

# Heart rate variability as a predictor of mortality in patients with AA and AL amyloidosis

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**Aims** Patients with AA and AL amyloidosis have a limited life-expectancy. The aim of this study was to investigate whether heart rate variability can predict mortality in these patients.

**Methods and Results** Twenty-two recently diagnosed patients with AA and 23 patients with AL amyloidosis were included. Fifteen patients (5 AA, 10 AL) died within 1 year. Twenty-four hour Holter recording was performed to quantify the mean of all normal to normal RR-intervals (mean NN) and the standard deviation of all normal to normal RR-intervals (SDNN). The SDNN predicted 1-year mortality in the total group of patients with amyloidosis. The median SDNN was 73 ms. In patients with an SDNN  $\leq 73$  ms, the risk of dying within 1 year was found to have increased 3.5-fold ( $P=0.0036$ ; 95% CI 1.1–11.0). An SDNN

$\leq 50$  ms, a predictor of mortality in other patient groups, increased the risk of dying within 1 year 22-fold ( $P=0.0001$ ; 95% CI 5.4–90.4). In contrast to patients with AA amyloidosis, in the subgroup analysis of patients with AL amyloidosis the SDNN remained a predictive parameter (SDNN  $\leq 50$  ms: risk ratio 11.5, 95% CI 2.4–56.2,  $P=0.0025$ ).

**Conclusion** The SDNN is a strong predictor of short-term mortality in patients with AL amyloidosis.

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**Key Words:** Autonomic nervous system, heart rate variability, amyloidosis.

## Introduction

Survival of patients with AA and AL amyloidosis is poor. The majority of patients with AL amyloidosis, formerly known as primary amyloidosis, die of cardiac causes. They develop heart failure or cardiac arrhythmia due to myocardial infiltration of the amyloid<sup>[1]</sup>. In line with these findings, median survival after diagnosing AL amyloidosis is limited to approximately 1.5 years<sup>[2,3]</sup>. Conversely, patients with AA amyloidosis, formerly known as secondary amyloidosis, usually die of causes not directly related to AA amyloidosis<sup>[4,5]</sup> and median survival is approximately 4 years after the diagnosis has been made<sup>[5,6]</sup>. Although the median survival of patients with AA and AL amyloidosis is poor, some patients survive more than 10 years<sup>[7–9]</sup>.

In patients with AL amyloidosis, Cueto-Garcia *et al.*<sup>[10]</sup> found that mortality correlates with septal wall thickness, measured with an echocardiogram. As cardiac amyloid deposits are not a prominent feature of AA

amyloidosis<sup>[11]</sup>, this method is not suitable to predict mortality in these patients.

Limited survival is associated with autonomic dysfunction, assessed by cardiovascular reflex tests, in patients with AL amyloidosis<sup>[12]</sup>. Autonomic failure is a feature of both AL amyloidosis and AA amyloidosis<sup>[13,14]</sup>. Autonomic function can be determined by the assessment of heart rate variability<sup>[15]</sup>, a simple, non-invasive method, which needs little co-operation of the patient. Heart rate variability is a predictor of mortality in patients with a myocardial infarction<sup>[16,17]</sup>, patients with heart failure<sup>[18]</sup> and in the general population<sup>[19]</sup>.

Therefore, this study was performed to investigate whether heart rate variability can predict mortality in patients with AL and AA amyloidosis.

## Methods

### Patients

All successive patients with AA and AL amyloidosis who visited our clinic of Rheumatology between March 1994 and November 1998 were included in the study. The follow-up period was 1 year. The study conforms

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**Table 1** The patients' characteristics, subdivided by survival at 1 year

	Dead within 1 year (n=15)	Alive after 1 year (n=30)	<i>P</i>
Age (years)	58 (46–81)	62 (40–80)	0.97
Male/female	6/9	14/16	0.76
AA/AL amyloidosis	5/10	17/13	0.21
Time interval between inclusion and histologically proven amyloidosis (months)	2 (0–148)	2.5 (0–118)	0.61
Duration of clinical symptoms of amyloidosis before inclusion (months)	8 (3–148)	20.5 (0–157)	0.23
Study variables			
Mean left ventricular wall thickness (mm)	14 (8–18)	9.2 (7–18.5)	0.002
Mean NN interval (ms)	663 (575–758)	717.5 (550–925)	0.1
SDNN (ms)	40 (22–96)	81 (46–139)	0.001

with the principles outlined in the declaration of Helsinki. The systemic nature of the amyloidosis was assessed by the detection of amyloid in biopsies from at least two different tissues or organs. AA amyloidosis was demonstrated by the presence of an underlying inflammatory disease and reactivity with only anti-AA antibodies in immunohistology. The AL-type was demonstrated by signs of a clonal plasma-cell dyscrasia, such as the presence of a light chain in serum or urine detected by immunofixation electrophoresis, or the presence in the bone marrow of a relative excess of cells producing one of the light chains and no reactivity with anti-AA and anti-transferrin antibodies in immunohistology.

