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ORIGINAL ARTICLE

Outcome prediction by myocardial external efficiency from ^{11}C-acetate positron emission tomography in cardiac amyloidosis

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Abstract

Aims This study aimed to study the prognostic value of myocardial oxygen consumption (MVO_2) and myocardial external efficiency (MEE) from ^{11}C-acetate positron emission tomography (PET) in cardiac amyloidosis (CA) patients.

Methods and results Forty-eight CA patients, both transthyretin (ATTR) and immunoglobulin light chain (AL) amyloidosis, and 20 controls were included. All subjects were examined with ^{11}C-acetate PET and echocardiography. MVO_2, forward stroke volume (FSV), and left ventricular mass (LVM) were derived from ^{11}C-acetate PET and used to calculate MEE. CA patients were followed for survival and the prognostic impact of clinical, echocardiographic, and ^{11}C-acetate PET parameters was analysed. MVO_2 and MEE were reduced in CA compared with controls, but without significant difference between deceased and surviving CA patients. The ratio of ^{11}C-acetate PET-derived FSV and LVM was also reduced in CA and significantly lowered in deceased patients compared with survivors. In univariate analysis, New York Heart Association class, N-terminal pro-brain natriuretic peptide, and the ^{11}C-acetate PET parameters FSV/LVM and MEE were the strongest prognostic factors. Of the ^{11}C-acetate PET parameters, FSV/LVM was the strongest survival predictor with hazard ratio of 0.56 per 0.1 mL/g (95% confidence interval 0.39–0.81, $P = 0.002$) and independently prognostic in a multivariate model. MEE significantly separated deceased from surviving CA patients with the cut-off of 15.7% ($P = 0.032$). Survival was significantly shorter with FSV/LVM below 0.27 mL/g ($P < 0.001$), also when separating AL- and ATTR-CA.

Conclusions Reduced MEE was associated with shorter survival in CA patients, but FSV/LVM was the strongest survival predictor and the only independently prognostic ^{11}C-acetate PET parameter in multivariate analysis.

Keywords PET; Acetate; Survival; Prognosis; Heart; Myocardial contraction fraction

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Introduction

Cardiac amyloidosis (CA) is a disease where amyloid fibrils of different origin are deposited progressively in the myocardium with increasing wall thickness leading to restrictive ventricular filling and clinical heart failure. The two main subtypes of CA are transthyretin (ATTR), wild-type or hereditary, and immunoglobulin light chain (AL) amyloidosis. CA is a serious condition with poor survival in both ATTR and AL subtypes. In the recent years, great progress has been made in diagnosis and therapy of both AL- and ATTR-CA, including introduction of new and potentially life-prolonging treatments, making strategies to select patients for different treatment options important.

Several different methods of predicting outcome in CA have been proposed. Cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponins are prognostic at diagnosis in both AL- and ATTR-CA and are used in the Mayo staging system for AL amyloidosis.[1,2] Furthermore, NT-proBNP and estimated glomerular filtration rate are used to predict outcome in ATTR-CA in the UK National Amyloidosis Centre staging system.[3] Stroke volume (SV), tricuspid annular plane systolic excursion (TAPSE), and global longitudinal strain (GLS) derived from echocardiography or cardiac magnetic resonance (CMR) are also shown to provide independently prognostic information for survival.[4–6] Left ventricular myocardial work index (LVMWI), a method that measures systolic myocardial deformation in relation to afterload conditions, is prognostic for both major adverse cardiac events and survival.[7] Higher extracellular volume (ECV) and left ventricular mass (LVM) represent greater amyloid burden. Mass together with SV can be used to calculate myocardial contraction fraction (MCF), which is defined as SV divided by the myocardial volume (MV). MV in turn is calculated as LVM divided by the mean density of myocardium (1.05 g/mL). MCF independently predicts survival in both AL- and ATTR-CA.[8,9] The prognostic value was validated by Mayo clinic with echocardiography in AL-CA patients[5] and confirmed in both AL and ATTR patients with CMR.[4,10]

The utilization of positron emission tomography (PET) in CA has mainly been focused on amyloid-binding tracers for diagnosis.[11,12] With the perfusion tracers ^{11}C-acetate and ^{15}O-water, PET can be used to measure myocardial oxygen consumption (MVO$_2$) and myocardial blood flow (MBF) and was recently validated for measuring FSV and LVM using both ^{11}C-acetate and ^{15}O-water.[13,14] Myocardial external efficiency (MEE) can be derived non-invasively with a high degree of automation and repeatability from ^{11}C-acetate PET as the energetic ratio of stroke work and oxidative energy consumption.[15,16]

MEE was previously used in CA to investigate the role of echocardiography-derived work index based on strain imaging.[7] As MEE incorporates measures of oxygen metabolism and mechanical work, both of which are affected in CA, it is potentially highly prognostic but has never been tested. MEE integrates the components of the MCF parameter, and we wanted to evaluate whether the addition of metabolic data enhances the predictive value of MCF.

