 933), Regionsjukhuset, Umeå, torsdagen den 27 maj 1982, kl 09.00.

av

Bert-Ove Olofsson
med lic

Umeå 1982
ABSTRACT

CARDIO-PULMONARY FUNCTION IN FAMILIAL AMYLOIDOSIS WITH POLYNEUROPATHY

A clinical study of cases from northern Sweden

Bert-Ove Olofsson, Departments of Internal Medicine and Clinical Physiology, University of Umeå, S-901 87 Umeå, Sweden

Familial amyloidosis with polyneuropathy (FAP) was first reported from Portugal in 1952, but since then this syndrome has been recognized in many countries including Sweden. In this investigation cardiac and pulmonary functions in the Swedish variety of FAP were studied. A retrospective survey of the ECG findings in 71 patients showed a high prevalence of atrioventricular (38%) and intraventricular (41%) conduction defects, and also a high prevalence of atrial fibrillation (14%). In several patients a progression in the conduction defects to advanced disturbances could be observed and 10 out of 71 patients (14%) in the present series required pacemaker treatment. A histopathological study of the atrioventricular part of the conduction system showed marked amyloid infiltration in each case, which may explain the high prevalence of conduction defects.

In an echocardiographic study which encompassed 22 consecutive patients, all but those two patients with the shortest duration of symptomatic disease showed abnormal features. The most frequent and characteristic findings were hypertrophy of the interventricular septum (86%) and a hyperrefractile appearance of the myocardium (68%). This unusual association of echocardiographic features is considered almost diagnostic of cardiac amyloidosis.

A hemodynamic study showed an essentially normal systolic heart function, but in several patients there were signs of impaired diastolic function with increased myocardial rigidity. Several patients showed signs of obstruction of the ventricular outflow tracts. This finding, as well as the echocardiographic features, is in accordance with altered anatomical and functional properties of the interventricular septum.

The major pulmonary function abnormalities were decreased maximum respiratory pressure which indicate that the neuropathy in FAP involves the respiratory musculature, and impaired diffusing capacity consistent with an alveo-capillary block caused by amyloid deposits.

Key words: amyloidosis, atrioventricular conduction, ECG, echocardiography, hemodynamics, pulmonary diffusing capacity.
CARDIO-PULMONARY FUNCTION
IN FAMILIAL AMYLOIDOSIS
WITH POLYNEUROPATHY
A clinical study of cases
from northern Sweden

by
BERT-OVE OLOFSSON

Umeå University
Umeå 1982
To
BRITT
ANNA and JOHAN
CONTENTS

ABBREVIATIONS ................................................................. 6
ORIGINAL PAPERS .............................................................. 7
INTRODUCTION ........................................................................ 9
Amyloidosis ................................................................. 9
Familial amyloidosis .................................................. 12
Familial amyloidosis with polyneuropathy .................. 13
Amyloid heart disease .............................................. 14
Amyloid lung disease .................................................. 16
AIMS OF THE STUDY ..................................................... 18
MATERIAL ........................................................................... 19
METHODS ........................................................................... 22
RESULTS ............................................................................. 25
Electrocardiography .....................................................
Histopathology of the atrioventricular conduction system
Echocardiography ..........................................................
Hemodynamics and angiocardiography ....................
Pulmonary function ......................................................
DISCUSSION ................................................................. 29
GENERAL SUMMARY AND CONCLUSIONS .................. 33
ACKNOWLEDGEMENTS ................................................. 34
REFERENCES ................................................................. 35
ABBREVIATIONS

FAP = familial amyloidosis with polyneuropathy, BSA = body surface area, AV = atrioventricular, $D_{LCO}$ = diffusing capacity for the carbon monoxide, VC = vital capacity, $FEV_1$ = forced expiratory volume in 1 sec, $FEV_1\%$ = $FEV_1$ as a percentage of VC, $FIV_1$ = forced inspiratory volume in 1 sec, $FIV_1\%$ = $FIV_1$ as a percentage of VC, FRC = functional residual capacity, $MVV_F$ = maximal voluntary ventilation with free breathing frequency, $MVV_{40}$ = maximal voluntary ventilation at 40 breaths/min, $P_{aO_2}$ = arterial oxygen tension, $P_{E\; max}$ = maximum expiratory pressure, $P_{I\; max}$ = maximum inspiratory pressure, RV = residual volume, TLC = total lung capacity, FAP = familial amyloidosis with polyneuropathy, BSA = body surface area, AV = atrioventricular, Aod = aortic diameter, APB = atrial premature beat, IVS = interventricular septum, LAD = left atrial diameter, LAH = left anterior hemiblock, LBBB = left bundle branch block, LVDD = left ventricular diastolic diameter, LVpW = left ventricular posterior wall, LVSD = left ventricular systolic diameter, $% D \; LV$ = per cent change in left ventricular diameter, $% Th \; LVpW$ = per cent change in left ventricular wall thickness, RBBB = right bundle branch block, RVD = right ventricular diameter, RVW = right ventricular wall, VPS = ventricular premature beat, $r$ = product moment correlation coefficient, $r_s$ = Spearman's rank correlation coefficient.
ORIGINAL PAPERS

The present thesis is based on the following papers:


IV Backman, C. and Olofsson, B.O.: Echocardiographic features in familial amyloidosis with polyneuropathy. Submitted for publication.


These papers will be referred to in the text with the Roman numerals I - V.
INTRODUCTION

Amyloidosis

The term amyloidosis encompasses a heterogeneous group of disorders, some systemic and some localized to particular organs. Common to all these conditions are extracellular deposits of fibrillar proteins, known collectively as amyloid, which progressively destroy normal tissue structures.

