

# Bioimpedance Analysis Parameters and Epicardial Adipose Tissue Assessed by Cardiac Magnetic Resonance Imaging in Patients With Heart Failure

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There is increasing evidence that body composition should be considered as a systemic marker of disease severity in congestive heart failure (CHF). Prior studies established bioelectrical impedance analysis (BIA) as an objective indicator of body composition. Epicardial adipose tissue (EAT) quantified by cardiac magnetic resonance (CMR) is the visceral fat around the heart secreting various bioactive molecules. Our purpose was to investigate the association between BIA parameters and EAT assessed by CMR in patients with CHF. BIA and CMR analysis were performed in 41 patients with CHF and in 16 healthy controls. Patients with CHF showed a decreased indexed EAT ( $22 \pm 5$  vs.  $34 \pm 4$  g/m<sup>2</sup>,  $P < 0.001$ ) and phase angle (PA) ( $5.5^\circ$  vs.  $6.4^\circ$ ,  $P < 0.02$ ) compared to healthy controls. Linear regression analysis showed a significant correlation of CMR indexed EAT with left ventricular ejection fraction (LV-EF) ( $r = 0.56$ ,  $P < 0.001$ ), PA ( $r = 0.31$ ,  $P = 0.01$ ), total body muscle mass (TBMM) ( $r = 0.41$ ,  $P = 0.001$ ), fat-free mass (FFM) ( $r = 0.30$ ,  $P = 0.02$ ), and intracellular water (ICW) ( $0.47$ ,  $P = 0.0003$ ). Multivariable analysis demonstrated that LV-EF was the only independent determinant of indexed EAT ( $P < 0.0001$ ). Receiver operating characteristic curve analysis indicated good predictive performance of PA and EAT (area under the curve (AUC) = 0.86 and 0.82, respectively) with respect to cardiac death. After a follow-up period of 5 years, 8/41 (19.5%) patients suffered from cardiac death. Only indexed EAT  $< 22$  g/m<sup>2</sup> revealed a statistically significant higher risk of cardiac death ( $P = 0.02$ ). EAT assessed by CMR correlated with the BIA-derived PA in patients with CHF. EAT and BIA-derived PA might serve as additional prognostic indicators for survival in these patients. However, further clinical studies are needed to elucidate the prognostic relevance of these new findings.

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## INTRODUCTION

Patients with congestive heart failure (CHF) develop important changes in body composition and the disease course is marked by periodic episodes of clinical decompensation (1). There is increasing evidence that body composition should be considered as a systemic marker of disease severity in CHF (2). An altered balance between catabolism and anabolism is known to contribute to disease progression and the transition from non-wasted heart failure to cardiac cachexia (3). Therefore, the early identification of changes in cellular membrane integrity and alterations in fluid balance is supposed to play a prognostic role in heart failure patients (4).

Bioelectrical impedance analysis (BIA) is a noninvasive and reproducible technique to evaluate changes in body composition (5). BIA measures body component resistance (R) and reactance (Xc) by recording a voltage drop in applied current. R is the restriction of flow due to the amount of water present in the tissues. Xc causes the current to lag behind the voltage, primarily related to the tissue interfaces and cell membranes creating a phase shift. This shift is quantified geometrically as the angular transformation of the ratio of Xc to R, or the phase angle (PA). By definition a lower PA suggests cell death or decreased cell integrity (6). PA has been found to be a prognostic marker for survival in several

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clinical conditions such as chronic obstructive pulmonary disease (7), haemodialysis (8), cancer (9,10), and liver cirrhosis (6). A recent study (11) showed a significantly lower PA in patients with New York Heart Association class III–IV heart failure. Beside the PA, the percentages of total body fat, total body muscle mass (TBMM), and total body water is used to describe the body composition. Timely identification of the body composition could help to improve patient outcome.

Human epicardial adipose tissue (EAT) is the true visceral fat depot around the heart and a metabolically active organ generating various bioactive molecules which might affect cardiac function. Cardiac magnetic resonance (CMR) imaging has proven to be useful for the detection of fatty tissue in and around the heart (12). Recently, our study group established a volumetric approach (13) that has proven to be a reproducible and feasible method for quantitative assessment of EAT.

It was the objective of this study to assess and then compare EAT and BIA-derived parameters of body composition among patients with severe CHF and healthy controls. Furthermore, we aimed to validate the impact of EAT, BIA-derived parameters, and left ventricular function on survival in patients with CHF.

