Diagnostic Performance and Prognostic Value of Extravascular Retention of ^{123}I-Labeled Serum Amyloid P Component in Systemic Amyloidosis

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Serum amyloid P component (SAP) binds to amyloid. ^{123}I-SAP scintigraphy is used to evaluate the extent and distribution of amyloid in systemic amyloidosis and has great clinical value in the detection of systemic amyloidosis. The aim of the study was to assess during scintigraphy the diagnostic performance and prognostic value of a simple parameter describing extravascular ^{123}I-SAP retention in systemic amyloidosis. **Methods:** Two hundred megabecquerels of ^{123}I-labeled human SAP was injected intravenously for scintigraphy in 20 controls and in 189 consecutive patients with systemic and localized amyloidosis. Extravascular retention of ^{123}I-SAP was quantified from serum and urine measurements after 24 h (EVR_{24}) and 48 h. Sensitivity and specificity were assessed, and retention was correlated with kidney, heart, liver, and nerve involvement and with survival. **Results:** The cutoff value representing a desired specificity of 90% of EVR_{24} was 50%. The associated sensitivity of EVR_{24} for detecting reactive systemic, immunocyte-derived (AL), and hereditary amyloidosis was 65%, 61%, and 22%, respectively, using a cutoff point of 50%. In AL amyloidosis, the EVR_{24} increased with the number of organs involved (from a mean of 43% for 1 organ to a mean of 81% for 4 organs). The EVR_{24} correlated with serum alkaline phosphatase ($r = 0.63$) and with creatinine clearance ($r = -0.36$). In AL amyloidosis, both cardiac involvement (hazard ratio, 3.9; 95% CI, 2.0–7.8) and EVR_{24} (hazard ratio, 2.0; 95% CI, 1.1–3.9) were independent predictors of survival. **Conclusion:** In AL amyloidosis, the EVR_{24} is strongly associated with organ involvement and with prognosis and might serve as an indicator of the body amyloid load. Quantification of SAP retention using the EVR_{24} has no additional value over ^{123}I-SAP scintigraphy in the detection of systemic amyloidosis.

Key Words: diagnostic accuracy; prognostic factor; serum amyloid P component; systemic amyloidosis

J Nucl Med 2007; 48:865–872
DOI: 10.2967/jnumed.106.039313

Received Dec. 25, 2006; revision accepted Feb. 22, 2007.
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Systemic amyloidosis is characterized by a loss of organ and tissue function caused by deposition of amyloid throughout the body (*1*). The 3 major systemic types of amyloidosis are reactive systemic (AA), immunocyte-derived (AL), and hereditary (ATTR). AA amyloidosis is associated with chronically elevated serum amyloid A levels produced by an underlying inflammatory disease process, and the main clinical feature is nephropathy. AL amyloidosis is associated with elevated immunoglobulin free light chains in serum produced by monoclonal plasma cells, and the clinical features are diverse. ATTR amyloidosis is associated with variant transthyretin levels in serum caused by mutations of the transthyretin gene, and the main clinical features are neuropathy and cardiomyopathy (*1*). Amyloid deposition is often systemic but may sometimes be localized, that is, restricted to a single organ or tissue such as the larynx, eyelids, or urinary tract (*2*).

All amyloid deposits contain the nonfibrillar glycoprotein amyloid P component, which is derived from and is identical to serum amyloid P component (SAP). SAP binds in a calcium-dependent way to amyloid fibrils of all types (*2,3*). SAP labeled with radioactive iodine, ^{123}I-SAP, has been used as a tracer to detect amyloid and to determine the extent and distribution of amyloid deposits in systemic AL, AA, and ATTR amyloidosis by scintigraphy (*4–10*) and retention studies (*4–6,11–14*). ^{123}I-SAP scintigraphy permits the noninvasive diagnosis of systemic amyloidosis in most patients with AA and AL types and enables deposits to be imaged in many organs before the condition is apparent clinically (*10*). ^{123}I-SAP turnover studies show different dynamics between controls and patients with systemic amyloidosis of the AA and AL types (*4,6,11*). The rationale for measuring SAP retention in blood and body is that binding of SAP to extracellular amyloid deposits causes increased disappearance of SAP from the blood into extravascular tissues (resulting in low plasma

retention) and decreased disappearance of SAP from the extravascular tissues out of the body (resulting in high body retention). Tissue retention of SAP may be related to survival in patients with systemic amyloidosis (*12,14*). However, measuring ^{123}I-SAP turnover and retention is laborious because several blood samples are needed to calculate the extrapolated distribution volume at the moment of injection (*4,12*).