Methods

Study population

This retrospective study included 48 patients with known CA, enrolled at Uppsala University Hospital in Sweden and Aarhus University Hospital in Denmark, 25 with ATTR-CA (18 wild-type and 7 hereditary) and 23 with AL subtype. We also included 14 healthy volunteers with normal echocardiograms and 6 patients with increased cardiac wall thickness but without amyloidosis, serving as controls. The hereditary ATTR group comprised four subjects with the Danish Leu111Met mutation and two with the Swedish His88Arg mutation; in one patient, the type of mutation was unknown. The diagnosis of CA was confirmed with endomyocardial biopsy in 33 patients and with abdominal fat pad biopsy together with echocardiography (in one patient with CMR) in 15 patients. In controls with increased cardiac wall thickness, the underlying cause was either hypertensive heart disease (n = 3) or idiopathic hypertrophic cardiomyopathy (n = 3), without any clinical suspicion of amyloidosis. The healthy controls were volunteers without any history of cardiac disease or hypertension. Volunteers older than 65 years were not selected due to the increasing incidence of wild-type ATTR amyloidosis with age[17] and the risk of subjects having undiagnosed ATTR amyloidosis.

All subjects were examined with ^{11}C-acetate PET and echocardiography at rest. Patients from the Uppsala cohort (15 CA subjects) also underwent ^{15}O-water PET at rest. Subjects were also examined with the amyloid-binding tracer ^{11}C-PIB PET as part of two previous studies,[11,18] in which ^{11}C-acetate and ^{15}O-water PET were performed prospectively to evaluate haemodynamic and metabolic heart function.

The investigation conforms with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all subjects before inclusion, and the study was performed with approval of the local ethics committees in Uppsala and Central Denmark Region.

Positron emission tomography

PET scans were performed with a Discovery ST or MI PET/CT (GE Healthcare, Waukesha, Wisconsin) in Uppsala and with a Biograph TruePoint TrueV 64 PET/CT (Siemens, Erlangen, Germany) in Aarhus according to the same protocol. After a low-dose computed tomography (CT) scan, ^{15}O-water (400 MBq) and/or ^{11}C-acetate (5 MBq/kg) was injected intravenously as a standardized bolus, and list mode data were collected for 6 and 27 min, respectively. ^{11}C-acetate was injected 12 min after ^{15}O-water to allow for isotopic decay. Heart rate and systemic blood pressures were collected after at least 15 min of rest and immediately before tracer injections. Images were reconstructed to dynamic time-series with standard vendor settings. Images were analysed with highly automated software developed in-house as previously described and validated kinetic models were used to calculate MVO$_2$ from ^{11}C-acetate PET.[15,16] Cardiac output was measured from first-pass images using indicator dilution techniques,[19] and forward stroke volume (FSV) was calculated as cardiac output divided by heart rate. LVM was assessed by segmentation of the left ventricle using pixel-wise images created from the most relevant kinetic model parameters.[13,14] MEE was calculated, as previously described,[20] by the following equation:

$$\mathrm{MEE} = \frac{\mathrm{EW} \times 1.33 \times 10^{-4}}{\mathrm{LVM} \times \mathrm{MVO_2} \times 20} \times 100.$$

EW (external work) was calculated as the product of PET-derived FSV, heart rate, and mean arterial blood pressure. The constants in the equation are used for conversion to joules. Echocardiography was performed according to current guidelines,[21] including measurement of interventricular septal wall thickness (IVST), left ventricular ejection fraction (LVEF), and TAPSE.

Statistics

Statistical analyses were performed with IBM SPSS 28. Distribution was assessed with the Shapiro–Wilk test, and parameters were not normally distributed. Numerical values are presented as median with interquartile range (IQR). The Mann–Whitney *U* test and the Kruskal–Wallis test were used for group comparison. Correlations were assessed using the Spearman rank correlation or linear regression (association of MEE towards FSV/LVM). Receiver operating characteristic (ROC) curves were used to establish the optimal cut-off values separating deceased CA patients from survivors. The Kaplan–Meier estimate was used for survival analysis, and the log-rank test was used to compare survival curves. Factors potentially influencing survival were first explored in univariate Cox regression analyses, and the significant parameters of interest were then analysed in multivariate Cox proportional hazard analysis. *P*-values < 0.05 were regarded as statistically significant.

Results

Patient characteristics

Characteristics of the study groups including echocardiography data are presented in *Table 1*. Comparing ATTR and AL groups, ATTR patients were significantly older (73 vs. 67 years) and had thicker IVST (18 vs. 16 mm).