Since the beginning of the 20th century several attempts have been made to differentiate the major types of amyloidoses on the basis of differences in their distribution in different organs, histological localization, and their staining properties. In fact, none of these classifications has ever become generally accepted and the clinical classification used most often is the one proposed by Reimann et al. (77): 1) primary amyloidosis, 2) amyloidosis associated with myeloma, 3) secondary amyloidosis. However, with this as well as with any other proposed systems of classification overlaps occur. Identification of new syndromes has led to an expansion of Reimann's classification to include 4) localized amyloidosis and 5) heredofamilial amyloidosis (61).

There are three physical properties which are common to all forms of amyloid: The staining reaction with Congo red, which brings about a green birefringence in polarised light (9, 72), the characteristic fibrillar structure on electron microscopy (26) and the diffraction pattern on x-ray crystallography (31). These properties result from a specific protein conformation, the twisted anti-parallel beta-pleated sheet fibril (39). This unusual protein conformation, characteristic of amyloid, and not normally found in mammalian tissues, is also responsible for its insolubility and its resistance to proteolysis. Amyloidosis is the first disease complex to be described that is caused by a specific protein conformation (39).

Research in the last decade has revealed several now well-defined amyloid proteins, each probably characteristic of a specific clinico-pathological entity. Thus, in the generalized form of amyloidosis, which appears in association with chronic inflammatory diseases and in pa-
Patients with familial Mediterranean fever, a distinctive fibrillar protein, now designated amyloid protein AA is identified (63). In primary amyloidosis, which may occur either as localized amyloid deposits e.g. in nodular pulmonary amyloidosis, or as a generalized disease, which is sometimes associated with myeloma, the amyloid protein consists of the light chains of an immunoglobulin and the corresponding amyloid fibril protein is designated AL (41). One localized form of amyloidosis appears in the stroma of medullary carcinoma of the thyroid, and the constituent protein has been shown to be a precalcitonin (88). In senile cardiac amyloidosis two fibrillar proteins, seemingly not related to any of those previously mentioned, have recently been identified (97). The composition of the amyloid in the several subgroups of familial amyloidosis is still largely unknown. However, recent reports indicate that varieties of prealbumin may constitute the amyloid protein found in familial amyloidosis with polyneuropathy (28, 87).

These new data about amyloid proteins have led to a reclassification of the amyloidosis syndromes (39). According to this, primary systemic amyloidosis and myeloma associated amyloidosis are designated immunocyte dyscrasia with amyloidosis. The term secondary amyloidosis has been replaced by reactive systemic amyloidosis, and localized amyloidosis is subdivided into organ limited amyloidosis and localized amyloid deposits. Heredofamilial amyloidosis stands unchanged.

Table I is a survey of this classification where amyloidoses with defined amyloid proteins are included. However, this new classification based on defined amyloid proteins is still not generally accepted. For this reason the classification of Reimann et al. (77), amplified by Kyle et al. (61), will be kept to in this thesis.
**Table I. Clinico-chemico-pathological classification of amyloidoses with defined amyloid proteins.**

<table>
<thead>
<tr>
<th>Clinical condition*</th>
<th>Amyloid protein</th>
<th>Protein designation**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocyte dyscrasias with amyloidosis (Primary amyloidosis, Myeloma associated amyloidosis)</td>
<td>Immunoglobulin</td>
<td>AL</td>
</tr>
<tr>
<td>Reactive systemic amyloidosis (Secondary amyloidosis)</td>
<td>Acute-phase serum protein</td>
<td>AA</td>
</tr>
<tr>
<td>Familial amyloidosis with polyneuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portuguese</td>
<td>Prealbumin variant</td>
<td>AFp</td>
</tr>
<tr>
<td>Japanese</td>
<td>Prealbumin variant</td>
<td>AFj</td>
</tr>
<tr>
<td>Swedish***</td>
<td>Prealbumin variant</td>
<td>AFs</td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>Precalcitonin</td>
<td>AET</td>
</tr>
<tr>
<td>Senile cardiac amyloidosis</td>
<td>?</td>
<td>ASC1, ASC2</td>
</tr>
<tr>
<td>Isolated atrial amyloidosis (localized)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Previous designations in brackets.
** According to Glenner et al. (39).
*** Amyloid protein isolated from cases recognized in USA with ancestors which emigrated from northern Sweden (87).
Familial amyloidosis

Familial or genetic amyloidosis has been the subject of several excellent reviews (40, 48, 66, 94). In the absence of knowledge about the biochemical background classification of the familial amyloidoses depends upon clinical features. The generalized syndromes are conveniently subdivided into non-neuropathic and neuropathic. In addition, there are several hereditary forms of localized amyloidosis.

The first description of inherited amyloidosis was that of Ostertag in 1932 (75). He described a family with several members affected by a generalized form of amyloidosis with neuropathy as a dominating feature. One additional family with a similar syndrome has later been described (97).

Familial Mediterranean fever was first described in 1945 (86), and is characterized by recurrent fever and abdominal pain (91). This disease, which is most common among Mediterranean Jews, is due to an autosomal recessive gene. Generalized amyloidosis with prominent renal involvement is a second major manifestation. Similar hereditary syndromes are, however, described in other ethnic groups, including a family living in northern Sweden (13).

Muckle and Wells (73) have described a family living in Derbyshire, England, with several members affected by systemic amyloidosis, nerve deafness, urticaria, limb pains and nephropathy. Similar syndromes are also described in families in the USA (15) and in France (62).

A family with amyloid disease especially affecting the heart and with early death from cardiac failure was described from Denmark (36). Another, Latin-American family with amyloid heart disease and persistent atrial standstill was reported by Allensworth (2). So far, these syndromes with isolated cardiac amyloidosis seem unique.