From 1990 until December 2003, 189 patients with amyloidosis were evaluated in our center using ^{123}I-SAP scintigraphy, and retention of SAP was measured in this population as well (*10*). The aim of the current study was to evaluate the diagnostic performance and prognostic value of a simple parameter describing extravascular ^{123}I-SAP retention.

MATERIALS AND METHODS

Patients

All 216 consecutive new patients with amyloidosis who were evaluated at the University Medical Center Groningen, a tertiary referral center, from February 1990 until December 2003 were prospectively screened for the study and subsequently followed until July 2006. Amyloidosis was diagnosed in all patients by the presence of typical apple-green birefringence in polarized light in a tissue specimen stained with Congo red dye. The definition and characterization of localized and systemic amyloidosis, the classification of systemic amyloidosis into AA, AL, and ATTR types, and the clinical evaluation of heart, liver, and kidney involvement have been described in detail elsewhere (*10*). Peripheral nerve involvement was defined to be present clinically if so judged by a consultant neurologist. Autonomic nerve involvement was defined to be present when the modified Ewing test battery yielded abnormal results (*15*). Twenty-five patients were not included: 10 because of logistical problems, 9 because of sudden death, and 6 because they did not want to participate. Twenty controls were studied. They were patients who had diseases that can underlie amyloidosis but in whom biopsies for amyloid had been negative and no features suggesting amyloidosis had developed during a follow-up of 3–9 y. The local Ethics Committee approved the study, and all 189 patients and 20 controls included gave informed consent to participate. The population used in this study was identical to an earlier-described population in which the diagnostic performance of ^{123}I-SAP scintigraphy was studied (*10*).

Radiolabeling and Quality Control

From 1990 to 1999, highly purified human SAP was obtained from London (kindly provided by Professor Philip Hawkins) (*4*). Since 1999, SAP has been purified and prepared from Dutch blood donors according to Dutch pharmaceutical standards in our center in Groningen. An essential part of these standards was the extensive screening of the donor blood for infectious diseases, including HIV. In all donors, this screening was repeated 6 mo after blood donation. Radiolabeling with radioactive iodine (^{123}I, half-life of 13.2 h, obtained from GE Healthcare [formerly Amersham Cygne]) and quality control were performed as described elsewhere (*12*).

Dose Administration, Blood Sampling, and Visual Assessment of Scintigraphy

Tracer administration and blood sampling were performed as reported earlier, with few modifications (*12*). In short, 200 MBq of ^{123}I-SAP containing 100 μg of protein were given as an intravenous bolus. The dose used was chosen for imaging. Venous plasma samples were drawn just before injection and 10 min, 4 h, 24 h, and 48 h after injection. Urine was collected for the first and second 24 h after administration. Thyroid uptake of free iodide was prevented by oral administration of potassium iodide. Subjects with a history of adverse reactions to iodide or to intravenous radiologic contrast media were excluded before administration.

Scintigraphy was performed 24 h after injection and assessed visually as described elsewhere (*10*). In short, total-body anterior and posterior views, as well as abdominal anterior and posterior spot views, were acquired. Two investigators who were blinded to the clinical data assessed normal or increased organ uptake (graded from 1+ to 3+) in patients with amyloidosis and controls. The highest organ score present in the patient determined the body uptake score.

SAP Retention Studies

One milliliter of each plasma sample and 2 mL of the urine portions were counted. Trichloroacetic acid–precipitable (protein-bound) radioactivity in plasma was used to measure the percentage of the injected dose still present in the vascular compartment, by using a calculated estimate of the plasma volume (*16*). The blood volume (in mL) was calculated by applying an algorithm using sex, body weight (in kg), and height (in m) (*17*): male blood volume = $(366.9 \times \text{height}^3) + (32.19 \times \text{weight}) + 604$, and female blood volume = $(356.1 \times \text{height}^3) + (33.08 \times \text{weight}) + 183.3$. Whole-body hematocrit was calculated from the venous hematocrit by multiplying by 0.91 (*18*). Plasma volume was calculated by subtracting the calculated red cell mass from the blood volume: plasma volume = blood volume – 0.91 × venous hematocrit × blood volume. The calculated plasma volume measurements were compared (Bland–Altman analysis) with the extrapolated distribution volumes at the moment of injection, as had been assessed previously (*12*) in 75 patients: After correction for the influence of 4 extreme outliers, the mean bias between distribution volume at injection and plasma volume was 11.7% (SD, 25.9%). Compared with other possible approximations, this calculation of the plasma volume appeared to be the closest to the extrapolated distribution volume. The plasma volume—multiplied by 1.12 to correct for the bias—was used to estimate the distribution volume of SAP, resulting in the following equation: distribution volume of SAP = 1.12 × plasma volume = 1.12(blood volume – 0.91 × venous hematocrit × blood volume). For practical use and simplicity, the ratio of the injected dose to the distribution volume of SAP was the concentration of radioactivity at the moment of injection and was set to 100%. Plasma samples (at 10 min and 4, 24, and 48 h) were thus expressed as percentage of injected dose. ^{123}I-SAP disappearance from the circulation was also measured independently of the distribution volume by calculating the ratio of plasma retention after 4 h to that after 10 min. This ratio was called the plasma SAP disappearance index (PSDI).