^{11}C-acetate positron emission tomography results in cardiac amyloidosis patients and controls

Figure 1 shows the ^{11}C-acetate PET results for deceased CA patients compared with survivors and controls. $\mathrm{MVO_2}$ was significantly reduced in CA (0.08 mL/min/g, IQR 0.06–0.1) compared with healthy controls (0.10 mL/min/g, IQR 0.08–0.12), with no significant difference between deceased and surviving CA patients. $\mathrm{MVO_2}$ was not significantly different between AL and ATTR, median 0.08 mL/min/g (IQR 0.06–0.1 mL/min/g) vs. 0.07 mL/min/g (IQR 0.06–0.1 mL/min/g), and did not differ significantly between deceased and surviving patients in either of the CA subtypes. MEE was significantly lowered in CA, in both deceased (13%, IQR 9–17) and surviving (16%, IQR 10–19) patients, compared with both hy-

Table 1 Subject characteristics and echocardiography data according to study group

	AL	ATTR	Hypertrophic	Healthy controls	*P*-value[a]
Number of subjects	23	25	6	14	—
Male [*n* (%)]	18 (78)	22 (88)	4 (67)	6 (43)	—
Age (years)	67 (60–70)[b]	73 (64–79)[b]	69 (62–72)	56 (51–62)	0.004
Positive EMB [*n* (%)]	11 (48)	21 (84)	—	—	—
NYHA class I/II/III/IV	3/7/12/1	3/8/14/0	2/3/1/0	—	—
NT-proBNP (ng/L)	3315 (1758–10 088)	2962 (1125–6348)	229 (76–1077)	—	0.007
Atrial fibrillation [*n* (%)]	3 (13)	3 (12)	0 (0)	—	—
Echocardiography					
IVST (mm)	16 (13–18)[b]	18 (14–22)[b]	16 (14–16)	8.0 (7.0–11)	<0.001
LVEF	0.58 (0.44–0.62)	0.55 (0.44–0.61)	0.67 (0.51–0.71)	0.66 (0.59–0.69)	0.031
LVEDd (mm)	4.3 (3.9–4.8)	4.6 (4.2–4.9)	4.1 (3.7–4.8)	4.5 (4.2–4.8)	0.58
LVGLS (−%)	13 (9.0–17)	11 (8.8–12)	14 (12–18)	21 (18–22)	<0.001
LA volume (mL/m^2)	38 (31–48)	43 (33–68)	31 (23–54)	34 (28–36)	0.047
TAPSE (cm)	1.6 (1.2–1.8)	1.6 (1.2–2.3)	1.8 (1.5–2.3)	2.6 (2.3–3.0)	0.001
E/A ratio	1.9 (1.6–3.2)	2.6 (1.3–3.9)	0.7 (0.6–1.2)	1.2 (0.9–1.6)	<0.001
E/e′	17 (15–21)	19 (16–26)	20 (12–28)	7.0 (5.5–9.0)	<0.001

AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; E/A, ratio of the Doppler peak velocity of E- and A-wave; E/e′, early filling velocity divided by the early relaxation velocity; EMB, endomyocardial biopsy; IVST, interventricular septum thickness; LA, left atrium; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.
Values are *n* (%) or median (interquartile range).
[a] Kruskal–Wallis test comparing all groups.
[b] $P < 0.05$ comparing AL and ATTR.

Figure 1 ^{11}C-acetate positron emission tomography parameters: (A) myocardial oxygen consumption (MVO$_2$), (B) myocardial external efficiency (MEE), and (C) forward stroke volume/left ventricular mass (FSV/LVM) for deceased and surviving cardiac amyloidosis (CA) patients [light chain (AL) and transthyretin (ATTR) amyloidosis], hypertrophic controls, and healthy controls. The *P*-value is derived from the Kruskal–Wallis test comparing the groups.