The initial description of familial amyloidosis with polyneuropathy (FAP) was in Portuguese subjects in 1952 (7). Since then, a variety of families in various parts of the world with some form of FAP have been reported. Thus, FAP syndromes are described from Japan (8), Sweden (3),
Finland (69), England (101), Italy (76), USA (1, 56, 83), and other parts of the world (40). In addition to neuropathy, nephropathy and cardiac disease are common features in many of these syndromes. In recent years it has become clear that a number of these syndromes resemble one another, at least from a clinical point of view. Therefore, classification of FAP, based on clinical features, in Type I - IV has been suggested (40). According to this, Type I comprises cases described from Portugal, Japan and Sweden, and is characterized by a sensomotor polyneuropathy affecting the lower extremities more severely than the upper and by autonomic neuropathy early in the course. Type II is characterized by carpal tunnel syndrome and upper extremity neuropathy. Large families with this disease have been reported in Indiana and Maryland, USA (66, 83). Type III is characterized by a neuropathy of the lower extremity, which is more severe than and preceedes neuropathy of the upper extremity, and by pronounced autonomic dysfunction. The unique feature in this type is renal insufficiency, which is the most common cause of death. This syndrome is described from Iowa, USA, in a family of Scottish, English and Irish origin (1). Type IV is characterized by lattice dystrophy of the cornea, cranial neuropathy and pendulous skin. The vast majority of patients are described from Finland (70).

A number of syndromes of hereditary localized amyloid deposits have been reported. A list of these has been presented by Glenner (40).

Familial amyloidosis with polyneuropathy - Swedish variety
The first cases of familial amyloidosis with polyneuropathy (FAP) in Sweden were diagnosed at the Department of Internal Medicine, University Hospital, Umeå, (6). Since then about 120 cases of FAP have been diagnosed, all living in the counties of Västerbotten and Norrbotten in northern Sweden.

Clinical and pathological findings in 60 patients were presented by Andersson in 1976 (4). Forty-two of these had close relatives who also had FAP, and 18 cases were classified as sporadic. The male to female ratio was 2:1. An autosomal dominant mode of inheritance has been suggested in this as well as in other varities of FAP (4, 40). The dis-
ease was systemic and involved many different organs and tissues. Biopsy specimens from skin, rectal mucosa and peripheral nerves showed the green birefringence of amyloid in polarized light (5).

The age at onset varied between 29 and 75 years (mean 53 years). The most impressive and constant clinical finding was polyneuropathy of the lower extremity with sensory and motor disturbances, muscular wasting and flaccid paralysis. Impotence, urinary bladder dysfunction, disturbances of motility of the gastro-intestinal tract and postural hypotension indicated autonomic neuropathy. Other clinical findings included malabsorption, weight loss, cardiac arrhythmias and conduction disturbances, and characteristic opacities of the vitreous body. Congestive heart failure and serious renal insufficiency were found only occasionally. The duration of symptomatic disease in the 27 patients who had succumbed, varied from 4 to 31 years (mean 12 years).

Histopathologically, extensive amyloid deposits were found in peripheral nerves. Extensive deposits were also observed in the walls of blood vessels of different sizes, in perivascular collagenous connective tissue and adjacent to smooth muscle. Furthermore, amyloid deposits were found in a great variety of organs and tissues. Myocardium and lung parenchyma were involved in all the cases examined.

A family of Swedish origin afflicted with a form of FAP resembling the disease described by Andersson have recently been reported from the USA (10). Genealogical studies have, however, so far failed to reveal any connection with the cases described in Sweden.

Amyloid heart disease

Cardiac amyloidosis is classified as "a specific heart muscle disease of metabolic origin" (99). Thus, it is not considered to be a subgroup of cardiomyopathy because by convention cardiomyopathy is defined as a disease of the heart muscle of unknown origin. Cardiac involvement is common to all forms of systemic amyloidosis. Thus, in a series comprising 42 cases, clinical cardiac disease was found in 80 per cent of those with primary amyloidosis, in 90 per cent of those with myeloma associated amyloidosis and in 60 per cent of those with secondary amy-
loidosis (25). In the various heredofamilial syndromes clinical find-
ings indicating cardiac involvement are common (37, 84, 101), and car-
diac amyloid deposits are also common autopsy findings (1, 50, 53, 70,
83, 101).

Senile cardiac amyloidosis is a form of organ limited amyloidosis and
is, as its name indicates found more frequently with increasing age
(100). The published prevalence in patients over 70 years ranges from
two to 70 per cent, which probably reflects differences in histopathol-
ogical techniques as well as selection of patients (49). In a recent
publication two different forms of senile cardiac amyloidosis, with
separate amyloid proteins, was suggested. One form appeared to be
limited to the atria and occurred at an earlier age. In the other form
both atria and ventricles are involved and extracardiac deposits of
amyloid, most often in the aorta and the pulmonary vessels, may be
found (98). However, the functional importance of senile cardiac amyl-
loidosis is still unclear (49).

The heredofamilial syndromes with localized cardiac amyloidosis de-
scribed by Frederiksen et al. (36) and Allensworth (2) have been men-
tioned previously.

The cardiac involvement in amyloidosis consists of vascular and/or
parenchymal depositions, and cardiac amyloidosis may also be classified
as an infiltrative cardiac disorder. Normal cardiac function may be
interfered with in several ways, which probably depends on the amount
and localization of the amyloid deposits.

Congestive heart failure is the most commonly described clinical mani-
festation. It was found in 185 of 399 cases (46%) reviewed by Buja et
al. (19) and was often the direct cause of death.

Amyloid infiltration of the myocardium may result in increased rigidity
of the muscle. This may interfere with normal diastolic filling and
give rise to a clinical and hemodynamic picture mimicking the one found
in constrictive pericarditis and restrictive cardiomyopathy (68, 92).
Disturbances of conduction and arrhythmias have been frequently report-
ed in cardiac amyloidosis (19, 37, 84, 96). Whether these are con-
sequences of direct amyloid infiltration of the specialized conduction system or not seems controversial (30, 57, 78).
Occasional cases with severe amyloid deposition in the coronary arteries with resultant angina pectoris and even myocardial infarction, have been reported (89).
Infiltration of the cardiac valves and papillary muscles may cause murmurs with or without significant valvular dysfunction (38).
Less common presentations of cardiac amyloidosis include cor pulmonale from amyloid deposits in the pulmonary vessels (17) and cardiac rupture (64).