Because there is no significant extrarenal excretion, the total-body retention was calculated by subtracting the cumulative urine radioactivity, expressed as a percentage of the injected dose, from the given dose. Total-body retention values after 24 and 48 h were thus calculated. Whole-body counting during scintigraphy may be an alternative way to measure total-body retention (*12*). Extravascular retention values after 24 and 48 h (EVR_{24} and EVR_{48}) were determined by subtracting the total-plasma radioactivity (expressed as a percentage of the injected dose) from the total-body retention (*12*).

Statistical Analysis

Statistical analysis was performed using the statistical package GraphPad Prism, version 4.02 (GraphPad Software Inc.). The Bland–Altman analysis was used to compare the distribution volume at injection with the calculated plasma volume. The 1-way ANOVA test was used in combination with the Bonferroni multiple-comparison test to detect differences in variables among groups. Receiver-operating characteristic curves were used to analyze the different possible diagnostic cutoff points for SAP retention studies. The Pearson test was used to detect correlations. Survival curves were constructed according to the Kaplan–Meier method, and the groups were compared using log-rank tests. In all tests, 2-tailed P values of less than 0.05 were considered significant.

SPSS 12.0.1 (SPSS Inc.) for Windows (Microsoft) was used for predictors of survival. We identified predictors of survival in univariate and multivariate Cox proportional-hazard models and calculated the relative hazards and 95% confidence intervals. Multivariate analyses were performed with a stepwise forward-regression model, with an entry probability for each variable set at 0.05.

RESULTS

Patient Characteristics

One hundred eighty-nine patients were included in the study: 60 with AA, 80 with AL, and 27 with ATTR amyloidosis and 22 with localized disease (*10*). In addition, 19 patients without amyloid (8 with chronic arthritis, 3 with plasma cell dyscrasia, 6 with transthyretin mutations, 1 with familial Mediterranean fever, and 1 with polyneuropathy) and 1 healthy person served as controls. Patient characteristics and organ involvement for the 4 most prominently affected organs are shown in Table 1. Patients with AL amyloidosis were older ($P < 0.05$) than controls. As expected, cardiac involvement (55%) and liver involvement (30%) were most prominent in AL amyloidosis. Kidney involvement was most prominent in both AA (90%) and AL types (83%) and was also frequently part of the clinical picture of the controls without amyloidosis (55%). Nerve involvement was most prominent in ATTR (85%) but was also frequent in AL amyloidosis (50%). Patients with the AL type most frequently had involvement of more than 2 of the 4 organ systems (39%). Visceral organ disease was judged to be a coincidental finding in 2 patients with localized amyloidosis (nerve and kidney), and in both cases amyloid deposition in the affected tissue and organ was excluded.

Diagnostic Sensitivity and Specificity

Table 2 shows retention values of plasma, total body, and extravascular ^{123}I-SAP at the 4 intervals after

