Myocardial Oxygen Consumption and Efficiency in Patients With Cardiac Amyloidosis

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Background—This study evaluated myocardial oxygen consumption (MVO$_2$) and myocardial external efficiency (MEE) in patients with cardiac amyloidosis (CA). Furthermore, we compared MEE and MVO$_2$ in subjects with light chain amyloidosis versus transthyretin (ATTR) amyloidosis.

Methods and Results—The study population comprised 40 subjects: 25 patients with confirmed CA and 15 control subjects. All subjects underwent an $^{11}$C-acetate positron emission tomography. Furthermore, the CA patients underwent comprehensive echocardiography and right heart catheterization during a symptom-limited, semi-supine exercise test. MEE was calculated from $^{11}$C-acetate positron emission tomography as the ratio of left ventricular (LV) stroke work and the energy equivalent of MVO$_2$. Myocardial work efficiency was calculated as echocardiography-derived work pressure product divided by three-dimensional LV mass. CA patients had significantly lower LV-ejection fraction (54±13% versus 63±4%, P<0.05) and LV-global longitudinal strain (LVGLS) (12.4±2% versus 19±2%, P<0.0001) and a more restrictive filling pattern (E/e'-ratio 18 [12–25] versus 8 [7–9], P<0.0001) than controls. MEE was severely reduced (13±5% versus 22±5%, P<0.0001) whereas total MVO$_2$ was higher (18±6 mL/min versus 13±3 mL/min, P<0.01) in CA patients than controls. MEE decreased with increasing New York Heart Association symptom burden (P<0.0001). We found a good relationship between MEE and peak exercise systolic performance (LVGLS: $R^2$=0.60, P<0.0001; myocardial work efficiency: $R^2=0.48$, P<0.0001; cardiac index: $R^2=0.52$, P<0.0001) and between MEE and myocardial blood flow ($R^2=0.44$, P<0.0001).

Conclusion—Myocardial oxidative metabolism is disturbed in CA patients with increased total MVO$_2$ and reduced MEE. MEE correlated significantly with echocardiographic derived systolic parameters such as myocardial work efficiency and LVGLS that might be used as surrogate MEE markers. (J Am Heart Assoc. 2018;7:e009974. DOI: 10.1161/JAHA.118.009974.)

Key Words: amyloid • efficiency measures • exercise physiology • myocardial metabolism • myocardial oxygen consumption • positron emission tomography • speckle tracking echocardiography • stress echocardiography

Cardiac amyloidosis (CA) is characterized by concentric biventricular wall thickness because of extracellular deposition of misfolded proteins. The resulting myocardial stiffness eventually leads to heart failure and death. However, it has been proposed that the heart failure pathogenesis is multifactorial involving both myocardial structural and vascular damage but also proteotoxicity from light chains, which leads to cellular and mitochondrial dysfunction. The inefficient energy exploitation and mitochondrial dysfunction may play an important role in heart failure development. A normal myocyte contractile state is highly dependent on the myocardial energy resources and consumption. Myocardial oxygen consumption (MVO$_2$), as well as myocardial blood flow (MBF), can be measured non-invasively by $^{11}$C-acetate positron emission tomography (PET). Subsequently, the mechanoenergetic coupling can be calculated as myocardial external efficiency (MEE), which reflects the ratio of LV external stroke work (EW) and the energy equivalent of MVO$_2$. MEE may provide as today unknown important information about myocardial function in CA patients and may benefit in the non-invasive diagnosis and risk stratification of patients with CA.

In the present study, we hypothesized that MVO$_2$ and MEE were key determinants of myocardial contractile and exercise...
capacity in patients with CA. We investigated MEE, MBF, and MVO$_2$ differences in light-chain amyloidosis (AL) and transthyretin amyloidosis patients and compared our findings with subjects without CA.

**Methods**

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure as our local scientific ethical committee have not provided data sharing approval.