Patients with autonomic dysfunction due to other causes (i.e. haemodynamically significant cardiac valve disease, vagotomy, sympathectomy, or the use of: beta-blockers or (anti)cholinergic drugs or other centrally acting drugs) were excluded from the study.

### Heart rate variability

Twenty-four-hour ambulatory ECG registration was performed using a Marquette Holter recorder (series 8500). As parameters of heart rate variability, the mean of all normal RR-intervals (mean NN) and the standard deviation of all normal to normal RR-intervals (SDNN) during 24 h were calculated<sup>[15]</sup>.

### Echocardiography

Cardiac involvement of systemic amyloidosis was assessed using two-dimensional echocardiography. The echocardiographer was unaware of the results of heart rate variability. The thickness of the interventricular septum and the left ventricular posterior wall were measured on-line in end-diastole. In the standard parasternal longitudinal view, interventricular septal thickness was measured close to the aortic valve, as the perpendicularly measured distance between the endocardium of the left and the right ventricle. The thickness of

the left ventricular posterior wall was measured close to the posterior mitral leaflet. The mean of these two measurements is considered as the mean left ventricular wall thickness. According to Cueto-Garcia *et al.*<sup>[10]</sup>, the results were divided into three groups: a mean left ventricular wall thickness  $\leq 12$  mm (group I), 12 to 15 mm (group II), and  $\geq 15$  mm (group III).

### Statistical analysis

The end-point of the study was total mortality after 1 year. Differences between groups were analysed with the Mann–Whitney test for continuous data and with the Fisher's exact test for categorical data.

Survival of patients with amyloidosis was assessed by heart rate variability parameters and mean left ventricular wall thickness. The median of both heart rate variability parameters was determined. By this median patients were divided into two groups. With the proportional hazards model regression analysis, survival between groups, with correction for age and sex, was assessed. This was performed for all patients, but also for the patients with AA and AL amyloidosis separately. As an SDNN  $\leq 50$  ms has been found to be a predictor of survival in patients post-myocardial infarction<sup>[17,20]</sup> this cut-off value has also been assessed in our patients. For the parameters which were discriminative, risk ratios with a 95% confidence interval were determined.

Sensitivity and specificity as well as positive and negative predictive values were assessed. Correlation between the mean left ventricular wall thickness and the two heart rate variability parameters was assessed with Pearson's correlation coefficient. Results are presented as median with range and as risk ratios with 95% confidence intervals. A two-sided *P*-value  $< 0.05$  was considered to indicate statistical significance.

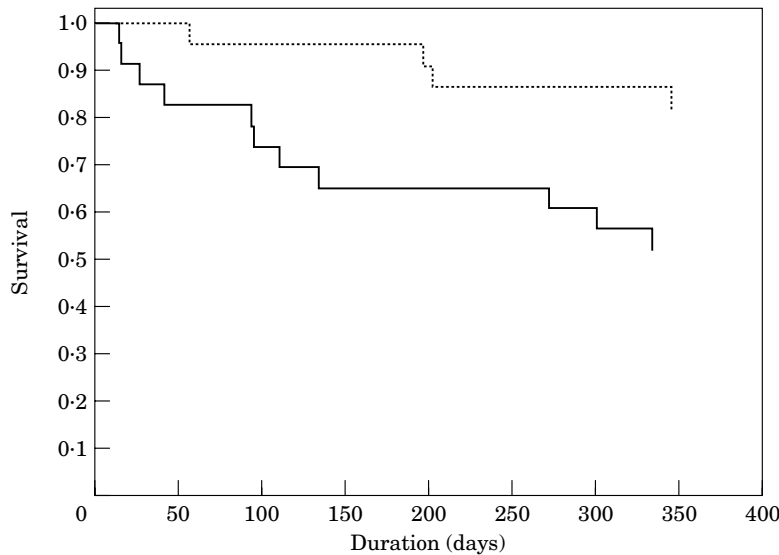
### Results

Forty-five patients were included (Table 1). Follow-up of all patients was 1 year. No differences in patient