**Amyloid lung disease**
Pulmonary involvement occurs in all the different forms of systemic amyloidosis. Histologically amyloid deposits may be found in the pulmonary blood vessels and in the alveolar septa or they may be localized only in the submucosal tissue of the trachea and bronchi. In the review of Briggs (18) pulmonary amyloidosis was found in 14 out of 20 cases with primary amyloidosis and in 10 out of 51 cases with secondary amyloidosis. In another series (21) encompassing 22 patients with systemic amyloidosis 11 out of 12 patients with primary amyloidosis had prominent interalveolar deposits. Extensive pulmonary deposits of amyloid were found in all three cases of amyloidosis associated with myeloma and Waldenström's macroglobulinemia. In five out of seven patients with secondary amyloidosis, the lungs were found to be involved on histological examination, but the deposits were less abundant than in primary amyloidosis and were mainly localized to perivascular and tracheobronchial areas. In the sparse autopsy reports on patients with familial amyloidosis with polyneuropathy, pulmonary involvement seems to be an almost constant finding (50, 90, 101).

Pulmonary involvement has often been considered of minor clinical importance in systemic amyloidosis, and symptoms such as dyspnea and cough are often attributed to cardiac failure. However, Celli et al. (21) found symptoms which they considered to be due to pulmonary amyloidosis, in all three patients with myeloma associated amyloidosis, but in none of their seven patients with secondary amyloidosis.
Symptoms attributable to pulmonary involvement have not been a significant feature in any of the reported types of FAP.

Apart from the generalized form of amyloidosis, there are rare syndromes due to amyloid deposits limited to the lower respiratory tract (82). Tracheobronchial deposits are the most common form and often give rise to symptoms of airway obstruction. The prognosis in this syndrome is uncertain, but a considerable number of the reported cases have died from respiratory insufficiency. Single or multiple pulmonary nodules are usually discovered incidentally. The prognosis seems to be good and surgical resection, undertaken because malignancy was suspected, has resulted in cure in all the cases reported. Diffuse parenchymal pulmonary amyloidosis is the most rare of these conditions. Here the prognosis seems poor and the patients succumb to progressive respiratory failure.
AIMS OF THE STUDY

The principal aims of the present study of patients with the Swedish variety of familial amyloidosis with polyneuropathy (FAP) were:

1. To study the prevalence and type of ECG changes in the large group of patients living in the Umeå region.

2. To investigate the possible correlate of the ECG changes by a detailed histopathological study of the atrioventricular conduction system.

3. To study the heart function by means of echocardiography, heart catheterization and angiocardiography.

4. To study the lung function.
MATERIAL

The material consists of series of patients with a diagnosis of FAP as established ante-mortem. Thus, they all had a typical clinical pattern including polyneuropathy, and amyloidosis was confirmed by histological examination of biopsy specimens from skin or rectal mucosa. Twenty-seven patients were included in the studies II to IV. Table II is a presentation which identifies the individual patients in the separate studies. In 11 of these 27 patients no close relatives with FAP have so far been identified and they are designated "sporadic".

Study I
Seventy-one patients, 46 men and 25 women, that is to say all patients in the Umeå region, with a verified diagnosis of FAP and at least one available ECG recorded after the onset of symptoms, constitute the material. Sixty-six of these patients were admitted to the Department of Internal Medicine, University Hospital, Umeå. Five patients were admitted to county hospitals in the Umeå region, but their case records were available for the study.

Study II
Embraced 14 patients in varying stages of FAP.

Study III
Eleven patients admitted to the Department of Internal Medicine, University Hospital, Umeå were investigated after having given their informed consent. The study comprises patients with a history, physical findings, ECG changes or roentgenologic heart enlargement suggesting cardiac involvement.

Study IV
Concerned 22 patients in varying stages of FAP, admitted consecutively to the Department of Internal Medicine, University Hospital, Umeå in 1979 and 1980.
Table II. Survey of the patients included in the studies II, III and IV. (Age, degree of polyneuropathy and duration of symptoms 1980).