## METHODS AND PROCEDURES

### Study population

In this prospective study, 50 consecutive patients with a confirmed diagnosis of heart failure, defined as the presence of cardiac dysfunction on echocardiography study (left ventricular function  $\leq 35\%$ ) and signs and symptoms of heart failure, referred for CMR examination between February 2003 and September 2003 were screened for study enrolment. Of 50 CHF patients, 9 patients were excluded due to claustrophobia ( $n = 2$ ), or implantation of a pacemaker or defibrillator ( $n = 7$ ), yielding a total of 41 patients finally included in this study (36 men and 5 women; mean age:  $63 \pm 12$  years). Within the study group 41 patients had CHF due to ischemic cardiomyopathy (ICM) ( $n = 22$ ) or dilated cardiomyopathy (DCM) ( $n = 19$ ). Sixteen age- and gender-matched healthy controls were included and served as reference group.

All patients and volunteers underwent CMR examination and BIA. In patients and volunteers identical protocols were used. Informed consent for the CMR protocol was obtained from all subjects and the study was approved by the local ethic committee. At 5 years, clinical information was obtained from patient telephone interviews, contact with the patients' physicians or hospital records.

### Image acquisition

All studies were performed using a 1.5-Tesla whole-body imaging system (Magnetom Sonata; Siemens Medical Systems, Erlangen, Germany). A dedicated four-element, phased-array cardiac coil was used. Images were acquired during repeated end-expiratory breath-holds. Scout images (coronal, sagittal, and axial planes) were obtained for planning of the final double-oblique long-axis and short-axis views. To evaluate functional parameters, electrocardiogram-gated cine images were then acquired using a segmented steady-state free precession (true-fast imaging with steady-state precession) sequence (time to echo/time of repetition 1.6/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution  $1.4 \times 1.8$  mm, slice thickness 5 mm, interslice gap 5 mm). Seven to twelve short-axis views covering the whole left and right ventricle were obtained.

For the assessment of the EAT, we used a dark blood prepared T1-weighted multislice turbo spin-echo pulse sequence with a water

suppression prepulse to obtain a transversal four-chamber view and short-axis images in the same orientations used for the cine short-axis images. Imaging parameters were as follows: time of repetition = 800 ms, time to echo = 24 ms, slice thickness = 4 mm, interslice gap = 2 mm, and field of view = 30–34 cm.

### Image analysis and determination of ventricular parameters

Image analysis and quantitative analysis was performed offline using dedicated software (ARGUS; Siemens, Erlangen, Germany). Each study was examined for abnormalities in the morphology of the right and left ventricle. End-diastolic and end-systolic volumes and left ventricular mass was analyzed with the serial short-axis true-fast imaging with steady-state precession cine loops, using manual segmentation. Stroke volumes and ejection fractions were calculated. Additionally, left- and right-ventricular diameters were measured.

### Volumetric assessment of the absolute amount of EAT

The amount of EAT was calculated by using the modified Simpson's rule with integration over the image slices. The contours of EAT were outlined at end diastole in the short-axis views covering the entire left and right ventricle. For EAT mass determination, the area subtended by the manual tracings was determined in each slice and multiplied by the slice thickness to yield the fat volume. Total EAT volume was obtained after the data summation of all slices. To obtain EAT mass, the volume of EAT was multiplied by the specific weight of fat (0.94 g/ml). The observer was blinded to patient details.

### Bioelectrical impedance analyses (BIA)

BIA was performed under highly standardized conditions (14) using a bioelectrical impedance analyzer, BIA101 of AKERN SRL. BIA was conducted while patients were lying supine on an exam table, with legs apart and arms not touching the torso. All evaluations were conducted on the patients' right side using the four surface standard electrode (tetra polar) technique on the hand and foot (15). R and Xc were directly measured in Ohms at 50 kHz, 800  $\mu$ A using RJL BIA. One assessment of R and Xc was made. PA was calculated using the following equation:  $PA = (R/Xc) \times (180/\pi)$ . The R, Xc values and the subject's height, weight, sex, and age were entered into a computer program (BodyGram version 1.31; Akern Bioresearch, Pontassieve (FI), Italy) to estimate total body water, extracellular water, intracellular water (ICW), total body fat, fat-free mass (FFM), and TBMM.