**Study Population**

We enrolled 35 subjects in the study at the Department of Cardiology, Aarhus University Hospital, Denmark from September 2015 to November 2016. Twenty-five subjects had confirmed CA and 10 subjects served as controls. The CA positive group comprised wild-type transthyretin (ATTRwt) patients (n=10), familial transthyretin amyloidosis mutation carriers (ATTRm) of the Danish ATTRm mutation (Leu111Met) and with cardiac involvement (n=5), and AL patients with cardiac involvement (n=10). CA was confirmed by endomyocardial biopsy using Congo red dye and immunohistochemistry in all but 1 patient. The last patient (ATTRm) was considered to have CA because of a positive $^{11}$C-Pittsburgh compound B (PIB) positron emission tomography (PET)$^{13-15}$ even though the patient was not subjected to endomyocardial biopsy. The control group consisted of 10 healthy controls. These healthy controls received no medication, had no cardiopulmonary symptoms, and had normal ECGs. The patients were included from our outpatient clinic. We excluded patients with significant valve disease. Four of the ATTRm patients with cardiac involvement were liver transplanted to postpone the cardiac amyloid progression.

The CA patients underwent both $^{11}$C-acetate PET and exercise stress test with simultaneous right heart catheterization, echocardiography, and oxygen consumption evaluation. The healthy controls underwent $^{11}$C-acetate PET and resting echocardiography.

All participants were aged ≥18 years and were included after having provided written informed consent according to the principles of the Helsinki Declaration. The local scientific ethical committee of the Central Denmark Region approved the study. Echocardiographic and hemodynamic data from these patients has previously been published.$^{16,17}$ The $^{11}$C-acetate PET was performed within 3 weeks of exercise stress test.

**$^{11}$C-Acetate Positron Emission Tomography**

An $^{11}$C-acetate PET scan was performed in all subjects in the resting state on a Siemens Biograph TruePoint TrueV 64 PET/CT scanner. We placed a catheter in an antecubital vein. The subjects rested for a minimum of 30 minutes. Subsequently, $^{11}$C-acetate (5 MBq/kg) was injected followed by a 27-minute list mode PET recording. The heart rate and arterial blood pressure was measured by sphygmomanometer at 5, 10, and 20 minutes after injection.

Reconstruction of dynamic images was performed as described in a previous paper from our group.$^{18}$ The aQuant software package was used for dynamic data sets analysis using automatically obtained image-derived and metabolites-corrected arterial input functions.$^{19}$ The average LV time-activity curve was obtained and fitted into a 1-tissue compartment model yielding the global myocardial clearance rate ($k_2$)$^{20,21}$ MBF was estimated using the global uptake rate ($K_v$), which was corrected for the incomplete extraction of $^{11}$C-acetate, which was calculated from $k_2$ as MVO$_2$=(135×$k_2$−0.96)/100.$^{20}$ CO was calculated using the indicator-dilution principle and the arterial input functions. In addition, LV mass was obtained from the dynamic data set using parametric images and contour detection, as described in detail elsewhere.$^{21}$

**Echocardiography**

We used a commercially available ultrasound system (Vivid E95; GE Healthcare, Horten, Norway) with a 3.5-MHz-phased array transducer (M5S).
At rest, CA patients and controls underwent a comprehensive echocardiographic assessment according to current guidelines.23

Only CA patients were subjected to exercise testing. At each stage of exercise, we assessed two-dimensional cine loops and tissue Doppler images from all 3 apical views of the LV along with pulsed wave Doppler of the mitral inflow and the left ventricular outflow tract (LVOT). Left ventricular ejection fraction (LVEF) was calculated by Simpson’s biplane method of disks. Peak systolic mitral annular velocities (S') were estimated from the tissue Doppler velocity images as an average of septal, lateral, anterior, and posterior velocities. The magnitude of LVGLS24 was obtained from frame-by-frame tracking of speckle patterns throughout the left-sided myocardium in standard two-dimensional cine loops with a frame rate >55 frames/s. LVGLS was calculated at the time in systole when the value peaked, using a 17-myocardial segment model.25 In this manuscript, strain and changes in strain are reported in absolute terms.