<table>
<thead>
<tr>
<th>Pat. no.</th>
<th>Age (y.)</th>
<th>Sex*</th>
<th>Pat. no. in study</th>
<th>Degree of polyneuropathy**</th>
<th>Duration of symptoms (y.)</th>
<th>Familial (F) or sporadic (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>48</td>
<td>M</td>
<td>1 6 17</td>
<td>+++</td>
<td>9</td>
<td>S</td>
</tr>
<tr>
<td>II</td>
<td>48</td>
<td>M</td>
<td>2 4 -</td>
<td>+++</td>
<td>10</td>
<td>S</td>
</tr>
<tr>
<td>III</td>
<td>47</td>
<td>F</td>
<td>3 - 14</td>
<td>+++</td>
<td>9</td>
<td>S</td>
</tr>
<tr>
<td>IV</td>
<td>68</td>
<td>M</td>
<td>4 - -</td>
<td>+</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>V</td>
<td>33</td>
<td>M</td>
<td>5 5 1</td>
<td>+++</td>
<td>8</td>
<td>F</td>
</tr>
<tr>
<td>VI</td>
<td>62</td>
<td>M</td>
<td>6 9 7</td>
<td>+++</td>
<td>12</td>
<td>S</td>
</tr>
<tr>
<td>VII</td>
<td>61</td>
<td>M</td>
<td>7 - -</td>
<td>++</td>
<td>8</td>
<td>F</td>
</tr>
<tr>
<td>VIII</td>
<td>65</td>
<td>M</td>
<td>8 - 20</td>
<td>+</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>IX</td>
<td>45</td>
<td>F</td>
<td>9 10 4</td>
<td>+++</td>
<td>12</td>
<td>F</td>
</tr>
<tr>
<td>X</td>
<td>69</td>
<td>M</td>
<td>10 8 2</td>
<td>+++</td>
<td>12</td>
<td>F</td>
</tr>
<tr>
<td>XI</td>
<td>55</td>
<td>M</td>
<td>11 - 9</td>
<td>+++</td>
<td>10</td>
<td>S</td>
</tr>
<tr>
<td>XII</td>
<td>66</td>
<td>F</td>
<td>12 - 10</td>
<td>++</td>
<td>4</td>
<td>F</td>
</tr>
<tr>
<td>XIII</td>
<td>74</td>
<td>M</td>
<td>13 3 22</td>
<td>+++</td>
<td>12</td>
<td>F</td>
</tr>
<tr>
<td>XIV</td>
<td>71</td>
<td>M</td>
<td>14 - -</td>
<td>++</td>
<td>5</td>
<td>F</td>
</tr>
<tr>
<td>XV</td>
<td>48</td>
<td>M</td>
<td>1 11</td>
<td>+++</td>
<td>5</td>
<td>F</td>
</tr>
<tr>
<td>XVI</td>
<td>61</td>
<td>F</td>
<td>2 15</td>
<td>+++</td>
<td>8</td>
<td>F</td>
</tr>
<tr>
<td>XVII</td>
<td>60</td>
<td>M</td>
<td>7 - -</td>
<td>++</td>
<td>5</td>
<td>S</td>
</tr>
<tr>
<td>XVIII</td>
<td>74</td>
<td>M</td>
<td>11 13</td>
<td>++</td>
<td>5</td>
<td>S</td>
</tr>
<tr>
<td>XIX</td>
<td>55</td>
<td>M</td>
<td>- 3</td>
<td>++</td>
<td>4</td>
<td>F</td>
</tr>
<tr>
<td>XX</td>
<td>51</td>
<td>M</td>
<td>- 5</td>
<td>+</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>XXI</td>
<td>48</td>
<td>M</td>
<td>- 6</td>
<td>+</td>
<td>1</td>
<td>F</td>
</tr>
<tr>
<td>XXII</td>
<td>58</td>
<td>F</td>
<td>- 8</td>
<td>+++</td>
<td>10</td>
<td>F</td>
</tr>
<tr>
<td>XXIII</td>
<td>64</td>
<td>M</td>
<td>- 12</td>
<td>++</td>
<td>3</td>
<td>F</td>
</tr>
<tr>
<td>XXIV</td>
<td>63</td>
<td>M</td>
<td>- 16</td>
<td>++</td>
<td>3</td>
<td>S</td>
</tr>
<tr>
<td>XXV</td>
<td>67</td>
<td>M</td>
<td>- 18</td>
<td>+++</td>
<td>13</td>
<td>F</td>
</tr>
<tr>
<td>XXVI</td>
<td>30</td>
<td>M</td>
<td>- 19</td>
<td>+</td>
<td>1</td>
<td>F</td>
</tr>
<tr>
<td>XXVII</td>
<td>60</td>
<td>M</td>
<td>- 21</td>
<td>+++</td>
<td>12</td>
<td>F</td>
</tr>
</tbody>
</table>

* F = female, M = male

**The degree of polyneuropathy was graded from + to ++++ on basis of the patient's ability to perform activities of daily living (defined in Methods).
Study V
The hearts from six patients with FAP which had been well documented ante-mortem were investigated. These patients are not included in studies II to IV. In three patients (nos 2, 4 and 5) ECG:s recorded less than one month before death were available. In patient no. 1 only one ECG was recorded five months prior to death. Patient no. 3 developed AV block III and was treated with a pacemaker during his last two years. Patient no. 6 also developed AV block III and received a pacemaker eight years prior to his death. This patient also had a murmur consistent with aortic stenosis and experienced symptoms of heart failure during his last two years. Patient no. 4 also succumbed to heart failure which had begun two months earlier.
METHODS

The degree of polyneuropathy, which in all patients was most marked in the legs, was graded from + to ++++ on the basis of their ability to perform activities of daily living. "+" means subjective symptoms of polyneuropathy but no functional disturbances, "++" means subjective symptoms of polyneuropathy and minor functional disturbances, but the patient is able to undertake all the activities of normal daily life, "+++" means subjective symptoms of polyneuropathy and major functional disturbances, the patient being partially incapable to undertake the activities of daily living, "++++" means that the patient is essentially bedridden and incapable of most activities of daily living.

Biopsies were taken for histological examinations from skin, and rectal mucosa and the specimens were examined by polarised light after staining with Congo red (72).

Twelve-lead ECG:s (I, II, III, aVR, aVL, aVF, and six chest leads) were recorded using a direct-writing ECG-apparatus with conventional amplification (1 mV = 10 mm) and a paper speed of 50 mm per second. The ECG-evaluation included a classification of the ECG-abnormalities according to the Minnesota-code (79). For hemiblocks the criteria of Castellanos and Lemberg (20) were used.

The radiological heart volume was determined with the patient in the upright position according to Jonsell (58) and Kjellberg et al. (60) and expressed in ml/m² BSA. Normal values: men 500 ml/m² BSA, women 450 ml/m² BSA.

Lung volumes (VC, TCL, FRC and RV) were measured spirometrically using the closed helium dilution method for the determination of FRC (51). Dynamic spirometry (MVVF, MVV40, FEV1", and FIV1") was performed using the Bernstein spirometer (14). Predicted values for static and dynamic lung volumes were taken from Berglund et al. (12). The maximum expiratory and inspiratory pressures (PEmax and Pi max) were measured in the sitting position using the method described by Ringqvist (79). Predicted values were taken from his publication.
The distribution uniformity of inspired gas was determined by a single breath nitrogen test (27). The diffusing capacity for carbon monoxide \((D_{LcO})\) was measured by the single breath technique using a slight modification of the method described by Ogilvie et al. (74), the gas mixture being 0.4% carbon monoxide, 0.1% neon and 20% oxygen in nitrogen. The gas analyses were performed by gas chromatography. Predicted values were taken from Ogilvie et al. (74). To analyse the anatomical shunt the patient breathed 100% oxygen for at least 20 minutes, and at the end of this period an arterial blood sample was taken (11). Five per cent of the cardiac output was considered as the upper limit normal. Blood gases were measured with \(P_{O2}\) and \(P_{CO2}\) electrodes. Predicted values for \(P_{A02}\) were taken from Harris et al. (45).