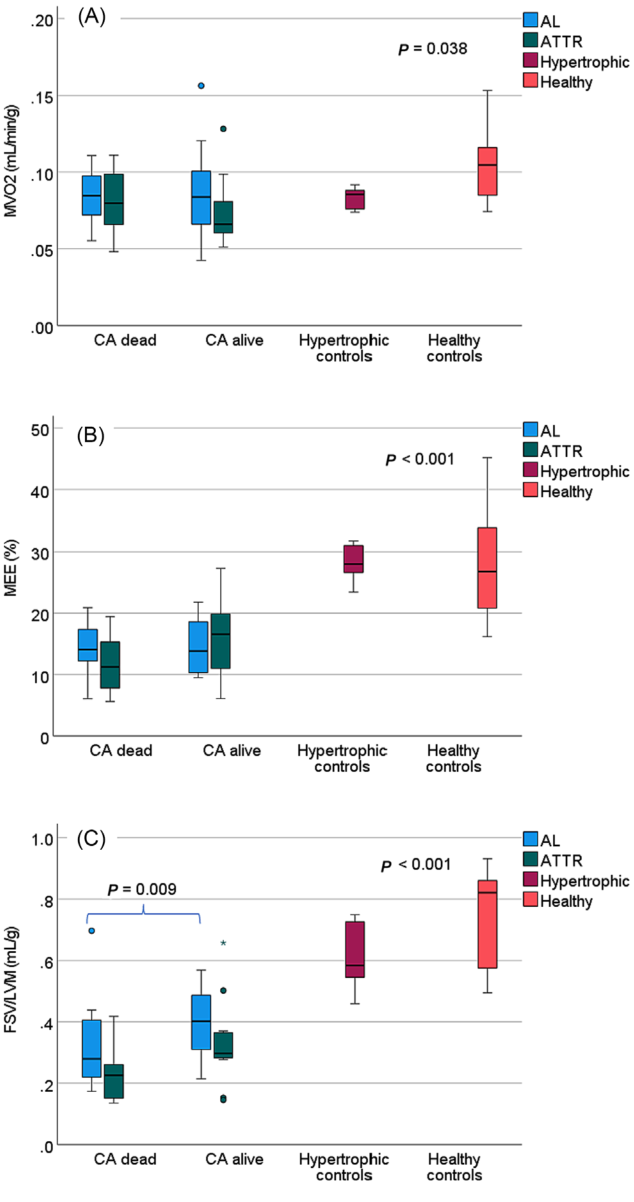
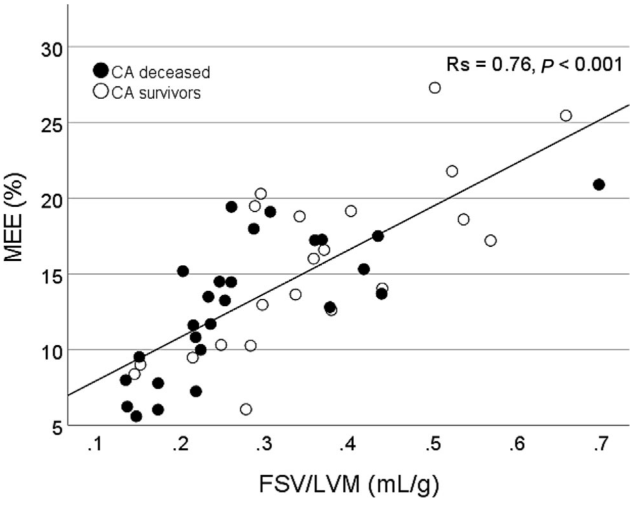


Figure 2 Correlation between forward stroke volume/left ventricular mass (FSV/LVM) and myocardial external efficiency (MEE) in deceased (black) and surviving (white) cardiac amyloidosis (CA) patients. R_s, Spearman's rho.



pertrophic (28%, IQR 26–31) and healthy (27%, IQR 21–34) controls. MEE did not differ significantly between AL and ATTR, median 13% (IQR 11–18%) vs. 14% (IQR 8–18%), and there was no significant difference between deceased and surviving patients in AL or ATTR. ^{11}C-acetate PET-derived FSV was significantly lower, and LVM was higher in CA patients compared with both hypertrophic and healthy controls, and the ratio between FSV/LVM significantly discriminated deceased from surviving CA (0.24 mL/g, IQR 0.20–0.36 vs. 0.35 mL/g, IQR 0.28–0.46; P = 0.009). FSV/LVM was significantly lower in ATTR (0.26 mL/g, IQR 0.16–0.35) than in AL (0.36 mL/g, IQR 0.25–0.44) and differed significantly between deceased and surviving ATTR, but not AL, patients.

There was a strong correlation between FSV/LVM and MEE in CA patients (R_s = 0.76, $P < 0.001$; *Figure 2*). Both MEE and FSV/LVM were correlated with standard echocardiographic indicators of left ventricular (LV) diastolic (E/e′), LV systolic (GLS), and right ventricular systolic function (TAPSE). As shown in *Figure 3*, both MEE and FSV/LVM were reduced in CA compared with healthy controls. Furthermore, E/e′, GLS, and TAPSE were all abnormal in CA patients as compared with healthy controls. FSV index (FSVI) was negatively associated with heart rate (R_s = −0.6, $P < 0.001$).