We obtained three-dimensional LV mass by sampling 6 heartbeats during breath-hold, aiming at a frame rate >25 frames/s using a 4V-D transducer. We measured both diastolic and systolic LV mass. An average of the 2 was used to calculate three-dimensional LV mass. Three-dimensional LV mass has been validated in several studies, which show that LV mass measured by three-dimensional echocardiography is similar to that measured by magnetic resonance imaging.26–29

Data were analyzed offline using dedicated software (EchoPAC PC SW-Only, 201, GE-Healthcare, Milwaukee, WI, USA and TomTec 4D RV-function, Munich, Germany).

**Exercise Protocol**

All patients with CA performed a multistage symptom-limited, semi-supine bicycle exercise test using the Echo Cardiac Stress Table (Lode B.V., Netherlands). Workload started at 0 W and was increased by 25 W every 3 minutes in New York Heart Association (NYHA) class ≤II patients and by 10 W in NYHA class ≥III patients. Patients were explicitly encouraged to maintain a fixed pedaling speed of 60 rounds per minute and to exercise until exhaustion (Borg >18).30 During exercise, external oxygen consumption (VO2) was measured by breath-by-breath analysis of expired gas. The ratio between cardiac output (CO) increase by thermodilution (peak CO—rest CO) and VO2 increase (peak VO2—rest VO2) was used as cardiac response marker to metabolic needs.31

**Right Heart Catheterization**

Right heart catheterization was performed in CA patients with a standard 7.5-F triple-lumen Swan-Ganz thermistor using a balloon-tipped catheter (Edwards Lifesciences, Irvine, CA). The catheter was introduced into the right jugular vein using an ultrasound-guided technique and advanced pressure waveforms and fluoroscopy guided into the pulmonary artery. A comprehensive, direct, and indirect assessment of hemodynamic parameters was performed at rest and during exercise as described in a previous publication.17

**Myocardial Work and Efficiency**

Average heart rate and mean arterial blood pressure measurements obtained during PET examination were used to calculate MEE.9

\[
MEE = \frac{EW \times 1.33 \times 10^{-4}}{\text{LV mass} \times \text{MVO2} \times 20} \times 100
\]

EW (mm Hg/mL per minute) was calculated as the product of PET derived stroke volume, heart rate, and mean arterial blood pressure. In this equation, the numerator represents EW (in joules) and the denominator represents the energetic value of the total O2 amount consumed by the left ventricle. The constants 1.33×10⁻³ and 20 were used for conversion of cardiac minute work and MVO₂ to joules.

In a similar manner, the average heart rate and mean arterial blood pressure measurements obtained during resting and exercise echocardiography was used to calculate echocardiographic MWE as:

\[
\text{MWE} = \frac{EW}{3D \text{ LV mass}}
\]

EW by echocardiography was calculated as the product of LVOT area, velocity time integral, heart rate, and mean arterial blood pressure.

**Statistical Analysis**

Normally distributed data are presented as mean±SD; non-normally distributed data are presented as median and interquartile range. Categorical data are presented as numbers with percentages. Histograms and Q-Q plots were used to check continuous values for normality. Between-group differences were assessed using the t test for normally distributed data, the Mann-Whitney U test for non-normally distributed data, and the Chi-squared test for dichotomized data. A linear regression model was used to compare continuous variables. We calculated Pearson’s coefficient of correlation in normally distributed data and Spearman’s coefficient of correlation in non-normally distributed data. All tests were 2-sided, and a P<0.05 was considered statistically significant. Analyses were performed using STATA (STATA/IC 13, StataCorp LP, College Station, TX).
Results

Patient Characteristics

Table 1 presents the demographics of patients and control subjects. We found no significant difference between age and sex comparing CA patients and controls. As depicted, the majority of CA patients were symptomatic with high use of diuretics. However, only few CA patients received angiotensin-converting-enzyme/ATII (ACE/ATII) inhibitors, beta-blockers, and aldosterone inhibitors. NT-ProBNP (N-terminal pro-B-type natriuretic peptide) was significantly higher in CA patients than controls.