At heart catheterization the blood pressures were measured by mechano-electrical transducers, calibrated with hydrostatic standards and recorded on a UV-recorder. The midthoracic level was used as the zero reference point. The direct Fick method was used for determining the cardiac output.

Values obtained for the central hemodynamics were compared with the normal values reported by Holmgren et al. (52). Left ventriculography was performed in the right anterior oblique and left anterior oblique projections perpendicular to each other. The right ventricle was investigated in the antero-posterior and lateral projections. Coronary angiography was performed according to Judkins' technique (59).

Left ventricular volume, stroke volume, and the ejection fraction were determined with the aid of a computer program using a biplane area-length method (65). The values obtained were compared with the normal values reported by Grossman (42). When mitral insufficiency was present, the amount of backflow was determined as the difference between angiographic stroke volume and the effective stroke volume as determined by Fick's method, and the regurgitation fraction (RGF) was calculated as being the quotient between the amount of backflow and the angiographic stroke volume.
Echocardiography was performed with a commercially available 90° wide angle sector scanner (ATL Mark III, Advanced Technical Laboratories, Bellevue, WA, USA).

The heart was scanned from three different positions, namely the para­
stellung (long and short axis views), the apical (two and four chamber views), and the subcostal (93). The sector scan was recorded on video­tape, using a Sanyo video tape recorder. M-mode registrations could be obtained from one of the transducers in the scanner head. Alternatively a single beam crystal was used. The M-mode traces were recorded with a fiberoptic strip chart recorder (ATL 100). Normal values for ventri­
cular dimensions and wall thickness were obtained from Feigenbaum (33).

In study V, the atrioventricular part of the conduction system was examined by serial sectioning. The atrioventricular node and bundle and the proximal parts of the bundle branches were cut out en bloc accord­
ing to the method of Hudson (55). These tissue blocks, after dehydra­
tion, were embedded in paraffin and serially sectioned at 6 μm inter­vals. Every 20th section was stained with van Gieson stain and the adjacent (21st) section was stained with alkaline Congo red for the identification of amyloid.

Amyloid deposits were graded on a scale of 0 to +++, ranging from none to severe (50).
RESULTS

I
Abnormal ECG:s were found in 62 out of 71 patients (87%) in this retrospective study. Atrioventricular and/or intraventricular conduction defects occurred in 48 (67%) of the patients. Atrial fibrillation was present in 10 (14%) patients. Low voltage was found in one patient, and post-infarction changes in none. Non-specific ECG-changes such as occasional ventricular or supraventricular premature beats or repolarization abnormalities were not analysed in detail. The prevalence of conduction disturbances increased with the duration of the disease.

Among 28 of the 47 patients, from whom more than one ECG-recording was available during the period of observation, a progression could be observed from a normal conduction of impulses to any form of atrioventricular or intraventricular disturbance of conduction, or from a low-degree disturbance of conduction to a more advanced one.

Ten of the patients required treatment by a pacemaker, seven because of AV-block III, one because of atrial fibrillation with slow ventricular rate, LBBB and fainting episodes, one because of atrial fibrillation, RBBB, LAH and fainting episodes, and one because of AV-block I, LBBB and suspected Adams-Stoke's attacks.

V
Moderate to severe deposits of amyloid were present in the bulk of the myocardium of all four chambers of all six hearts examined. Amyloid deposits were especially abundant in the subendocardium, where they were often nodular. Intramural vessels often exhibited amyloid infiltration of their walls, but their lumina seemed to be patent.

In all hearts examined there was marked amyloid infiltration in all parts of the conduction system, although there was some variability within and between the hearts. The degree of amyloid infiltration seemed in most cases to be slightly less in the AV node and bundle when compared with that in the bundle branches. Sometimes the deposits of
amyloid were extensive and almost totally replaced the conduction cells, with disappearance of fibres distal to the infiltrates. Slight or moderate fatty infiltration of the AV node was seen in three cases. Severe fibrosis of the right bundle branch was seen in two cases. In one case calcific deposits were seen in the proximity of the AV bundle.

IV

Echocardiographically the diastolic left ventricular diameter was normal (<56 mm) in 17, and increased in one of 18 patients where it could be measured precisely. Increased thickness of the interventricular septum (IVS > 11 mm) was noted in 19 patients (86%) and an increased thickness of the left ventricular posterior wall (LVpW > 11 mm) in 8 patients (36%). The interventricular septum was asymmetrically thickened (IVS/LVPW > 1.3) in 10 patients (45%). In six patients the hypertrophy of the interventricular septum occurred in a non-uniform pattern, often reached its greatest extent in the middle third and tapered toward the base and the apex. The right ventricular diameter was increased (>26 mm) in 8 out of 17 patients (47%). The thickness of the right ventricular wall was increased (> 7 mm) in only one patient. The ratio between the left atrial diameter and the aortic diameter was normal (LAD/AoD < 1.3) in all 21 patients where it could be calculated. Decreased left ventricular posterior wall thickening during systole (%v Th LVpW < 30) was present in four of the 10 patients where it could be measured. The percentage change in left ventricular diameter during systole was decreased (%vD LV < 30) in 3 out of 12 patients. Seven patients had pericardial effusion, but the volume of fluid was small and generally limited to a part of the pericardial sac. Ten patients had thickened cardiac valves. The aortic valve was abnormal in six, the mitral valve in one, and both the aortic and the mitral valves were abnormal in three patients. Fifteen patients (68%) had an unusual hyperrefractile appearance of the whole or parts of the myocardium. The pattern was most often granular and the interventricular septum was the part most often affected.