TABLE 1
Patient Characteristics and Organ Involvement

Parameter	Control	AA	AL	ATTR	Localized amyloidosis
Number of patients	20	60	80	27	22
Male:female	14:6	19:41	46:34	13:14	12:10
Age (y)	53.3 (17.0)	56.5 (14.7)	61.8 (10.2)	51.8 (10.5)	50.6 (12.1)
I. Heart					
a. Mean thickness* > 12 mm	1 (5%)	7 (12%)	36 (45%)	9 (33%)	0 (0%)
b. Heart failure†	1 (5%)	3 (5%)	24 (30%)	2 (7%)	0 (0%)
c. Low-voltage electrocardiography	0 (0%)	4 (7%)	23 (29%)	1 (4%)	0 (0%)
Heart involvement (a, b, or c)	2 (10%)	11 (18%)	44 (55%)	9 (33%)	0 (0%)
II. Kidney					
d. Proteinuria > 0.5 g/24 h	8 (40%)	39 (65%)	51 (64%)	1 (4%)	0 (0%)
e. Creatinine clearance < 60 mL/min	10 (50%)	41 (68%)	38 (48%)	3 (11%)	1 (5%)
Kidney involvement (d or e)	11 (55%)	54 (90%)	66 (83%)	4 (15%)	1 (5%)
III. Liver					
f. Liver span > 16 cm	0 (0%)	0 (0%)	15 (19%)	0 (0%)	0 (0%)
g. Alkaline phosphatase > 180 kU/L	0 (0%)	3 (5%)	18 (23%)	0 (0%)	0 (0%)
Liver involvement (f or g)	0 (0%)	3 (5%)	24 (30%)	0 (0%)	0 (0%)
IV. Nervous tissue					
h. Peripheral polyneuropathy	2 (10%)	2 (3%)	26 (33%)	21 (78%)	1 (5%)
i. Autonomic neuropathy	1 (5%)	7 (12%)	33 (41%)	20 (74%)	1 (5%)
Nerve involvement (h or i)	2 (10%)	8 (13%)	40 (50%)	23 (85%)	1 (5%)
Number of organs involved:					
0	6 (30%)	4 (7%)	2 (3%)	2 (7%)	20 (91%)
1	12 (60%)	41 (68%)	20 (25%)	15 (56%)	2 (9%)
2	2 (10%)	10 (17%)	27 (34%)	9 (33%)	0 (0%)
3	0 (0%)	5 (8%)	24 (30%)	1 (4%)	0 (0%)
4	0 (0%)	0 (0%)	7 (9%)	0 (0%)	0 (0%)

*Of cardiac septum and left ventricular wall.
†According to New York Heart Association grades 3 or 4.
Data are mean, with SD in parentheses, or number, with percentage in parentheses.

TABLE 2
Retention Figures of ^{123}I-SAP (Percentage of Dose) at Different Intervals After Injection in Patients

Parameter	Control	AA	AL	ATTR	Localized amyloidosis
Plasma retention					
10 min	105 (21)	95 (23)	90 (28)*	99 (22)	105 (18)
4 h	72 (19)	56 (23)*	52 (28)†	68 (19)	74 (17)
PSDI	0.69 (0.13)	0.57 (0.17)*	0.55 (0.19)†	0.68 (0.11)	0.71 (0.11)
24 h	40 (13)	32 (16)	29 (17)*	40 (14)	41 (12)
48 h	20 (10)	18 (9)	16 (10)	21 (7)	22 (8)
Body retention					
TBR 24 h	76 (13)	86 (11)†	85 (11)†	75 (10)	69 (14)
TBR 48 h	56 (17)	71 (16)†	71 (18)†	53 (15)	47 (17)
EVR_{24}	36 (15)	54 (19)†	56 (22)†	35 (17)	29 (10)
EVR_{48}	36 (18)	53 (18)†	55 (22)†	32 (15)	26 (12)

*$P < 0.05$ vs. controls.
†$P < 0.01$ vs. controls.
TBR = total body retention.
Retention was measured in plasma, total body, and extravascular compartment of body. Data are mean, with SD in parentheses.

injection. Patients with AA and AL amyloidosis had lower plasma retention 4 h after injection, as well as higher total-body and extravascular retention 24 and 48 h after injection, compared with controls. Patients with ATTR and localized amyloidosis did not differ from controls.

Receiver-operating characteristic curves were used to assess diagnostic cutoff points for the ^{123}I-SAP retention studies. All patients with systemic amyloidosis were merged into a "systemic amyloidosis" group, and controls and patients with localized amyloidosis were merged into a "nonsystemic amyloidosis" control group to calculate diagnostic specificity for systemic amyloidosis. Analysis of plasma retention measurements showed that PSDI discriminated best, with an area under the curve of 0.73. When a cutoff value of 0.51 was chosen for PSDI, reflecting a desired specificity of 90%, the sensitivity figures turned out to be 30% for AA, 38% for AL, and 11% for ATTR amyloidosis. Analysis of body retention measurements showed that EVR_{24} discriminated best, with an area under the curve of 0.83. When a cutoff value of 50% was chosen for EVR_{24}, reflecting a desired specificity of 90%, the sensitivity figures turned out to be 65% for AA, 61% for AL, and 22% for ATTR amyloidosis. The combination of the 2 parameters using their cutoff values (PSDI $>$ 0.51 and $EVR_{24} < 50\%$) produced an associated specificity of 86% and associated sensitivities of 70% for AA, 63% for AL, and 26% for ATTR amyloidosis.