Transthoracic Echocardiography

The CA patients had significantly reduced LV systolic function compared with controls at rest (LV-EF 54±13% versus 63±4%, P<0.05; LV-S’ 4.4±1.8 cm/s versus 6.4±1.2 cm/s, P<0.001; LV-GLS 12±4% versus 19±2%, P<0.0001). The regional strain analysis reveal apical sparring pattern in the CA patients with a mean difference between apical segments and basal segments of 9.7±4.2%. The basal segments showed no deformation increase during exercise whereas strain in the apical segments was more pronounced at peak exercise. The mean increase in apical to basal strain difference with exercise was 3.2±5.2%. We found a significant relationship between the exercise induced apical to basal strain difference and symptom burden by New York Heart Association (NYHA) functional class (r²=0.23, P<0.05) and peak exercise metabolic equivalent of tasks (r²=0.19, P<0.05) and peak exercise VO₂ (r²=0.28, P<0.05).

The CA patients had a more restrictive LV filling pattern than controls (E/A ratio: 1.7 [1.2–3.2] versus 1.1 [1.0–1.6], P<0.05; E-deceleration time 168±52 ms versus 210±49 ms, P<0.05; E/e’ 18 [12–25] versus 8 [7–9], P<0.0001).

Echocardiographic parameters in CA patients at rest and at peak exercise are depicted in Table 2.

Invasive Hemodynamics

Invasive hemodynamic parameters at rest and at peak exercise are shown in Table 2. During resting conditions, mean LV and right ventricular filling pressure were only slightly elevated and cardiac index (CI) was within normal range in the majority of patients. However, during exercise, a profound increase in LV and right ventricular filling pressure were noted with only a small increase in CI despite adequate increase in heart rate.

MVO₂ and External Efficiency

Table 3 shows the results from ¹¹C-acetate PET in CA patients and controls whereas Table 4 shows the relationship between MEE and myocardial function in CA patients. Total MVO₂ (mL/min) was significantly higher in CA patients than controls. Furthermore, patients with CA had significantly lower EW than controls. Subsequently, MEE was severely reduced in CA patients compared with controls. MEE decreased with advanced symptom burden by NYHA functional class (Figure 1). We found a good relationship between MEE and LVGLS and between MEE and echocardiographic derived MWE (Figures 2 and 3). Likewise, we found a good relationship between MEE and invasively derived pulmonary arterial compliance and CI (Figures 2 and 4). These relationships were seen both at rest and during exercise. In contrast, MEE poorly correlated with invasive filling pressures and non-invasive LV filling pattern by echocardiography both at resting and during exercise (Figure 4 and Table 4). We found no difference in MEE between AL and ATTR CA patients (14.3±6.4% versus 12.4±6.6%, P=0.41). Likewise, we found no difference in total MVO₂ between AL and ATTR CA patients (17±6 versus 19±6, P=0.44).

Data are presented as absolute number and present or mean±SD or median and interquartile range. ACE indicates acetylcholinesterase; BMI, body mass index; BSA, body surface area; NT-ProBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
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Table 2. Myocardial Function by Right Heart Catheterization and by Echocardiography in Cardiac Amyloidosis Patients

| Hemodynamics                        | Resting Conditions | Peak Exercise | P Value |
|-------------------------------------|--------------------|---------------|---------|
| MAP, mm Hg                          | 90±10              | 104±27        | <0.05   |
| HR, beats/min                       | 76±17              | 123±27        | <0.0001 |
| CI, L/min per m²                    | 2.3±0.6            | 4.4±2.1       | <0.0001 |
| VO₂, mL/min per kg                  | 301±89             | 1156±496      | <0.0001 |
| mRAP, mm Hg                         | 6.8±4.4            | 16±9          | <0.0001 |
| mPAP, mm Hg                         | 25±9               | 46±11         | <0.0001 |
| mPCWP, mm Hg                        | 15±7               | 31±8          | <0.0001 |
| PAC, mL/mm Hg                       | 3.6±2.3            | 2.6±1.7       | <0.01   |