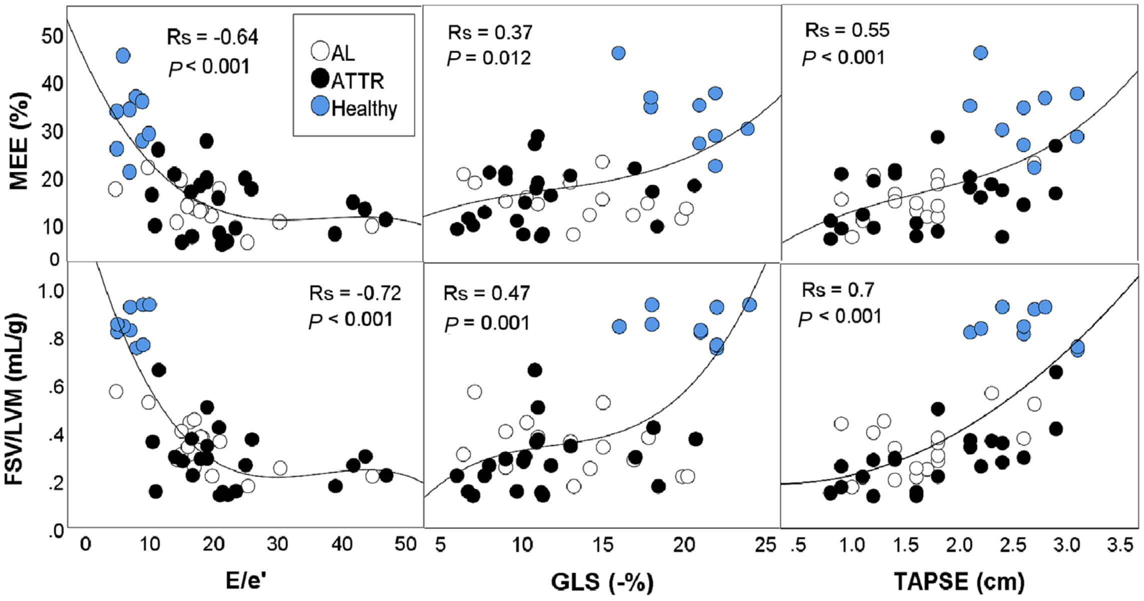
FSV measured with ^{11}C-acetate PET correlated well with FSV from ^{15}O-water PET (R_s = 0.76, $P < 0.001$). There were also strong correlations for LVM and FSV/LVM between the two PET scans (R_s = 0.94, $P < 0.001$ and R_s = 0.92, $P < 0.001$). Figures showing correlations between ^{11}C-acetate and ^{15}O-water PET parameters are presented in the Supporting Information, *Figure S1*.

Outcome prediction by ^{11}C-acetate positron emission tomography

Median time from PET to death or end of follow-up was 41 (IQR 22–135) months for CA patients. Total mortality during the follow-up period was 54.2% (n = 26).

ROC analysis was performed on ^{11}C-acetate PET parameters to determine the cut-off values that best discriminated

Figure 3 Associations of myocardial external efficiency (MEE) and forward stroke volume/left ventricular mass (FSV/LVM) from ^{11}C-acetate positron emission tomography towards echocardiographic indicators of systolic and diastolic function in cardiac amyloidosis. Subjects enrolled in dedicated study with near-simultaneous positron emission tomography and echocardiography [*n* = 19 light chain (AL), 23 transthyretin (ATTR) amyloidosis, and 9 healthy controls]. E/e′, early filling velocity divided by the early relaxation velocity; GLS, global longitudinal strain; R_s, Spearman's rho; TAPSE, tricuspid annular plane systolic excursion.



between deceased and surviving CA patients. For MEE, the optimal cut-off was 15.7% with area under the curve (AUC) of 0.63 [95% confidence interval (CI) 0.47–0.79]. FSV/LVM best discriminated deceased from survivors in all CA patients (cut-off 0.27 mL/g; AUC 0.72, 95% CI 0.57–0.87), as well as in AL and ATTR separately. The optimal prognostic cut-off value of FSV/LVM in AL patients was 0.39 mL/g, and that in ATTR was 0.27 mL/g.

Survival was significantly shorter in patients with low vs. high MEE, using the cut-off value of 15.7%, with median survival of 35 (IQR 7–71) vs. 135 (IQR 29–135) months (P = 0.032; *Figure 4*). When analysing AL and ATTR groups separately, statistically significant hazard ratios were not reached using FSV/LVM as a continuous variable. With FSV/LVM lower than the cut-off of 0.27 mL/g, survival was significantly impaired with median survival of 23 (IQR 6–40) vs. 135 (IQR 41–135) months ($P < 0.001$). The survival difference between FSV/LVM below and above the cut-off point was significant also for AL and ATTR separately (P = 0.011 and P = 0.004).

In univariate Cox regression analysis, New York Heart Association (NYHA) class, NT-proBNP, LVEF, and left atrium (LA) volume from echocardiography, as well as the ^{11}C-acetate PET parameters heart rate, FSVI, FSV/LVM, and MEE, were all significantly associated with overall survival in CA (*Table 2*). FSV/LVM remained independently significant compared with all other univariate predictors in bivariate analysis.

The ^{11}C-acetate PET parameters FSVI, FSV/LVM, and MEE were selected for multivariate analysis, where FSV/LVM was the only independent predictor for survival (hazard ratio 0.52 per 0.1 mL/g, 95% CI 0.28–0.96, P = 0.038).

When separated into CA subtypes and using the continuous ^{11}C-acetate PET variables and not cut-off values, the significant prognostic factors were NYHA class, FSVI, and FSV/LVM in AL and NT-proBNP, LVEF, and TAPSE in ATTR. All results of the univariate Cox regression analysis in AL and ATTR separately are included in Supporting Information, *Tables S1* and *S2*.