All 167 patients with systemic AA, AL, or ATTR amyloidosis were subdivided on the basis of the intensity of scintigraphic uptake from 0 to 3+. Figure 1 illustrates the sensitivity figures of 18%, 44%, 53%, and 92% for these patients with scores of 0, 1+, 2+, and 3+, respectively (i.e., the percentage of patients in each group with values outside the combined reference area).

EVR_{24} and Organ Involvement

The EVR_{24} was higher in AL ($P < 0.001$) and ATTR ($P < 0.05$) patients with heart involvement (means of 64% and 45%, respectively) than in such patients without heart involvement (means of 47% and 30%, respectively). The EVR_{24} did not differ between patients with and without nerve involvement in any of the amyloid groups.

In AL amyloidosis, the EVR_{24} correlated modestly well with serum alkaline phosphatase ($r = 0.63$, $P < 0.0001$, Fig. 2A) after log transformation and correlated weakly with the endogenous creatinine clearance ($r = -0.36$, $P < 0.005$, Fig. 2B). In AA amyloidosis, the correlation of EVR_{24} with these liver and kidney function tests was poor

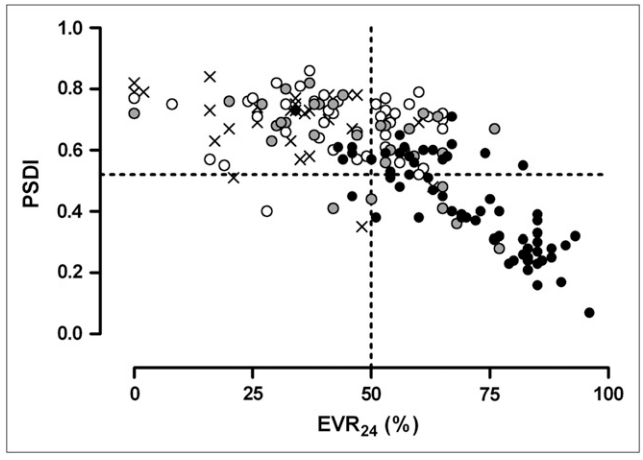

FIGURE 1. PSDI and EVR_{24} of all 167 patients with systemic amyloidosis (AA, AL, and ATTR types). Patients are subdivided according to intensity of scintigraphic uptake, represented by × (negative, $n = 28$), ○ (score 1+, $n = 45$), ◍ (score 2+, $n = 32$), and ● (score 3+, $n = 62$). Dotted lines are reference limits of controls (>0.51 for PSDI and <50% for EVR_{24}), resulting in reference area in upper left quadrant.

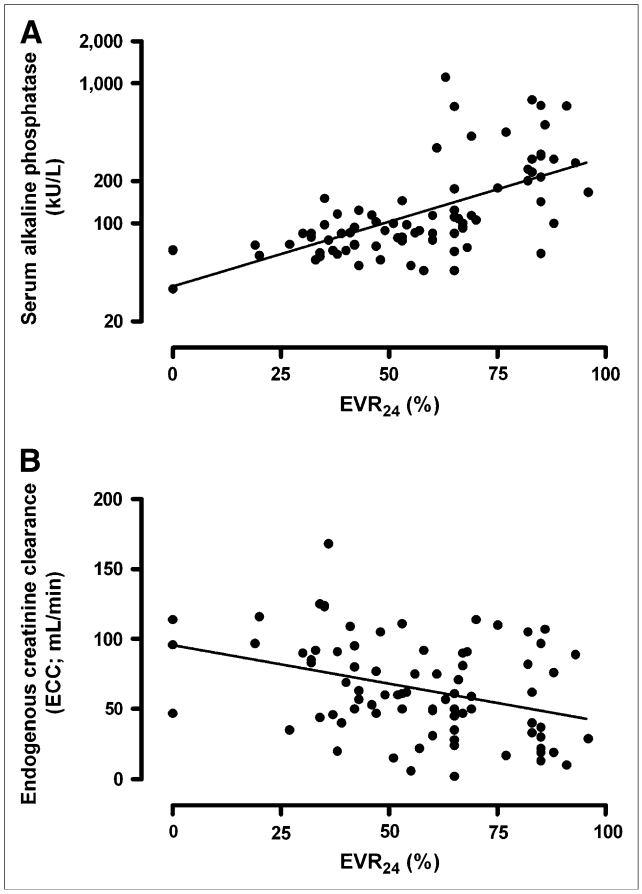

FIGURE 2. Relationship between EVR_{24}, serum alkaline phosphatase (A), and endogenous creatinine clearance (B) in patients with AL amyloidosis. Solid lines are linear regression lines.

($r = 0.11$ and $r = -0.21$, respectively) and statistically not significant. In all groups with amyloidosis, no correlation was found between EVR_{24} and proteinuria.