Echocardiography

| IVS, mm                             | 15.8±5.0           |               |         |
| PWT, mm                             | 13.8±3.6           |               |         |
| 3D LV mass, g/m²                    | 129±33             |               |         |
| 2D LVEF Simpson Biplane, %          | 54±13              | 57±14         | 0.10    |
| LVGLS, %                            | 12±4               | 13±6          | 0.12    |
| Strain apical segments, %           | 17±5               | 21±8          | <0.01   |
| Strain basal segments, %            | 7.5±5.3            | 7.7±6.4       | 0.74    |
| A-B strain diff, %                  | 9.7±4.2            | 12.9±4.7      | <0.01   |
| MWE, mm Hg/L/min per g              | 1.9±1.0            | 4.4±3.6       | <0.001  |
| E/A (ratio)                         | 2.2±1.4            | 2.4±1.2       | 0.97    |
| E/e’ (ratio)                        | 22±13              | 22±14         | 0.76    |
| LA volume, mL/m²                    | 42±19              |               |         |
| RA volume, mL/m²                    | 34±22              |               |         |
| TAPSE, cm                           | 1.8±0.7            |               |         |
| RVs, cm/s                           | 8.9±2.4            |               |         |

2D indicates two-dimensional; 3D, three-dimensional; A-B, apical to basal; CI, cardiac index; HR, heart rate; IVS, interventricular septal thickness; LA, left atrium; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; MAP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; MWE, myocardial work efficiency; PAC, pulmonary arterial compliance; PWT, posterior wall thickness; RA, right atrium; RVs, peak systolic velocity of tricuspid annulus; TAPSE, tricuspid annular plane systolic excursion; VO₂, external oxygen consumption.

Myocardial Blood Flow

MBF tended to be lower in CA patients than controls (Table 3). We found a significant relationship between MBF and systolic performance (LVGLS: $r^2=0.45$, $P<0.0001$ CI: $r^2=0.31$, $P<0.001$) and between MBF and LV mass ($r^2=0.25$, $P=0.05$). In contrast, MBF did not correlate with LV or right ventricular filling pressure (PCWP: $r^2=0.03$, $P=0.44$; right atrial pressure: $r^2=0.04$, $P=0.37$).

In CA patients MVO₂ (per gram tissue) correlated significantly with MBF ($r^2=0.42$, $P<0.0001$), whereas the total MVO₂ did not correlate with MBF ($r^2=0.01$, $P=0.61$). Furthermore, a strong relationship was seen between MEE and MBF in the CA patients ($r^2=0.44$, $P<0.0001$).

Discussion

This is the first study to evaluate myocardial oxidative metabolism, myocardial perfusion, and the coupling to invasive and non-invasive myocardial contractile work parameters in CA patients. The 4 main findings were (1) that CA patients display substantially increased total MVO₂ and reduced MEE independent of etiology; (2) MEE correlates significantly with MBF; (3) the observed reduction in MEE is associated with decreasing systolic myocardial performance and with increasing symptom burden; and (4) MEE did not correlate with invasive or non-invasive parameters of LV filling pressure.

Myocardial function is highly dependent on myocardial oxidative metabolism and the coupling to contractile work. In CA, the oxidative metabolism may be affected by both structural damage (both AL and transthyretin-related [TTR]) and proteotoxicity (AL). In the latter, circulating cardiotropic light chains are suggested to produce cellular damage through various pathways ie, increase in cellular reactive oxygen species and up-regulation of heme oxygenase both leading to impaired contractility and relaxation. MEE integrates contractile function, loading conditions and metabolic processes, ventricular interdependence and diastolic function, the coupling to contractile work, and oxidative metabolism.