**Table 2 Prediction of mortality by the mean NN or the SDNN**

Parameters	Subdivision of groups		P	Risk ratio	95% CI
All patients (n=45)					
Mean NN interval (ms)	≤684	>684	0.091		
SDNN (ms)	≤73	>73	0.036	3.5	1.1–11.0
SDNN (ms)	≤50	>50	0.0001	22.1	5.4–90.4
AA amyloidosis (n=22)					
Mean NN interval (ms)	≤703.5	>703.5	0.60		
SDNN (ms)	≤74	>74	0.66		
SDNN (ms)	≤50	>50	0.94		
AL amyloidosis (n=23)					
Mean NN interval (ms)	≤663	>663	0.25		
SDNN (ms)	≤72	>72	0.043	6.4	1.1–39.1
SDNN (ms)	≤50	>50	0.0025	11.5	2.4–56.2

Patients were subdivided by the median of the mean NN, the median of the SDNN or by an SDNN ≤50 ms. With the proportional hazards model differences in survival between the two groups, with correction for age and sex, were examined. In case a significant difference in survival between the two groups was found, a risk ratio with 95% confidence intervals was calculated.



Patients at risk

AA amyloidosis	22	21	20	19
AL amyloidosis	23	17	15	14

**Figure 1 Kaplan-Meier survival curve of patients with AA and AL amyloidosis subdivided by an SDNN ≤73 ms (—) or SDNN >73 ms (···).**

characteristics, such as age, sex, type of amyloidosis and duration of amyloidosis were found between patients alive and dead after 1 year. Five of the 22 patients with AA amyloidosis died within 1 year, whereas 10 of the 23 patients with AL amyloidosis died within 1 year.

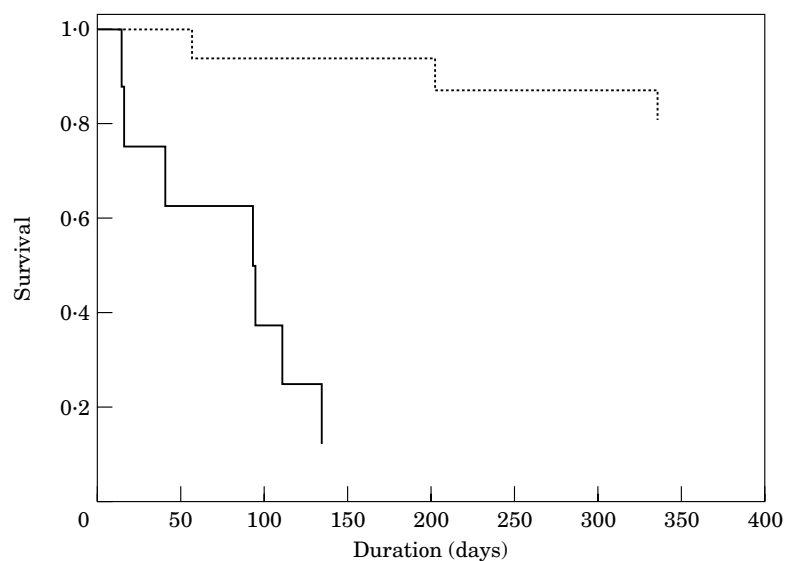
### Heart rate variability

Patients who survived 1 year had a higher SDNN than patients who died within the first year after being included (Table 1). The median SDNN was 73 ms (Table 2). Eleven of the 15 patients who died within the

first year had an SDNN ≤73 ms, vs 18 of the 30 patients who survived the first year ( $P=0.036$ ; Table 2 and Fig. 1).

In the subgroup of patients with AL amyloidosis the SDNN was also discriminative between survivors and non-survivors after 1 year (Table 2). However, the SDNN was not discriminative in patients with AA amyloidosis.

Ten patients had an SDNN ≤50 ms. Eight of these patients died within the first year in contrast to seven of the 35 patients with an SDNN >50 ms ( $P=0.0001$ ; Table 2). Of the 23 patients with AL amyloidosis eight patients had an SDNN ≤50 ms. Seven of them died



**Figure 2** Kaplan–Meier survival curve of patients with AL amyloidosis subdivided by an SDNN  $\leq 50$  ms (—) or SDNN  $> 50$  ms (· · ·).

within 1 year vs three of the 15 patients with an SDNN  $> 50$  ms ( $P=0.0025$ ; Table 2 and Fig. 2). Only two patients with AA amyloidosis had an SDNN  $\leq 50$  ms, of whom one patient died within 1 year.

