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Reduced longitudinal cardiac strain in asthma patients

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Running head: Cardiac strain in asthma

Objective:

There is limited knowledge about the potential relationship between asthma and heart function.

Aim of our present study was to examine if asthma may be associated with manifest or subclinical heart dysfunction.

Methods:

72 allergic mild-to-moderate and severe asthma patients and 20 matched controls were enrolled in the study. Depending on the anti-asthmatic therapy, four subgroups of asthma patients were created: patients under long-acting beta2-agonists (LABA) and inhaled cortisone without oral

cortisone treatment with (1a) versus without (1b) additional omalizumab therapy; patients with LABA, inhaled cortisone and omalizumab treatment with (2a) versus without (2b) oral cortisone. Standard echocardiographic parameters as well as global longitudinal left and right ventricular strains as determined by ultrasound-based speckle-tracking method were evaluated. Further, NT-pro-BNP, IgE, CRP and blood count were assessed in asthma and control groups.

Results:

There were no relevant differences in standard echocardiographic measures between both asthma groups and the control collective. Longitudinal left ventricular strain values were reduced significantly in severe and mild-to-moderate asthma groups ($-12.91 \pm 0.24\%$, $-13.92 \pm 1.55\%$, respectively), whereas longitudinal right ventricular strain values were additionally relevantly decreased in severe asthma ($-10.35 \pm 1.04\%$) compared to the control ($-16.55 \pm 0.49\%$, $-18.48 \pm 1.90\%$, resp.). Cardiac strains were similar in subgroups 1a and 1b. In contrast, patients from subgroup 2a presented reduced heart strains and decreased lung function compared to those from 2b. CRP, IgE and eosinophils were significantly increased in asthma versus control individuals.

Conclusions:

Allergic asthma, especially severe asthma is associated with subclinical impaired left and right ventricular function as determined by speckle-tracking analysis.

Key words: allergic asthma, heart dysfunction, echocardiography, speckle-tracking analysis, longitudinal ventricular strain

Introduction:

The prevalence of allergic asthma is increasing worldwide [1]. In contrast to chronic obstructive pulmonary disease (COPD) which frequently coexists with cardiovascular diseases [2], little is known about the interaction between asthma and cardiovascular disorders. An increased risk of coronary heart disease was demonstrated in adult-onset asthmatics [3]. However, the results concerning this

issue are inconsistent, as other studies showed either that the above mentioned association was sex-dependent and only found in women [4] or there was no such association, irrespective of sex or other factors [5]. In systolic heart failure airflow obstruction was frequent due to acute or chronic congestion and distinctly underdiagnosed [6]. Inversely, the diagnosis of asthma was related to an increased hazard of heart failure [7]. In contrast, in other work, individuals with asthma did not have an enhanced likelihood for heart failure compared to the control group [3]. Further, there are no conclusive reports on the impact of allergy on the cardiovascular disease. Comorbid allergy was not a modifying factor in asthma-associated increased cardiovascular disease risk [7]. On the contrary, allergy detected in the skin test was linked to an enhanced cardiovascular mortality [8].

The above cited studies on asthma and heart failure examined potential influence of asthma on the occurrence of heart failure, defined as a clinical syndrome with typical symptoms caused by a structural and/or functional cardiac abnormality/dysfunction [9]. Negative results of some of the studies do not necessarily mean that asthma has no impact on the heart function, since patients may present with asymptomatic structural or functional cardiac abnormalities which are precursors of heart failure [9].

Therefore, aim of our study was to examine heart function by means of not only standard echocardiographic parameters including the assessment of left ventricular ejection fraction as well as tricuspid annular plane systolic excursion (TAPSE) as a surrogate of right ventricle systolic function, but also ultrasound-based speckle-tracking method, in order to detect very early signs of heart dysfunction in asymptomatic patients with mild-to-moderate and severe allergic asthma compared to the control group. Additionally, heart dysfunction- and inflammation-associated serum markers were determined.