Table 3. ¹¹C-Acetate Positron Emission Tomography

|                     | Controls (n=10) | All CA Patients (n=25) | P Value    |
|---------------------|---------------|-----------------------|-----------|
| MEE, %              | 24±5          | 13±5                  | <0.0001   |
| EW, mm Hg× mL/min×10³ | 446±103      | 346±142               | 0.05      |
| Total MVO₂, mL/min  | 13±3          | 18±6                  | <0.01     |
| MVO₂, mL/min per g  | 0.10±0.02     | 0.09±0.02             | 0.22      |
| MBF, mL/min per g   | 0.67±0.11     | 0.59±0.18             | 0.11      |
| Total work, J       | 59±14         | 46±19                 | 0.05      |
| HR, beats/min       | 62±8          | 73±12                 | <0.01     |
| MAP, mm Hg          | 94±7          | 78±11                 | <0.001    |
| LV mass index, g/m² | 63±12         | 103±29                | <0.001    |
| CI, L/min per m²    | 2.4±0.6       | 2.2±0.6               | 0.46      |
| S VI, mL/m²         | 39±7          | 31±9                  | <0.05     |

Data are presented as mean±SD or median and interquartile range. CI indicates cardiac index; EW, external stroke work; HR, heart rate; LV, left ventricular; MAP, mean arterial blood pressure; MBF, myocardial blood flow; MEE, myocardial external efficiency; MVO₂, myocardial oxygen consumption; S VI, stroke volume index.
Table 4. Univariate and LV Mass Adjusted Correlations Between PET-Derived Myocardial External Efficiency and Myocardial Function in CA Patients

|                         | Unadjusted | LV Mass Adjusted |
|-------------------------|------------|------------------|
|                         | R²         | P Value          | R²         | P Value          |
| **Echocardiography**    |            |                  |            |                  |
| E/er                   | 0.14       | 0.07             | ...        | ...              |
| MWE<sub>rest</sub>     | 0.51       | <0.0001          | 0.57       | <0.0001          |
| MWE<sub>peak</sub>     | 0.48       | <0.0001          | 0.50       | <0.01            |
| LVGLS<sub>rest</sub>   | 0.61       | <0.0001          | 0.61       | <0.0001          |
| LVGLS<sub>peak</sub>   | 0.60       | <0.0001          | 0.60       | <0.0001          |
| ΔA-B strain difference | 0.27       | <0.01            | 0.40       | <0.05            |
| 3D LV mass             | 0.39       | <0.01            | ...        | ...              |
| **Invasive hemodynamics** |          |                  |            |                  |
| ΔCO<sub>1</sub>/ΔVO<sub>2</sub> | 0.21     | <0.05            | 0.35       | <0.05            |
| Cr<sub>rest</sub>      | 0.36       | <0.01            | 0.46       | <0.01            |
| Cr<sub>peak</sub>      | 0.52       | <0.0001          | 0.55       | <0.01            |
| SV<sub>rest</sub>      | 0.37       | <0.01            | 0.53       | <0.01            |
| SV<sub>peak</sub>      | 0.44       | <0.01            | 0.63       | <0.0001          |
| VO<sub>2peak</sub>     | 0.31       | <0.01            | 0.42       | <0.01            |
| PCWP<sub>rest</sub>    | 0.11       | 0.13             | ...        | ...              |
| PCWP<sub>peak</sub>    | 0.04       | 0.40             | ...        | ...              |
| PAC<sub>rest</sub>     | 0.43       | <0.01            | 0.46       | <0.01            |
| PAC<sub>peak</sub>     | 0.43       | <0.01            | 0.45       | <0.01            |
| RAP<sub>rest</sub>     | 0.11       | 0.14             | ...        | ...              |
| RAP<sub>peak</sub>     | 0.13       | 0.11             | ...        | ...              |
| **PET-derived parameters** |        |                  |            |                  |
| MBF                    | 0.44       | <0.0001          | 0.46       | <0.01            |
| Total work             | 0.44       | <0.0001          | 0.76       | <0.0001          |
| Total MVO<sub>2</sub>  | 0.14       | 0.07             | ...        | ...              |