The mean EVR_{24} increased significantly ($P < 0.001$) with the number of organs involved in AL amyloidosis (from 43% for 1 organ to 81% for 4 organs), whereas this increase was not found in AA amyloidosis. The number of ATTR patients was too small to show differences, but a linear trend was present ($P < 0.05$).

Survival Analysis

After the ^{123}I-SAP retention study, the median follow-up of the 167 patients with systemic amyloidosis was 54 mo. Lost to follow-up were 5 AL patients (after a median of 3 mo), 12 AA patients (after a median of 20 mo), and 1 ATTR patient (after 11 mo). Fifty-five AL patients, 38 AA patients, and 12 ATTR patients had died. Median survival differed among the groups ($P < 0.005$): 12 mo in AL patients, 37 mo in AA patients, and 134 mo in ATTR patients.

Univariate survival analysis was performed on all groups of patients during the first 5 y after the study. Significant results were seen only in patients with AL amyloidosis, as shown in Table 3. A significantly elevated hazard ratio was found for elevated EVR_{24}, underlying multiple myeloma, heart involvement, and number of organs. Multivariate survival analysis in AL amyloidosis showed that elevated EVR_{24} still remained a predictor of survival (hazard ratio, 2.0) after clinical heart involvement (hazard ratio, 3.9) or heart failure (hazard ratio, 5.0) had first been entered, as shown in Table 3, whereas the number of organs and underlying multiple myeloma lost their significance as predictors of survival.

The predictive role of both cardiac involvement and EVR_{24} is shown in Figure 3. Figure 3A demonstrates the survival curves of AL amyloidosis patients with cardiac involvement (median survival, 6 mo) and without cardiac involvement (median survival not reached after 60 mo).

TABLE 3
Predictors of Survival of Patients with AL Amyloidosis During First 5 Years After Inclusion

Predictor	Hazard ratio	*P*
Univariate analysis		
$EVR_{24} > 50\%$	2.3 (1.2–4.5)	0.01
The male sex	1.2 (0.7–2.1)	0.6
Age > 60	0.9 (0.5–1.5)	0.6
Multiple myeloma	2.2 (1.2–4.0)	0.01
I. Heart		
a. Mean thickness* > 12 mm	3.3 (1.8–5.9)	<0.001
b. Heart failure†	5.1 (2.8–9.3)	<0.001
c. Low voltage electrocardiography	2.5 (1.4–4.5)	0.002
Heart clinical (a, b, or c)	4.2 (2.1–8.3)	<0.001
II. Kidney		
d. Proteinuria > 0.5 g/24 h	1.2 (0.7–2.3)	0.5
e. Creatinine clearance < 60 mL/min	0.8 (0.4–1.3)	0.3
Kidney clinical (d or e)	1.6 (0.7–3.5)	0.3
III. Liver		
f. Liver span > 16 cm	0.8 (0.4–1.8)	0.6
g. Alkaline phosphatase > 180 kU/L	1.4 (0.7–2.7)	0.3
Liver clinical (f or g)	1.2 (0.7–2.2)	0.6
IV. Nerves		
h. Peripheral polyneuropathy	0.9 (0.5–1.7)	0.8
i. Autonomic neuropathy	1.2 (0.7–2.2)	0.5
Neuropathy clinical (h or i)	1.3 (0.7–2.3)	0.3
Number of organs involved (I–IV) > 2	2.4 (1.4–4.3)	0.002
Multivariate analysis (1)		
Heart clinical	3.9 (2.0–7.8)	<0.001
$EVR_{24} > 50\%$	2.0 (1.1–3.9)	0.04
Multivariate analysis (2)		
Heart failure†	4.9 (2.6–9.1)	<0.001
$EVR_{24} > 50\%$	2.1 (1.1–4.0)	0.03

*Of cardiac septum and left ventricular wall.
†According to New York Heart Association grades 3 or 4.
Data in parentheses are 95% confidence intervals.