### Statistical analysis

The data are presented as mean value  $\pm$  s.d. BMI was calculated by the common formula:  $BMI (kg/m^2) = \text{weight (kg)}/\text{height (m)}^2$ . Body surface area was assessed by a variation of the DuBois and DuBois formula:  $\text{body surface area (m}^2) = (\text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}) \times 0.007184$  (16). The Student *t*-test for paired collectives was used for parametric data. Shapiro–Wilk test was used to test data for normal distribution. The Mann–Whitney test was applied for nonparametric data. A *P* value  $\leq 0.05$  was considered significant for all comparisons. Linear regression analysis was performed on clinical, CMR and BIA parameters to identify correlates of EAT. Multivariable analysis was performed with logistic regression analysis using block entry of the following variables: PA, left ventricular ejection fraction (LV-EF), TBMM, ICW, FFM to evaluate whether these variables were independent predictors of indexed EAT, provided to have a *P* < 0.05 in univariate analysis. The area under the curve (AUC) was calculated to determine the accuracy of PA, indexed EAT, and LV-EF to identify patients at risk. Additionally, receiver operating characteristic curve analysis was used to determine the optional cut-off value to predict cardiac death. Kaplan–Meier method was used to calculate survival of death from cardiovascular cause. Event classification was performed by an investigator blinded to the BIA and CMR results. Analysis was performed using SPSS statistical software (version 14.0; SPSS, Chicago, IL).

## RESULTS

## Baseline characteristics

The baseline anthropometric, BIA, and clinical parameters of all subjects studied are shown in **Table 1**. There were no significant differences regarding age, BMI, and body surface area between patients with CHF and healthy controls. BMI in all study participants was within normal range. Comparing the baseline characteristics of patients with ICM and DCM, patients with ICM were older ( $68 \pm 8$  vs.  $57 \pm 13$  years,  $P = 0.02$ ) and had a significantly reduced body weight ( $77 \pm 12$  vs.  $89 \pm 19$  kg,  $P = 0.03$ ) as well as a lower BMI ( $26 \pm 4$  vs.  $29 \pm 5$  kg/m<sup>2</sup>,  $P = 0.02$ ) compared to patients with DCM. The distribution of New York Heart Association class (**Table 1**) was comparable in patients with ICM and DCM.

## Body composition

There were no significant differences in total body water among controls and patients with heart failure indicating that all patients were compensated (**Table 1**). The ICW ( $24 \pm 6$  l vs.  $26 \pm 6$  l,  $P = 0.30$ ) and the extracellular water ( $22 \pm 5$  l vs.  $20 \pm 3$  l,  $P = 0.13$ ) did not differ significantly among patients with heart failure and healthy controls. Total body fat was reduced in patients with heart failure ( $21 \pm 7$  vs.  $26 \pm 12$  kg) compared to healthy controls but did not reach statistical significance ( $P = 0.07$ ). The distribution of PA among CHF patients and

controls revealed a statistically significant higher median PA among controls ( $6.4^\circ$  vs.  $5.5^\circ$ ,  $P = 0.02$ ). Among patients with ICM and DCM PA did not differ significantly ( $5.3^\circ$  vs.  $5.8^\circ$ ,  $P = 0.28$ ).

## CMR studies

The CMR characteristics of our study cohort are summarized in **Table 2**. As illustrated in **Figure 1** indexed EAT in patients with CHF was significantly lower compared to controls ( $22 \pm 5$  vs.  $34 \pm 4$  g/m<sup>2</sup>,  $P < 0.001$ ). Subgroup analysis of CMR parameters in patients with ischemic and DCM revealed a comparable LV-EF ( $27 \pm 9\%$  vs.  $28 \pm 9\%$ ,  $P = 0.73$ ) as well as an equally reduced indexed EAT ( $23 \pm 8$  vs.  $22 \pm 9$  g/m<sup>2</sup>,  $P = 0.36$ ) in both patient cohorts. The left and right ventricular volumes were similarly increased.

## Correlation of EAT, BIA parameters, and left ventricular function

Linear regression analysis (**Table 3**) revealed a significant correlation of CMR indexed EAT with LV-EF ( $r = 0.56$ ,  $P < 0.001$ ), PA ( $r = 0.31$ ,  $P = 0.01$ ), TBMM ( $r = 0.41$ ,  $P = 0.001$ ), FFM ( $r = 0.30$ ,  $P = 0.02$ ), and ICW ( $r = 0.47$ ,  $P = 0.0003$ ). The correlation between EAT and PA is shown in **Figure 2**.

With multivariable logistic regression analysis, a model using both the LV-EF, PA, TBMM, FFM, and ICW to predict the