3D indicates three-dimensional; A-B, apical to basal; CA, cardiac amyloidosis; CI, cardiac index; CO, cardiac output; LV, left ventricular; LVGLS, left ventricular global longitudinal strain; MBF, myocardial blood flow; MVO<sub>2</sub>, myocardial oxygen consumption; MWE, myocardial work efficiency; PAC, pulmonary arterial compliance; PCWP, pulmonary capillary wedge pressure; PET, positron emission tomography; RAP, right atrial pressure; SV, stroke volume; VO<sub>2</sub>, external oxygen consumption.

requirements and is potentially a robust marker of cardiac function irrespective of underlying pathology. To our knowledge, the current study is the first to investigate MEE in CA patients.

The myocardial thickness in CA is mediated both by interstitial amyloid deposits and by myocardial hypertrophy. Thus, the oxidative metabolism per gram heart tissue does not reflect the overall metabolic state of the myocytes. In contrast, the increase in total myocardial oxygen consumption during resting conditions clearly indicates that the myocyte mitochondrial oxidative phosphorylation rate is abnormal in the CA population. Interestingly, it was demonstrated that total MVO<sub>2</sub> and MEE was abnormal even in CA patients in NYHA class I. This indicates that myocardial oxidative metabolism may deteriorate before the development of symptoms. Thus, the inefficient myocardial energy exploitation and mitochondrial uncoupling may play a central role in the transition to symptomatic heart failure in CA patients as also suggested in heart failure patients with different etiologies than CA.

Traditionally, the amyloid-induced restrictive cardiomyopathy is characterized by abnormal LV filling with reduced cardiac output despite preserved LVEF. However, our recent studies suggests, that exercise capacity and symptoms in CA patients are strongly associated with the myocardial perfusion reserve and systolic myocardial capacity in terms of peak exercise CI and LVGLS. The latter has emerged as a novel non-invasive parameter to determine the functional CA burden and possesses great prognostic value in these patients. In the present study, we demonstrate a good relationship between LVGLS and MBF, between LVGLS and MEE, and between MEE and MBF. It is noteworthy that both resting LVGLS, peak exercise LVGLS and the exercise induced apical to basal strain difference correlated with MEE. Apical sparing of longitudinal strain is a well-known finding in CA patients but the underlying pathophysiology is not fully elucidated. Our results suggest that the apical myocardial contractile reserve is of significant importance to preserve overall MEE. Perfusion abnormalities may result in an energy-starved myocardium. Because of the endocardial location of the longitudinally orientated fibers, these are the myocardial fibers most vulnerable to reduced perfusion. This may explain the good correlation between LVGLS and MBF. Similar findings have been demonstrated in a small study by Dorbala.
et al, who evaluated the myocardial perfusion by using \textsuperscript{13}N-ammonia PET. Dorbala et al found a profound coronary microcirculatory dysfunction in CA patients compared with left ventricular hypertrophy subjects with non-amyloid etiology. The abnormal myocardial perfusion was also demonstrated to be significantly associated with longitudinal myocardial deformation by two-dimensional echocardiography. We speculate that regional myocardial perfusion abnormalities may be associated with regional myocardial deformation differences and subsequently the development of relative apical sparing of longitudinal strain. However, in addition to the perfusion abnormalities, the amyloid deposits might lead to inefficient energy exploitation and mitochondrial uncoupling subsequently resulting in decreased myocardial contractility. Therefore, the increased oxygen consumption noted in CA patients may be a compensatory mechanism to maintain adequate cardiac output despite perfusion abnormalities and inefficient energy exploitation. Cardiac output will usually decrease when either preload or myocardial contractility is reduced or when the afterload increases. Yet, both left and right side resting filling pressures in CA patients were slightly higher than normal range. Furthermore, the CA patients had lower blood pressure than controls. Therefore, the reduced cardiac output demonstrated in CA patients seems most likely to be induced by an inherently reduced contractility. Potentially, the reduced MEE may be an important component in the poor myocardial contractility seen in CA patients.