IV

At heart catheterization the cardiac index was normal in five patients (>2.8 l/min/m² BSA) and decreased in the other six. One patient with a
normal cardiac index had a patent ductus arteriosus. Low systolic and diastolic pressures in the brachial artery were found in four patients; one had mild arterial hypertension. The left ventricular end-diastolic pressure was elevated in two patients and at the upper limit of normal in another two. These four patients, and also one patient investigated only by right heart catheterization, had mean pulmonary capillary wedge pressures which were elevated or at the upper limit of normal. No valvular aortic stenosis was found, but one patient had a subvalvular systolic pressure gradient within the left ventricle. The right ventricular end-diastolic pressure was elevated in four patients. In three of these, and also in one additional patient with normal right ventricular end-diastolic pressure there was a diastolic dip-plateau configuration in the tracings from the right ventricle. In five patients there was a subpulmonary systolic pressure gradient within the right ventricle.

Left ventriculography revealed a normal ejection fraction (>50%) in all patients except one. One patient had a dilated left ventricle but a normal ejection fraction. Two patients had mitral insufficiency with regurgitation fractions of 0.29 and 0.65. In one patient a patent ductus arteriosus was demonstrated. In three patients right ventriculography demonstrated a distortion of the right ventricle by a hypertrophied ventricular septum, which bulged into the cavity (Fig. 1). Significant coronary artery stenosis was found in only one patient.
Fig. 1.
Right ventriculography of pat. no. XVI. Arrow indicating systolic narrowing of the outflow tract.
II
Spirometrical determination of the lung volumes revealed a slightly restrictive pattern in several of the patients. Thus, the vital capacity was below the lower normal limit in seven patients, the functional residual capacity in five. The residual volume varied considerably. Values above the upper limit of normal were found in three patients and below the lower limit of normal in five. The total lung capacity was low in five patients.
The ventilatory function tests were essentially normal in the patients without symptoms or signs of pulmonary or heart disease. Findings indicating airway obstruction were found in one patient who suffered from cardiac failure and in another patient who was under treatment for obstructive airway disease.
The maximum expiratory pressure was below the lower limit of normal in eleven patients; the maximum inspiratory pressure was below the lower limit of normal in five.
The single breath nitrogen test gave normal values in all patients, which indicated an even intrapulmonary gas distribution. The diffusing capacity varied considerably. Values below the predicted were found in ten patients.
The anatomical shunt was increased in six patients.
\( P_{\text{aO}_2} \) during air breathing was within the normal limits in all patients. No significant correlations were found between the relative values for static and dynamic lung volumes and the duration of the disease, or the degree of polyneuropathy. \( P_{\text{emax}} \) covaried in a statistically significant way with both the duration of disease and the degree of polyneuropathy (\( p < 0.01 \)), while \( P_{\text{imax}} \) was significantly correlated only with the duration of disease (\( p < 0.05 \)). The diffusing capacity was also significantly correlated (\( p < 0.01 \)) with both the duration of the disease and the degree of polyneuropathy. There were no significant correlations between the single breath nitrogen test, anatomical shunt or \( P_{\text{aO}_2} \), on the one hand, and the duration of disease or the degree of polyneuropathy, on the other.
DISCUSSION

Familial amyloidosis with polyneuropathy (FAP) is now generally accepted name for a syndrome originally described in cases which occurred in Portugal and which has since been recognized in several other countries including Sweden (40).

In the present study about one-third of the patients are so far the only members of their respective families with established FAP. However, the uniform and characteristic clinical picture without differences between clear familial and so-called sporadic cases, and its occurrence in a geographically restricted region justifies the designation "familial" for the Swedish variety of the disease. Further genealogic analysis has not been performed in this study.

All the patients had histopathologically verified amyloidosis. Since myocardial biopsies were not performed cardiac involvement was mostly deduced from indirect evidence. However, in the present (V) and in a previous (50) autopsy study of the myocardium from patients with the Swedish variety of FAP, amyloid deposits were found in every case. There are also another five patients who succumbed after the study began on whom histology of the heart has been carried out and who showed amyloid in the myocardium (to be published). This means that all 17 cases with the Swedish variety of FAP on whom histology of the myocardium has been undertaken have had undisputable evidence of cardiac involvement.

The high prevalence of disturbances of conduction, which are often demonstrably time-dependant and the very high prevalence of echocardiographic abnormalities, constitute additional evidence of significant cardiac involvement in FAP.

Histology (I) in each case showed sufficient deposits of amyloid within the conduction system to explain fully the defects of conduction. The pathogenetical background to the high prevalence of atrial fibrillation is however still not clear. The presence of amyloid within the sinus node or the atrial walls, especially the internodal tracts, suggests one possible mechanism. Atrial fibrillation may also be a result of
atrial dilatation secondary to an increase of pressure due to cardiac failure. Not much is yet known about the influence of disease of the cardiac nerves on cardiac rhythm and conduction. It cannot be excluded, however, that disturbances of nerve conduction may contribute to the development of rhythm and conduction disturbances (19, 81).

The high prevalence of atrial fibrillation and the disturbances of conduction described in study I are consistent with the findings reported in the Portuguese variety of FAP. These findings represent, however, an entirely different ECG pattern from the one described previously as typical for cardiac amyloidosis, where low voltage and abnormal QS-complexes in V₁ to V₃ were the prevalent changes (19, 67, 96). However, previous ECG studies have been performed mainly on cases with primary or secondary systemic amyloidosis, and different amyloid proteins may have a different affinity for different cardiac structures. Secondly, Buja et al.'s often cited review of ECG changes in cardiac amyloidosis (19) is based mainly on autopsy cases (333 out of 339). Thus, there is reason to believe that the pattern that Buja et al. have described represents a late and perhaps sometimes terminal stage of amyloid disease of the heart.