**Table 1** Anthropometric, BIA, and clinical parameters

|                                  | Controls             |                      | <i>P</i> <sup>a</sup> | Patients with heart failure |                      |                       |
|----------------------------------|----------------------|----------------------|-----------------------|-----------------------------|----------------------|-----------------------|
|                                  | All<br><i>n</i> = 16 | All<br><i>n</i> = 41 |                       | ICM<br><i>n</i> = 22        | DCM<br><i>n</i> = 19 | <i>P</i> <sup>b</sup> |
| <i>Anthropometric parameters</i> |                      |                      |                       |                             |                      |                       |
| Age                              | 61 ± 11              | 63 ± 12              | 0.45                  | 68 ± 8                      | 57 ± 13              | 0.02                  |
| Male sex                         | 12 (75%)             | 36 (88%)             | 0.60                  | 20 (91%)                    | 16 (84%)             | 0.55                  |
| BW (kg)                          | 84 ± 15              | 83 ± 17              | 0.70                  | 77 ± 12                     | 89 ± 19              | 0.03                  |
| BSA (m <sup>2</sup> )            | 1.99 ± 0.2           | 1.96 ± 0.2           | 0.68                  | 1.9 ± 0.2                   | 2.0 ± 0.3            | 0.09                  |
| BMI (kg/m <sup>2</sup> )         | 28 ± 5               | 27 ± 4               | 0.67                  | 26 ± 4                      | 29 ± 5               | 0.02                  |
| <i>BIA parameters</i>            |                      |                      |                       |                             |                      |                       |
| TBW (l)                          | 45.6 ± 9.6           | 45.7 ± 9.4           | 0.96                  | 43.5 ± 7.3                  | 48.9 ± 11.0          | 0.12                  |
| TBF (kg)                         | 26 ± 12              | 21 ± 7               | 0.07                  | 20 ± 7                      | 23 ± 8               | 0.21                  |
| TBMM (kg)                        | 36 ± 9               | 34 ± 8               | 0.27                  | 31 ± 7                      | 36 ± 8               | 0.03                  |
| FFM (kg)                         | 59 ± 14              | 61 ± 14              | 0.55                  | 58 ± 11                     | 65 ± 16              | 0.09                  |
| Phase angle (°)                  | 6.4                  | 5.5                  | 0.02                  | 5.3                         | 5.8                  | 0.28                  |
| ICW (l)                          | 26 ± 6               | 24 ± 6               | 0.30                  | 22 ± 5                      | 26 ± 7               | 0.03                  |
| ECW (l)                          | 20 ± 3               | 22 ± 5               | 0.13                  | 21 ± 4                      | 22 ± 6               | 0.51                  |
| <i>NYHA class</i>                |                      |                      |                       |                             |                      |                       |
| NYHA I                           | 0/16                 | 0/41                 |                       | 0/22                        | 0/19                 |                       |
| NYHA II                          | 0/16                 | 4/41 (10%)           | < 0.001               | 1/22 (5%)                   | 3/19 (16%)           | 0.24                  |
| NYHA III                         | 0/16                 | 14/41 (34%)          | < 0.001               | 8/22 (36%)                  | 6/19 (32%)           | 0.75                  |
| NYHA IV                          | 0/16                 | 23/41 (56%)          | < 0.001               | 13/22 (59%)                 | 13/19 (68%)          | 0.69                  |

BIA, bioimpedance analysis; BSA, body surface area; BW, body weight; DCM, dilatative cardiomyopathy; ECW, extracellular water; FFM, fat-free mass; ICM, ischemic cardiomyopathy; ICW, intracellular water; NYHA, New York Heart Association; TBF, total body fat; TBMM, total body muscle mass; TBW, total body water.

<sup>a</sup>Heart failure patients vs. controls. <sup>b</sup>ICM vs. DCM.

Table 2 CMR characteristics

|                                    | Controls             |                      | <i>P</i> <sup>a</sup> | Patients with heart failure |                      |                       |
|------------------------------------|----------------------|----------------------|-----------------------|-----------------------------|----------------------|-----------------------|
|                                    | All<br><i>n</i> = 16 | All<br><i>n</i> = 41 |                       | ICM<br><i>n</i> = 22        | DCM<br><i>n</i> = 19 | <i>P</i> <sup>b</sup> |
| LV-EF (%)                          | 57 ± 6               | 27 ± 9               | <0.001                | 27 ± 9                      | 28 ± 9               | 0.73                  |
| LV-EDM (g)                         | 127 ± 29             | 215 ± 51             | <0.001                | 203 ± 43                    | 228 ± 58             | 0.13                  |
| Indexed LV-EDM (g/m <sup>2</sup> ) | 64 ± 13              | 112 ± 25             | <0.001                | 109 ± 22                    | 115 ± 28             | 0.43                  |
| LV-ESV (ml)                        | 66 ± 24              | 218 ± 89             | <0.001                | 214 ± 82                    | 222 ± 99             | 0.76                  |
| LV-EDV (ml)                        | 140 ± 28             | 298 ± 93             | <0.001                | 286 ± 78                    | 312 ± 109            | 0.37                  |
| LV-EDD (mm)                        | 50 ± 4               | 69 ± 8               | <0.001                | 68 ± 7                      | 71 ± 8               | 0.33                  |
| RV-EF (%)                          | 57 ± 8               | 40 ± 16              | 0.001                 | 41 ± 17                     | 39 ± 14              | 0.57                  |
| RV-ESV (ml)                        | 56 ± 18              | 111 ± 73             | 0.004                 | 97 ± 52                     | 127 ± 90             | 0.19                  |
| RV-EDV (ml)                        | 138 ± 27             | 174 ± 77             | 0.08                  | 159 ± 52                    | 192 ± 96             | 0.17                  |
| EAT (g)                            | 67 ± 10              | 44 ± 11              | <0.001                | 45 ± 11                     | 44 ± 15              | 0.12                  |
| Indexed EAT (g/m <sup>2</sup> )    | 34 ± 4               | 22 ± 5               | <0.001                | 23 ± 8                      | 22 ± 9               | 0.36                  |