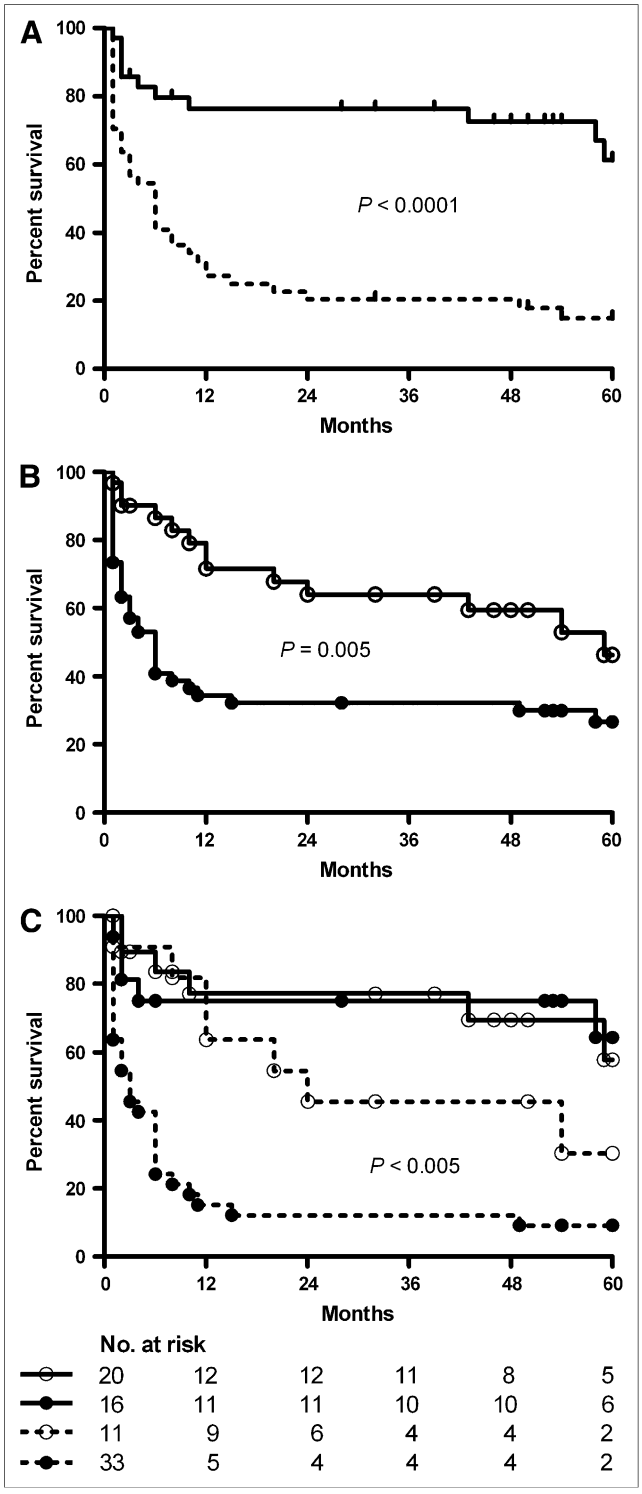

FIGURE 3. Five-year survival of 80 patients with AL amyloidosis. (A) Patients with (dotted line) and without (solid line) clinical involvement of heart. (B) Patients with high (>50%) (●) and with low (<50%) (○) EVR_{24}. (C) Patients stratified according to high (>50%) (●) and low (<50%) (○) EVR_{24} and presence (dotted line) or absence (solid line) of clinical involvement of heart.

Figure 3B demonstrates the survival curves of AL amyloidosis patients with elevated EVR_{24} (median survival, 6 mo) and normal EVR_{24} (median survival, 59 mo). Figure 3C demonstrates the survival curves for the group with or without cardiac involvement further subdivided into patients with normal or elevated EVR_{24}: The effect of EVR_{24} on survival was particularly evident in the group with cardiac involvement (median survival was 4 mo for members of this group with elevated EVR_{24} and 25 mo for members of this group with normal EVR_{24}; $P < 0.05$), whereas this effect of EVR_{24} was not found in the group with normal cardiac function (median survival had not been reached for either group by 5 y).

DISCUSSION

The diagnostic performance of EVR_{24} was suboptimal for detecting AA and AL amyloidosis and was inferior for detecting ATTR amyloidosis because of low sensitivity values: 65%, 61%, and 22%, respectively. However, in AL amyloidosis, EVR_{24} was strongly associated with organ disease—such as of the heart, kidney, or liver—and with the number of organs affected by disease. EVR_{24} is a distinct predictor of survival in AL amyloidosis patients and appears to be independent of cardiac involvement, the most important predictor of survival (*19*). In this respect, EVR_{24} behaves as an indicator of the amyloid load of the body. One should keep in mind that these conclusions are biased by application of criteria to the same population that was used to establish the criteria. Therefore, the results need to be confirmed in another independent series of patients.

The two ^{123}I-SAP retention parameters with the highest sensitivity are PSDI for blood retention and EVR_{24} for body retention. However, the sensitivity of both retention parameters (associated with a desired specificity of 90%) was much lower than the sensitivity of ^{123}I-SAP scintigraphy: 90%, 90%, and 48% for AA, AL, and ATTR amyloidosis, respectively (*10*). Because the sensitivity of EVR_{24} in patients with systemic amyloidosis and negative ^{123}I-SAP scintigraphy findings was low, only 18%, measuring EVR_{24} had no additional value in the negative scintigraphy group.