In the echocardiographic study (V), which was done on consecutive cases, all but the two patients with the shortest history of symptomatic disease showed abnormal features. The most characteristic findings were a hyperrefractile appearance of the myocardium, which most often involved the interventricular septum, and asymmetrical hypertrophy of the septum. This unusual association of echocardiographic findings, which was probably due to deposits of amyloid, is almost diagnostic of cardiac amyloidosis. These results thus indicate that the interventricular septum is a part of the myocardium which is particularly involved in this disease.

The identification of altered acoustic properties of the myocardium found on examination by ultrasound is a new and rapidly developing area of echocardiography (71) which may develop in the future into a valuable aid in the identification and characterization of myocardial disease. The appearance of echocardiographic changes early in the
course of the disease, even before any other symptoms or signs of cardiac disease have appeared may prove to be of value in the identification of FAP and other forms of cardiac amyloidosis.

No entirely uniform pattern could be identified in respect of hemodynamics (III). Congestive heart failure, often reported as typical for cardiac amyloidosis (97), was found only in one patient. This was a 74-year-old man, who also had, however, significant coronary artery occlusions and in this case the pathological changes caused by coronary artery disease cannot be distinguished from those caused by cardiac amyloidosis.

Changes consistent with increased myocardial rigidity, found in three of the patients, have often been described in cardiac amyloidosis (22, 23, 68, 92).

Obstructions of the ventricular outflow tracts, found in six of the patients in the present study, were unexpected findings not previously described in association with cardiac amyloidosis. They are, however, consistent with the echocardiographic appearances that indicated altered anatomical and probably functional qualities of the interventricular septum, and they are reported in other infiltrative disorders of the myocardium (32).

Most of the hemodynamic studied on patients with cardiac amyloidosis, published previously consist of reports on patients investigated at an advanced stage of the disease, often a short time before death in cardiac failure, and in which coronary artery disease was not excluded (16, 22, 23, 24, 29, 34, 38, 43, 44, 46, 47, 54, 68, 85, 92, 95). This make comparison between the present and previous reports difficult.

In Paper II the pulmonary function in FAP was investigated. The main pathological findings were decreased maximum inspiratory and expiratory pressures, and decreased diffusing capacity. These changes were progressive and covaried with both the duration of symptomatic disease and the degree of polyneuropathy.
The decreased respiratory pressures suggest that the neuropathy in FAP also involves the respiratory musculature. The low diffusing capacity might be due to an alveo-capillary block caused by amyloid deposits.

The very few previous reports on studies of pulmonary function in any form of systemic amyloidosis were performed on highly selected cases, (21), but a decreased diffusing capacity seems to have been a frequent feature.

It seems however reasonable to suppose that the impairment of pulmonary function observed in the present study has only minor functional significance, especially since the polyneuropathy in FAP does not allow any form of physical activity requiring high oxygen uptake.
GENERAL SUMMARY AND CONCLUSIONS

1. There is a high prevalence of atrioventricular and intraventricular conduction disturbances, and atrial fibrillation in FAP. This represents an ECG pattern which is entirely different from the one described previously as typical for cardiac involvement in other forms of systemic amyloidosis, in which low voltage and abnormal QS-complexes in the precordial leads V₁ to V₃ were the most frequent changes.

2. The disturbances of conduction are often progressive and there is a high prevalence of pacemaker treated patients in the present series.

3. Histopathologically a marked amyloid infiltration in all parts of the atrioventricular conduction system is found, which may explain the ECG changes.

4. There is a high prevalence of echocardiographic abnormalities in FAP, even in the absence of symptoms attributable to cardiac disease. The most prevalent findings are septal hypertrophy and a hyperrefractile appearance of the myocardium. The interventricular septum seems to be involved more often than other parts of the myocardium.

5. Hemodynamic investigations show signs of increased myocardial rigidity, with impaired diastolic heart function and obstructions of the ventricular outflow tracts in several FAP patients. The findings are consistent with amyloid deposits within the myocardium, with predilection for the interventricular septum.

6. The major abnormalities in the pulmonary function in FAP are decreased maximum respiratory pressures and impaired diffusing capacity. The first of these findings indicates that the neuropathy in FAP involves the respiratory musculature, the second indicates an alveo-capillary block caused by amyloid deposits.
ACKNOWLEDGEMENTS

I wish to express my gratitude to:

- Professor P.O. Wester, head of the Department of Internal Medicine, and Professor Håkan Linderholm, head of the Department of Clinical Physiology, for placing time and facilities at my disposal and for their personal support and interest

- Dr K.A. Jacobsson, head of the Section of Cardiology, my teacher in clinical cardiology, for advices and positive criticism

- Docent Per Bjerle, who throughout these studies has been my close teacher in clinical physiology and coworker. His guidance, constructive criticism and creative spirit is greatly appreciated

- Dr Rune Andersson, Dr Christer Backman, Docent Anders Eriksson, Dr Peter Eriksson, Docent Bengt Furberg, Dr Göran Osterman and Professor Lars-Eric Thornell for stimulating cooperation

- Miss Margareta Wickman and Mrs Kristin Öberg, nurses at ward no. 5, the Department of Internal Medicine, and the entire staff at the Department of Clinical Physiology, for their support and interest, which was a prerequisite for this study

- Mrs Solveig Andersen, Mrs Inger G. Andersson and Miss Lolomai Örne-hult for typing the manuscripts

- Dr H.E. Vickers, Liverpool, who skilfully corrected the English text of this thesis.

This study was supported by grants from the Faculty of Medicine, University of Umeå, and the Swedish Medical Research Council (12X-3934).
REFERENCES