The risk ratio for 1-year mortality with an SDNN  $\leq 50$  ms is 22.1 (95% CI: 5.4–90.4; Table 2). The sensitivity of an SDNN  $\leq 50$  ms as a predictor of mortality within 1 year is 53%, the specificity 93%, the positive predictive value 80% and the negative predictive value 80%. Patients with an SDNN  $\leq 50$  ms had a median survival of 93 days, whereas 80% of the patients with an SDNN  $> 50$  ms were alive after 1 year.

For the subgroup of patients with AL amyloidosis the sensitivity is 70%, the specificity 92%, the positive predictive value 88%, and the negative predictive value 80% for an SDNN  $\leq 50$  ms as a predictor of mortality within 1 year.

### Mean left ventricular wall thickness

Echocardiographic measurements of the mean left ventricular wall thickness could be obtained in 40 of the 45 patients (Table 3; chi-square test:  $P=0.002$ ). None of the patients with AA amyloidosis had a mean wall thickness  $\geq 15$  mm. Of the 13 patients who died within the first year, six had a mean wall thickness  $\geq 15$  mm. In our study, the positive predictive value for dying within 1 year with a mean wall thickness  $\geq 15$  mm is 85%. The sensitivity and specificity of this parameter are 46% and 96%, respectively.

### Combining heart rate variability and mean left ventricular wall thickness

With an SDNN  $\leq 50$  ms and/or a mean left ventricular wall thickness  $\geq 15$  mm mortality within 1 year can be predicted with a sensitivity of 71% and a specificity of 92%. The positive predictive value is 83%, with a negative predictive value of 86%.

A thicker mean left ventricular wall thickness correlates with a lower SDNN:  $r = -0.42$ ,  $P=0.007$ . No correlation was found between the mean NN-interval and the left ventricular wall thickness.

## Discussion

Our results confirm the overall grim prognosis, with a 30% mortality at 1 year in AL and AA amyloidosis. A simple measure of heart rate variability, the SDNN, appears to have a high positive and negative predictive value for 1-year mortality in these patients. In this study we found that with an SDNN  $\leq 50$  ms, patients have a 22-fold increased risk of dying within 1 year in contrast to patients with an SDNN  $> 50$  ms.

In AA amyloidosis heart rate variability measures, including the SDNN, were not discriminative for 1 year survival. Because of the lower 1-year mortality in patients with AA amyloidosis, this apparent lack of discriminative power of SDNN might be due to insufficient power.

As it is known that heart rate variability predicts mortality in patients with cardiac failure due to

**Table 3 Mean left ventricular wall thickness in relation to 1-year survival**

Mean left ventricular wall thickness	Alive (n=27)	Dead (n=13)
≤ 12 mm	21	4
12–15 mm	5	3
≥ 15 mm	1	6

myocardial infarction, it is not surprising that heart rate variability also predicts mortality in patients with AL amyloidosis. These patients often develop cardiac failure due to myocardial amyloid depositions. This study does not elucidate whether the low SDNN was an expression of autonomic dysfunction due to cardiac failure, or due to amyloidosis, or a combination of both. Recently, it has been established that low heart rate variability is an indicator of mortality in healthy persons<sup>[21]</sup>. The cause of the low heart rate variability in this population has not been established.

Cueto-Garcia *et al.*<sup>[10]</sup> found that the mean left ventricular wall thickness could predict survival in patients with AL amyloidosis. In their study they found a positive predictive value of 73% for an echocardiographic mean left ventricular wall thickness ≥ 15 mm. However, the authors do not specify the period of follow-up. In this study we found a positive predictive value of 85% for mortality within 1 year with a mean wall thickness ≥ 15 mm. Of the 13 patients who died within the first year, three patients with a SDNN ≤ 50 ms had a mean left ventricular wall thickness < 15 mm. However, the SDNN and the mean left ventricular wall thickness were correlated. In fact, heart rate variability and echocardiographic measures seem complementary prognostic indicators. Because heart rate variability is easy to perform and demands little co-operation of patients, it forms a valuable additional tool.

A limitation of our study is that we determined heart rate variability over 24 h without standardization of patient activities. Further investigation should reveal whether it would be possible to predict survival with short-term heart rate variability under standardized circumstances.

Although this study was performed in a small group of patients, a SDNN ≤ 50 ms was found to be highly predictive of mortality within 1 year in patients with AL amyloidosis. Further investigation should reveal whether this is also true in patients with AA amyloidosis.

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