BSA, body surface area; CMR, cardiac magnetic resonance; DCM, dilatative cardiomyopathy; EAT, epicardial adipose tissue; ICM, ischemic cardiomyopathy; LV-EDD, left ventricular end-diastolic diameter; LV-EDM, left ventricular end-diastolic mass; LV-EDV, left ventricular end-diastolic volume; LV-EF, left ventricular ejection fraction; LV-ESV, left ventricular end-systolic volume; RV-EDV, right ventricular end-diastolic volume; RV-EF, right ventricular ejection fraction; RV-ESV, right ventricular end-systolic volume.

<sup>a</sup>Heart failure patients vs. control subjects. <sup>b</sup>ICM vs. DCM.

indexed EAT, LV-EF had an  $r^2$  of 0.45,  $P < 0.0001$ , and revealed that LV-EF was the only parameter that was independently associated with the indexed EAT ( $P < 0.0001$ ).

### Clinical follow-up

During the follow-up period of 5 years, 8/41 (19.5%) patients died from cardiac events; 1 of sudden cardiac death, 1 of cardiogenic shock in acute coronary syndrome and 6 of decompensated heart failure. **Figure 3** shows the receiver operating characteristic curve for indexed EAT, PA, LV-EF, TBMM, ICW, and FFM.

Receiver operating characteristic analysis indicates good predictive performance of PA (AUC = 0.86; 95% confidence interval (CI) = 0.72–1.0,  $P = 0.01$ ), indexed EAT (AUC = 0.82; 95% CI = 0.70–0.94,  $P = 0.04$ ) ICW (AUC = 0.83; 95% CI = 0.68–0.97,  $P = 0.03$ ) as well as TBMM (AUC = 0.82, 95% CI = 0.69–0.95,  $P = 0.04$ ) to predict future cardiac death in our study cohort. LV-EF (AUC = 0.68; 95% CI = 0.51–0.88,  $P = 0.09$ ), and FFM (AUC = 0.66; 95% CI = 0.45–0.88,  $P = 0.11$ ) only provide modest diagnostic accuracy to identify patients at risk for cardiac death.

The optimal cut-off value to predict cardiac death was 22 g/m<sup>2</sup> for indexed EAT (sensitivity 88%, specificity 67%), 34 kg for TBMM (sensitivity 88%, specificity 46%), 251 for ICW (sensitivity 88%, specificity 52%), 5.5° for PA (sensitivity 75%, specificity 65%), 30% for LV-EF (sensitivity 63%, specificity 65%), and 69 kg for FFM (sensitivity 75%, specificity 73%).

A risk stratification among patients with CHF based on indexed EAT <22 g/m<sup>2</sup> revealed a statistically significant higher risk of cardiac death (**Figure 4a**,  $P = 0.02$ ). TBMM >34 kg (**Figure 4b**,  $P = 0.06$ ), ICW >251 (**Figure 4c**,  $P = 0.07$ ), and PA >5.5° (**Figure 4d**,  $P = 0.13$ ) showed a trend toward a better survival. Whereas LV-EF below and above 30% (**Figure 4e**,  $P = 0.71$ ) and FFM below and above 69 kg (**Figure 4f**,  $P = 0.76$ ) did

Table 3 Correlation of indexed EAT (g/m<sup>2</sup>) with LV-EF and BIA parameters

| Correlation of indexed EAT (g/m <sup>2</sup> ) with | Simple regression analysis |          |
|---|----------------------------|----------|
|   | <i>r</i>                   | <i>P</i> |
| LV-EF (%)   | 0.56                       | <0.001   |
| Phase angle (°)                                     | 0.31                       | 0.01     |
| TBMM (kg)   | 0.41                       | 0.001    |
| FFM (kg)  | 0.30                       | 0.02     |
| ICW (l)   | 0.47                       | 0.0003   |