Discussion

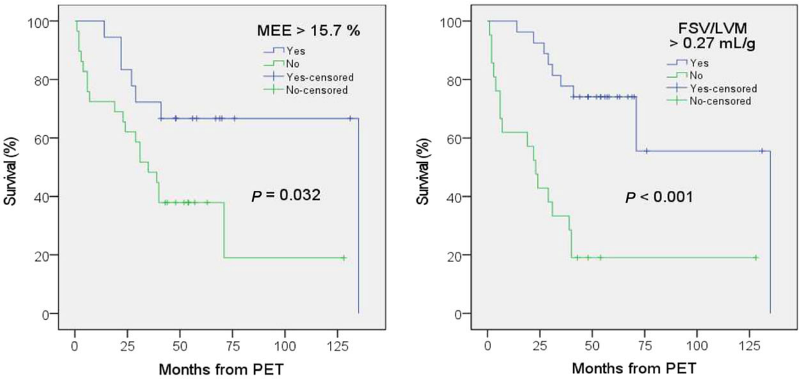
The key findings of the study were the following:

1. MEE, MVO_2, and FSV/LVM are reduced in CA compared with controls.
2. MEE and FSV/LVM derived from ^{11}C-acetate PET are significant outcome predictors.
3. FSV/LVM is the only independent predictor of survival.

FSV/LVM was superior to MEE and echocardiography parameters for prediction of outcome in CA. FSV/LVM resembles MCF (SV/MV), which was previously shown, with both echocardiography and CMR, to be an independent predictor

Figure 4 Survival with myocardial external efficiency (MEE) and forward stroke volume/left ventricular mass (FSV/LVM) above or below the cut-off levels in (A) all cardiac amyloidosis (CA) patients, (B) light chain-CA (AL-CA), and (C) transthyretin-CA (ATTR-CA).