Previous studies have demonstrated that the prognosis in AL patients is poorer as compared with ATTR CA patients, even though the myocardial thickness is more pronounced in ATTR patients indicating a higher degree of amyloid deposition. Therefore, it has been speculated that AL fibers may induce a greater proteotoxicity than ATTR fibers. In the present study, we found no statistically or clinically significant differences in MEE and total MVO\textsubscript{2} between AL and ATTR CA patients. Therefore, the present study does not support the hypothesis that poor prognosis in AL patients is induced by abnormal mitochondrial function. However, the differences in myocardial performance and oxidative metabolism between

Figure 2. Box plots showing myocardial external efficiency (MEE) and myocardial oxygen consumption (MVO\textsubscript{2}) in controls and CA patients stratified into tertiles of resting left ventricular ejection fraction (LVEF), left ventricular global longitudinal strain (LVGLS), myocardial work efficiency (MWE), cardiac index (CI), pulmonary capillary wedge pressure (PCWP), and pulmonary arterial compliance (PAC).
ATTR and AL subjects should be investigated in a larger study.

In the present study, we assessed MEE solely by $^{11}$C-acetate PET. This approach has been validated against the combination of $^{11}$C-acetate PET and cardiac magnetic resonance (MR), which until today has been considered the gold-standard method for non-invasive quantification of MEE. A strong association has been demonstrated between LV mass and stroke volume by $^{11}$C-acetate PET and cardiac MR. The simultaneous acquisition of both EW and total MVO$_2$ makes MEE less affected by changes in loading conditions. MVO$_2$ per gram myocardial tissue is a rather stable parameter in patients with myocardial hypertrophy attributable to aortic valve stenosis. With the assumption that MVO$_2$ per gram myocardial tissue is a stable parameter in CA patients, myocardial efficiency can be calculated by MWE, which reflects the myocardial ability to conduct work. The present study demonstrated, that MVO$_2$ per gram myocardial tissue was indeed similar between healthy controls and CA patients. Therefore, MWE assessment may prove beneficial as a simple and more accessible alternative to MEE assessment by PET; moreover, it can be performed bedside, rapidly, and without radiation.

Routine surveillance of CA patients is of great importance to optimize loading conditions and detect deterioration of myocardial function. Even though $^{11}$C-acetate PET may harbor...
great value in the assessment of MEE and MBF, the technique is currently only available in a few highly specialized centers. In contrast, the good relationship between echocardiographic LVGLS and PET determined MEE and MBF emphasizes the importance of routine LVGLS assessment in CA patients.

**Conclusion**

The total oxidative myocardial metabolism is significantly increased without any correlation to myocardial perfusion or external efficiency in CA patients. Myocardial external efficiency is significantly reduced in CA patients and correlated significantly with echocardiographic-derived systolic parameters such as MWE and LVGLS that might be used as surrogate MEE markers.

**Limitations**

This study is a single-centered experience with a relatively limited number of patients. Therefore, we were unable to simultaneously control for several variables in the study and to define the causal relationship of the described associations. ATTRwt were older and more likely to be men than AL patients and controls. Age and sex may influence both myocardial perfusion, myocardial oxidative metabolism, and
LV deformation capacity. In our MEE and MWE calculations, we assumed that all LV mass is myocardial mass. Yet, LV mass in CA patients consists of both myocardial and non-myocardial tissue (ie amyloid deposits). MVO₂ is based on washout rate and consequently represents MVO₂ in oxygen-consuming tissue only. Therefore, MVO₂ could be myocardial-only-MVO₂ while LV mass is both myocardial and amyloid mass. This could be an explanation for the similar MVO₂/g but difference in total MVO₂. The calculated MEE and MWE therefore does not reflect the efficiency of the isolated myocytes but rather the efficiency of the total myocardium.

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Disclosures

None.

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