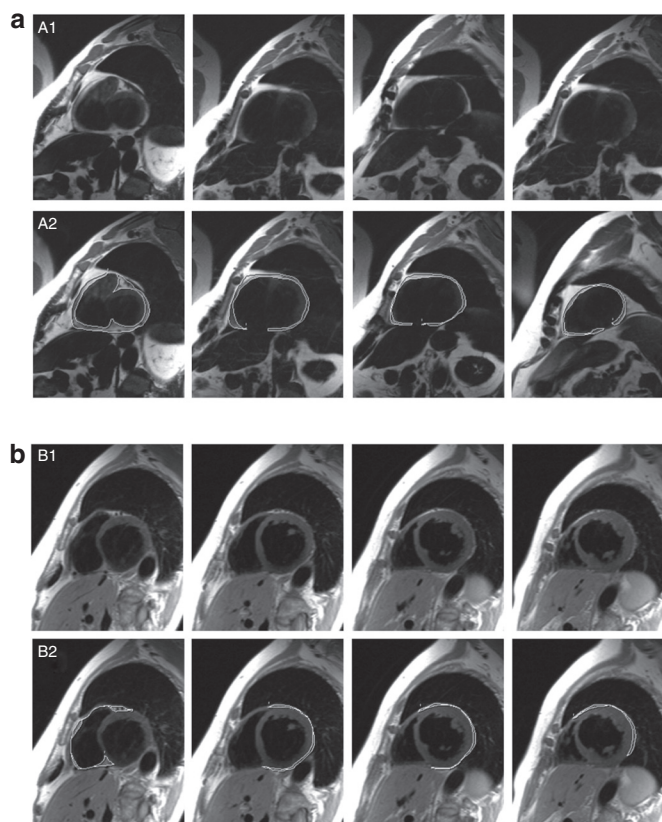
BIA, bioelectrical impedance analysis; EAT, epicardial adipose tissue; FFM, fat-free mass; ICW, intracellular water; LV-EF, left ventricular ejection fraction; TBMM, total body muscle mass.

not show a statistically significant difference regarding cardiac death.

### DISCUSSION

The main findings of the present study are: firstly, patients with severe heart failure have decreased EAT measured by CMR and reduced PA determined by BIA in comparison to healthy controls. Secondly, the reduction of indexed EAT and PA is irrespective of the underlying aetiology of the cardiomyopathy. Thirdly, the results indicate that indexed EAT constitutes an additional predictor of cardiac death in patients with CHF comparable to BIA-derived PA that might help to improve risk stratification in patients with severely reduced LV-EF.

So far, the role of EAT and its contribution to the development of cardiac pathology is quite ambiguous. Under physiological conditions, EAT is supposed to act as a buffering system between the myocardium and the local vascular bed (17,18). There is growing evidence of a close functional and anatomical relationship (19) between the adipose tissue and muscular components of the heart and a constant ratio of fat to muscle

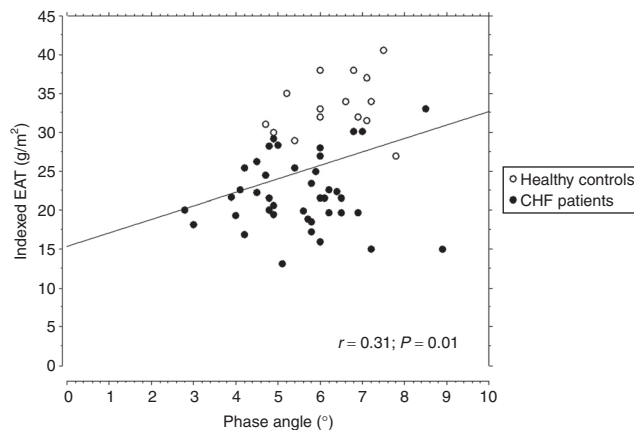


**Figure 1** Difference in EAT mass in healthy controls and patients with CHF. (a) Normal EAT mass in a healthy control. (A1) CMR imaging of EAT in a healthy control with normal EAT mass. (A2) Volumetric measurement of EAT outlining the contours of EAT in end-diastolic images of short axis covering the left and right ventricle. (b) Reduced EAT mass in a CHF patient. (B1) CMR imaging of EAT in a patient with CHF with significantly reduced EAT mass. (B2) Volumetric measurement of EAT outlining the contours of EAT in end-diastolic images of short axis covering the left and right ventricle. CHF, congestive heart failure; CMR, cardiac magnetic resonance; EAT, epicardial adipose tissue.