(A) **All CA**



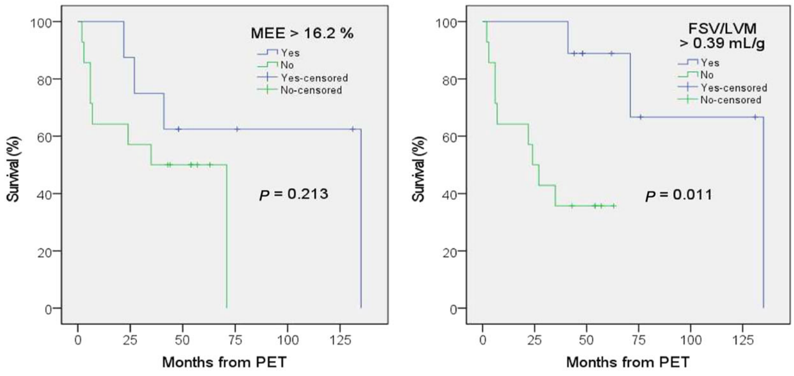
Numbers at risk

MEE high
18 15 8 3 2 2
MEE low
29 18 8 1 1 1

Numbers at risk

FSV/LVM high
27 25 15 3 2 2
FSV/LVM low
21 9 2 1 1 1

(B) **AL CA**



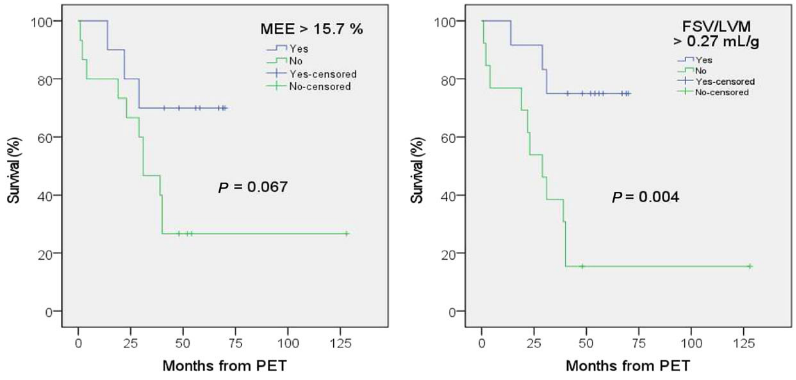
Numbers at risk

MEE high
8 7 3 3 2 2
MEE low
14 8 5 0 0 0

Numbers at risk

FSV/LVM high
9 9 5 3 2 2
FSV/LVM low
14 7 4 0 0 0

(C) **ATTR CA**



Numbers at risk

MEE high
10 8 5 0 0 0
MEE low
15 10 3 1 1 1

Numbers at risk

FSV/LVM high
12 11 7 0 0 0
FSV/LVM low
13 7 1 1 1 1

Table 2 Univariate and multivariate survival analysis

Univariate Cox regression	Hazard ratio	95% CI	*P*-value
Gender	0.16	0.02–1.18	0.072
Age	1.03	0.99–1.07	0.16
NYHA class	4.19	1.76–10.0	<**0.001**
Log NT-proBNP	1.49	1.07–2.08	**0.017**
Echocardiography			
IVST	1.06	0.96–1.16	0.27
LVEF	0.96	0.93–0.99	**0.005**
LVEDd	1.28	0.69–2.38	0.44
LA volume	1.03	1.01–1.05	**0.015**
TAPSE	0.93	0.87–1.01	0.09
E/A ratio	1.28	0.95–1.72	0.11
E/e′	1.02	0.98–1.06	0.30
^{11}C-acetate PET			
HR	1.04	1.01–1.07	**0.019**
MAP	1.02	0.98–1.05	0.36
MVO$_2$ (per 0.01 mL/min/g)	1.02	0.87–1.20	0.83
FCO index	0.95	0.87–10.4	0.27
FSV index	0.93	0.88–0.98	**0.007**
LVM index	1.01	1.00–1.02	0.06
FSV/LVM (per 0.1 mL/g)	0.56	0.39–0.81	**0.002**
MEE	0.92	0.85–1.00	**0.042**
Multivariate Cox regression	**Hazard ratio**	**95% CI**	***P*-value**
^{11}C-acetate PET			
FSV index	0.97	0.89–1.05	0.43
FSV/LVM (per 0.1 mL/g)	0.52	0.28–0.96	**0.038**
MEE	1.08	0.95–1.23	0.26

CI, confidence interval; E/A, ratio of the Doppler peak velocity of E- and A-wave; E/e′, early filling velocity divided by the early relaxation velocity; FCO, forward cardiac output; FSV, forward stroke volume; HR, heart rate; IVST, interventricular septum thickness; LA, left atrium; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; MAP, mean arterial pressure; MEE, myocardial external efficiency; MVO$_2$, myocardial oxygen consumption; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PET, positron emission tomography; TAPSE, tricuspid annular plane systolic excursion.
Bold indicates significant *P*-values.

of survival in CA and having a progressively increasing likelihood of being abnormal with increasing amyloid burden.[4]

FSV/LVM measured with PET was reproducible across different scanners and across two different perfusion tracers (^{11}C-acetate and ^{15}O-water), which means that it might be useful in a clinical routine. MCF can be measured with echocardiography and CMR but is typically constructed using a geometric total SV (end-diastolic volume–end-systolic volume) instead of FSV. The use of FSV for MCF assessments might have incremental value over the geometric volume because total SV disregards valvular insufficiencies often seen in CA.

FSV/LVM appears to have a very high accuracy for outcome prediction, suggesting that this index is at the core of CA pathology. In proportion to overall amyloid infiltration, LVM increases, leading to reduced filling capacity, stiffness, and lowered FSV, making the ratio FSV/LVM a sensitive measure of disease progression and can explain why FSV/LVM is a strong prognostic marker. The cut-off FSV/LVM of 0.27 mL/g might represent a ‘point-of-no-return’ where amyloid burden is increased, and systolic and diastolic function decreased to the extent that adequate systemic circulation can no longer be maintained. As an attempt to compensate for a low FSV, heart rate is increased, and higher heart rate was also significantly associated with worse survival. Higher LVM is associated with lowering of resting MBF, which can lead to further worsening of the contractile capacity in a vicious cycle.

In this study, the standard echocardiographic parameters used for evaluation of prognosis were all inferior to FSV/LVM. The best echocardiographic predictors were LVEF and LA volume, considered indicators of late-stage disease, supported by the high prevalence of NYHA class III patients in the CA cohort. The multivariate outcome might have been different in a cohort with earlier disease. However, there was a distinctly lowered FSV/LVM also in non-fatal CA, compared with hypertrophic controls, suggesting that low FSV/LVM can be indicative of CA diagnosis as opposed to non-CA causes of hypertrophy. In addition, FSV/LVM was correlated with echocardiographic indicators of systolic and diastolic dysfunction but appears to be lowered earlier in the disease process, suggesting that FSV/LVM could be a useful parameter in the pursuit of early CA diagnosis.