EVR_{24} was associated with heart, kidney, and liver disease and with the number of organs involved in patients with AL amyloidosis, whereas these associations were not found for AA and ATTR amyloidosis. The main reason for this difference probably is that AL amyloidosis is the most serious of the 3 diseases, as reflected by a higher number of organs involved; by rapidly ongoing deposition of amyloid, resulting in progressive loss of organ function; and by the worst survival. In this progressive disease with extensive deposition of amyloid, a relationship with SAP retention may be detected earlier and more easily than in diseases with a slower course and moderate deposition of amyloid. EVR_{24} appears to also be a predictor of survival in AL amyloidosis. It may be important to recognize this risk factor because of its independence from other risk factors such as cardiac involvement and the number of involved organs. Especially in the group of patients with cardiac

involvement, a normal EVR_{24} (Fig. 3C) may identify patients with an intermediate prognosis who possibly may have lower risks and more time left to respond to and benefit from chemotherapy. Recently, the serum levels of N-terminal pro-B-type natriuretic peptide and troponin have been identified as additional important cardiac predictors of survival in patients with AL amyloidosis (*19,20*). The relationship between these new serum markers of cardiac involvement and EVR_{24} should be the subject of a more extensive future study in which other identified predictors of survival in AL amyloidosis, such as β2-microglobulin (*19*) and response to chemotherapy (*21*), also need to be evaluated.

In this study, a simple parameter was introduced for EVR_{24} to facilitate the routine measurement of body retention of SAP in patients with amyloidosis. In addition to the ^{123}I-SAP scintigraphy planned about 24 h after injection, one needs only patient data such as sex, length, and weight; a single blood sample for the hematocrit and for counting radioactivity; and the volume of the urine collected for 24 h after injection. The EVR_{24} obtained in this way is indeed a useful measurement of body retention of SAP for routine clinical practice. Major drawbacks of the method, however, are high costs and the limited availability of purified SAP and ^{123}I. Recombinant biotechnology for the production of SAP and the use of cheaper and more widely available isotopes such as technetium might be a possible way to solve this problem. However, labeling of SAP with technetium, a metal nuclide, is demanding, and its degradation products accumulate in the kidneys and liver, increasing the nonspecific background at these sites. Therefore, currently technetium is not a realistic alternative to iodine. A second possible way to proceed is to unravel the binding mechanisms of SAP and Congo red to amyloid, eventually resulting in the development of new ligands to amyloid that can be used as tracers instead of SAP (*22,23*). A third possible way is the generation of antibodies directed against conformational epitopes shared by all types of amyloid (such as antibody 11-1F4 in the mouse) that can be used as tracers (*24*).

CONCLUSION

In summary, EVR_{24} has distinct clinical value as an independent predictor of survival in patients with AL amyloidosis. Because of its association with liver and kidney involvement and with the number of organs involved, EVR_{24} seems to be an indicator of the amyloid load of the body in AL amyloidosis. For the detection of systemic amyloidosis, however, the body retention of SAP measured by EVR_{24} has no additional value over ^{123}I-SAP scintigraphy (*10*).

ACKNOWLEDGMENTS

The Dutch Arthritis Association and the Jan Kornelis de Cock Stichting provided financial support for this study. We thank Professors Mark Pepys and Philip Hawkins (Royal Free Hospital in London) for kindly supplying us with SAP during the first years of the study and for their continuing reliable and stimulating support during preparation, implementation, and evaluation of our SAP labeling and scintigraphic procedures. We also thank Cees Th. Smit Sibinga, Willem Tuuk Adriani, Pieter C. Limburg, and Johan Bijzet for manufacturing SAP in Groningen; the nuclear medicine technicians for making the scintigraphs of the patients; and Annie van Zanten, Chris Harms, Hans Pol, Hugo Nijnuis, and Jelle Boorsma for performing labeling studies and laboratory analysis.

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Erratum

The article "Treatment of Thyrotoxicosis," by Iagaru and McDougall (*J Nucl Med.* 2007;48:379–389), contained some errors. On page 380, in the fourth line from the bottom of the right column, "1,500 mm" should be "1,500/mm^3." On page 382, in the seventh line from the bottom of the left column, "160 mCi" should be "160 μCi." On page 383, in the twelfth line from the top of the left column, "MBq" should be "MBq/g" and "μCi" should be "μCi/g."