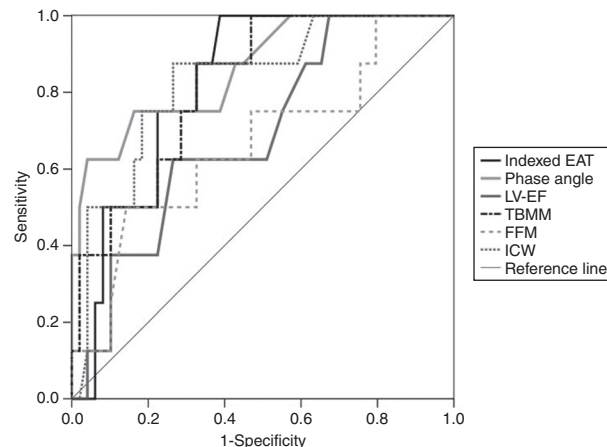
in each ventricle was described by Corradi *et al.* (20). EAT is a metabolically active organ and a source of several bioactive molecules that may influence cardiac morphology and function (21–23). On the other hand, excessive EAT detected by coronary computed tomography was shown to be associated with elevated coronary calcium scores, metabolic syndrome and is therefore supposed to contribute to coronary atherosclerosis (24–27).

EAT is known to correlate closely to visceral fat (28) but not to total fat mass (29). According to preceding studies (28,29), we only observed a statistical trend between EAT and BMI ( $P = 0.07$ ) however, the level of statistical significance was not reached.

Patients with severely reduced heart failure display significantly reduced indexed EAT compared to healthy controls ( $P < 0.001$ ). This finding is in line with the results of Flüchter *et al.* (13) and a postmortem study by Schejbal (30), who also found reduced EAT in patients with CHF. In the present patient cohort, patients with ICM had significantly less body weight than DCM patients. However, the reduction of EAT is comparable in ICM patients and DCM patients. Therefore, we



**Figure 2** Relationship between indexed EAT and PA in controls and patients with congestive heart failure. Regression plot illustrating the relationship between indexed EAT ( $\text{g}/\text{m}^2$ ) and PA ( $^\circ$ ) in controls and patients with congestive heart failure (CHF). EAT, epicardial adipose tissue; PA, phase angle.

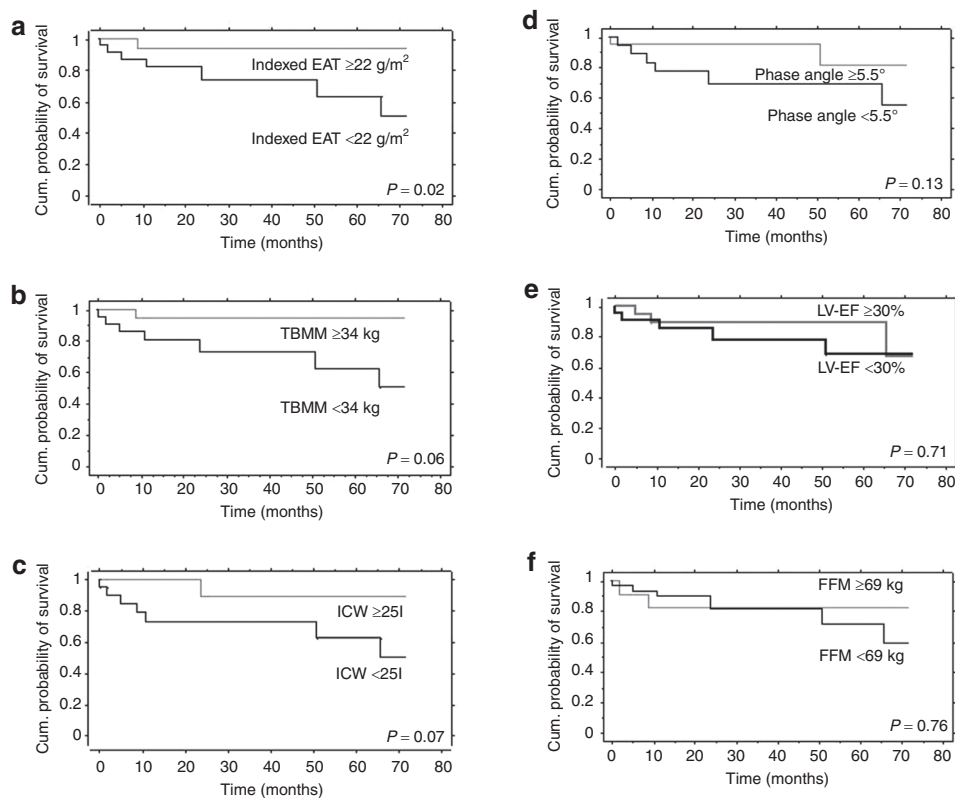


**Figure 3** ROC curve predicting cardiac death. ROC curve of indexed EAT ( $\text{g}/\text{m}^2$ ), PA ( $^\circ$ ), LV-EF (%), TBMM (kg), ICW (l), and FFM (kg) predicting cardiac death. EAT, epicardial adipose tissue; FFM, fat-free mass; ICW, intracellular water; LV-EF, left ventricular ejection fraction; PA, phase angle; ROC, receiver operating characteristic; TBMM, total body muscle mass.

assume that EAT reduction in patients with severely reduced LV-EF goes beyond a global fat reduction due to disease related wasting. But it seems more likely to be a manifestation of disease progression, indicating a decreased buffering capacity for excess fatty free acids, a diminished responsiveness to adjust to special energy demands of the heart (21) as well as a reduced production of cardioprotective molecules (31). However, the triggering factors and the underlying pathological mechanism causing EAT diminution are not known, yet.