MEE was highly different between controls and CA patients independent of outcome. The generally lowered MEE in all CA subjects suggests that poor energetic efficiency is an early pathophysiologic response to amyloid infiltration. MEE incorporates FSV/LVM but the measure also includes MVO$_2$. MVO$_2$ was not significantly different in deceased and surviving CA patients, suggesting that this parameter does not improve the prognostic value of MEE in CA generally. MVO_2 was in fact reduced in CA compared with healthy controls leading to elevation of MEE. Reduced MVO_2 indicates an altered oxygen metabolism in CA, which can be caused by factors such as amyloid affecting blood vessels, different levels of myocardial oxidative stress and mitochondrial function,[22] and the direct energy-sparing effect of drugs such as beta-blockers.[23]

MEE in CA is also confounded by the degree of amyloid burden because both myocytes and ECV were integrated in LVM calculation, and MVO_2 measured by ^{11}C-acetate PET is probably a reflection of oxidative metabolism in viable myocytes only. In CA survivors, septal thickness, LVM index, and MVO_2 were comparable with hypertrophic controls, while MEE was dramatically lowered in CA. In contrast, MEE in hypertrophic and healthy controls was similar. This could reflect the fact that ECV is higher in CA patients than in hypertrophic controls, because the latter is characterized by hypertrophy of myocytes and not expansion of the extracellular space. There is currently no method by which ECV can be determined by ^{11}C-acetate PET. Further studies of myocardial oxidative metabolism in CA might be relevant for research regarding novel therapeutics but would potentially require combined PET/magnetic resonance studies to correct the PET signal for differences in ECV.

PET-FSV has been validated against both gold standards right heart catheterization (RHC) and CMR[19,24] and was, as previously shown and repeated here, highly reproducible across tracers. Similarly, ^{11}C-acetate PET LVM estimates have high accuracies compared with CMR.[20,25] Different measurement techniques are required for different tracers but produce comparable LVM estimates in both normal and hypertrophied hearts. In theory, FSV/LVM or MCF measurements are available with any cardiac perfusion tracer and might be useful for early detection of concentrically hypertrophied hearts with altered haemodynamics, including CA, and in patients evaluated for heart-related symptoms. MEE correlates well to FSV/LVM, but the addition of oxygen consumption does not seem to add prognostic value to FSV/LVM in CA.

Given the increasing availability of targeted therapies and the known diagnostic delays in CA, detection of an FSV/LVM below the normal range in a subject with early symptoms or signs of heart failure with preserved LVEF should potentially raise a diagnostic red flag and further CA-specific work-up should be considered. FSV/LVM can also be measured with more generally available imaging methods than ^{11}C-acetate PET, and if reported from echocardiography or CMR, it can give an indication of possible CA. However, low FSV/LVM is not specific for CA and more targeted diagnostic methods such as PET with amyloid-binding tracers or scintigraphy with bone-seeking agents are then required. FSV/LVM is a strong survival predictor and might be used for patient stratification in clinical trials either to focus on early CA treatment in patients with relatively preserved contractile function or to aim at reducing mortality in CA subjects with severely affected contractile function. There is also a need for methods to monitor the CA disease and treatment response. FSV/LVM could be a parameter of interest in evaluation of cardiac response to amyloid-specific treatment.

As AL and ATTR are separate diseases where different underlying pathogeneses are involved, it is reasonable to evaluate the two groups separately. However, when divided into subgroups of CA, the patient numbers in this study were small. We did see some differences in the prognostic value of the ^{11}C-acetate PET parameters between AL and ATTR. In univariate analysis, FSVI and FSV/LVM, but not LVM itself, had significant impact on survival in AL, suggesting that FSV is a more important prognostic factor than LVM in AL. In ATTR, FSV/LVM was significantly lower in the deceased patients compared with the survivors. However, in univariate Cox regression analysis where the aspect of survival time is included, FSV/LVM only reached borderline significance ($P = 0.07$) for predicting survival in ATTR. These findings could indicate differences in prognostic parameters between AL and ATTR, but larger patient numbers would be needed to elucidate potential differences between subtypes of CA.

Limitations of the study include the relatively small number of subjects, which reduced the number of parameters that was possible to include in multivariate analysis. Especially when separated in amyloid subtypes, the study groups were small. The study population also included patients at different disease stages, and both patients who were untreated and those undergoing treatment for amyloidosis, factors that could influence outcome.

We conclude that MEE is prognostic for survival in CA, but the strongest and only independently prognostic parameter derived by ^{11}C-acetate PET was FSV/LVM. The finding is in line with previous research that has identified the ratio of SV and LV volume (MCF) as an important prognostic factor in CA.

Further studies are indicated to explore the underlying mechanisms of altered oxidative metabolism in CA, and the inclusion of ECV measurement using PET–magnetic resonance imaging could be beneficial in this aspect. Larger and more uniform patient cohorts would be needed to investigate potential differences in oxidative metabolism and the prognostic value in the different subgroups of CA.

Conflict of interest

T.S.C. declares honoraria for lectures from AstraZeneca and Pfizer. L.T. is stockholder of MedTrace Pharma A/S. H.J.H. is stockholder of MedTrace Pharma A/S. G.W. declares honoraria for lectures from AstraZeneca, Pfizer, and Johnson & Johnson. J.S. is board member and stockholder of MedTrace Pharma A/S.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Correlations between 11C-acetate and 15O-water PET measuring FSV (A), LVM (B) and FSV/LVM (C). R: Spearman rho.

Table S1. Univariate survival analysis in AL patients.

Table S2. Univariate survival analysis in ATTR patients.

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