In our study, diminished EAT is not only associated with a significantly reduced LV-EF but also with a significantly lower PA, a lower TBMM, a lower ICW as well as a reduced FFM. However, multivariable analysis revealed LV-EF as the only independent predictor of EAT ( $P < 0.001$ ).

BIA-derived PA reflects not only body cell mass, but is also one of the best indicators of cell membrane function, related



**Figure 4** Kaplan–Meier curve for cardiac death in patients with congestive heart failure. Survival stratified by (a) indexed EAT ( $\text{g}/\text{m}^2$ ) cutoff  $<22 \text{ g}/\text{m}^2$  (black line),  $\geq 22 \text{ g}/\text{m}^2$  (gray line), (b) TBMM (kg) cutoff  $<34 \text{ kg}$  (black line),  $\geq 34 \text{ kg}$  (gray line), (c) ICW (l) cutoff  $<251$  (black line),  $\geq 251$  (gray line), (d) PA ( $^\circ$ ) cutoff  $<5.5^\circ$  (black line),  $\geq 5.5^\circ$  (gray line), (e) LV-EF (%) cutoff  $<30\%$  (black line),  $\geq 30\%$  (gray line), and (f) FFM (kg) cutoff  $<69 \text{ kg}$  (black line),  $\geq 69 \text{ kg}$  (gray line).  $P$  values were derived using the Mantel–Cox log-rank test. CHF, congestive heart failure; EAT, epicardial adipose tissue; FFM, fat-free mass; ICW, intracellular water; LV-EF, left ventricular ejection fraction; PA, phase angle; TBMM, total body muscle mass.

to the ratio between extracellular water and ICW (32). In the past decade, several studies have investigated the role of PA as a prognostic, nutritional, membrane cell function, or health marker in various disease conditions relating a reduced PA to an unfavorable prognosis (6,7,9,33–37). In CHF, a reduced PA has shown to be associated with a higher functional New York Heart Association class (11). According to these findings, our results showed significantly reduced PA values in patients with CHF compared to matched healthy controls. All other BIA parameters were comparable in both groups. In our study, a PA cut-off value of  $5.5^\circ$  had a good discriminative power to predict cardiac death, yielding a sensitivity of 75% and a specificity of 65%. This cut-off value is comparable with those reported by previous studies from Schwenk *et al.* (37), Selberg and Selberg (6), Gupta *et al.* (10), and Toso *et al.* (38) evaluating the prognostic role of PA in other clinical conditions.

Furthermore, using Kaplan–Meier analysis an indexed EAT below a mean value of  $22 \text{ g}/\text{m}^2$  correlates significantly with a higher risk of cardiac death during follow-up. However, these cut-off values have to be interpreted with great caution as they are derived from the whole patient cohort and the partition value of the underlying aetiology of the heart failure to overall survival has not been accounted for. Additionally, no prospective validation of the partition values was performed.

Thus, our results suggest that a reduced indexed EAT as well as a low PA might suit as surrogate markers to predict a poor prognosis in patients with severe CHF.

As CMR is considered as the gold standard for noninvasive determination of LV function, many patients with severe heart failure undergo CMR. In these patients, the additional EAT determination seems to be reasonable adding further prognostic information. In contrast to BIA-derived PA determination, EAT quantification by CMR is not dependent on hydration status and can also be applied in decompensated CHF patients.

#### Limitations

Limitations of the present study relate to the relatively small study cohort. The fact that only indexed EAT above the cut-off value and neither BIA-derived parameters nor LV-EF could show a significant survival benefit at Kaplan–Meier analysis might be related to the small sample size. Larger randomized trials are needed to establish EAT as predictors of survival in CHF.

In summary, EAT assessed by CMR correlates with the BIA-derived PA in patients with CHF. The reduction of EAT and PA is irrespective of the underlying aetiology of the cardiomyopathy. EAT and BIA-derived PA could serve as a prognostic indicator in patients with severe CHF. However, further clinical

studies are needed to elucidate the prognostic relevance of these new findings.

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#### DISCLOSURE

The authors declared no conflict of interest.

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