Methods:

Study design

72 patients with allergic asthma and 20 respectively matched controls were enrolled between October 2015 and August 2016 in the present study. All study participants underwent echocardiography in order to obtain standard parameters as well as global longitudinal left and right ventricular strains as determined by ultrasound-based speckle-tracking method. Additionally, NT-pro-BNP, IgE, CRP and blood count were assessed.

Patient characteristics

A total of 72 consecutive outpatients with allergic asthma have been enrolled between October 2015 and August 2016 in the study during control visits in our pneumological department. Patients with other pulmonary disorders such as COPD, interstitial lung diseases, lung tumors or sleep apnea and heart failure were excluded from the study. 20 control individuals were matched for sex, age, body mass index (BMI) and the presence of cardiovascular risk factors/cardiovascular comorbidities. Inclusion criterion for all asthma patients and control individuals was age ≥ 18 years (range: for asthma: 28-74 years, for control: 24-69 years).

Allergic asthma was confirmed based on the results from lung function (positive reversibility test or bronchial challenge test with methacholine) and sensitization tests (detection of at least three allergens in specific IgE blood measurements or in skin prick test). Asthma patients were divided into two groups: mild-to-moderate (patients under therapy with short acting beta-2 agonists = SABA, inhaled glucocorticoids, long acting beta-2 agonists = LABA and/or long-acting muscarinic antagonists = LAMA, n=25) and severe asthma (patients under maximal inhaled treatment consisting of SABA, inhaled glucocorticoids, LABA and/or LAMA as well as additional therapy with oral glucocorticoids and/or humanized recombinant monoclonal anti-IgE antibody = omalizumab, n=47).

Based on the Global Initiative for Asthma (GINA) stepwise approach to the asthma treatment patients with mild-to-moderate asthma corresponded to the groups treated with the medication comprised at the steps 1-4. Patients with severe asthma were under add-on therapy (step 5) [10].

Asthma symptoms were well or partly controlled in all patients according to the GINA guidelines [10]. There were no significant differences in demographics and the presence of cardiovascular risk factors between both asthma groups and the control collective at baseline (table 1). Control group was characterized by the absence of the above mentioned asthma medication and the normal lung function compared to the asthma individuals (table 1).

In order to prove if there are any changes in cardiac strain parameters depending on the anti-asthmatic therapy, four main subgroups of patients were created: patients under LABA and inhaled cortisone without oral cortisone treatment with (1a, n=27) versus without (1b, n=21) additional omalizumab therapy as well as patients with LABA and inhaled cortisone and omalizumab treatment with (2a, n=12) versus without (2b, n=27) oral cortisone. All patients from subgroups 1a, 2a and 2b were recruited from the collective with severe asthma. In contrast, all patients creating subgroup 1b were characterized by mild-to-moderate asthma. There were no relevant differences in the demographics and known cardiovascular risk factors/diseases or the frequency of the LAMA therapy between the subgroups 1a and 1b (44.4% and 42.9%, resp.) as well as 2a and 2b (83.3% and 51.9%, resp.).

The research was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committees. Written informed consent has been obtained from all subjects.

Body plethysmography, bronchodilator reversibility test, bronchial challenge test with methacholine

Total lung capacity (TLC), forced expiratory volume in 1 second (FEV₁), residual volume (RV) and dynamic total pulmonary resistance (R_{tot}) were measured by body plethysmography (Jaeger MasterScreen Body Version 01.00, CareFusion Germany 234 GmbH, Höchberg). Predicted values for

TLC, FEV1, RV and Rtot were calculated automatically based on age, sex, height and race, as previously described [11].

In case of decreased FEV1 value at baseline, bronchodilator was applied to prove bronchial reversibility. 10–15 minutes after administration of 200 µg salbutamol, spirometry was repeated. Increase in FEV1 of >12% and >200ml from baseline identified patients with variable expiratory airflow limitation [10].

To assess airway responsiveness in patients with probability of asthma and with no obstruction signs at baseline lung function test, methacholine provocation test was performed, according to the 2-min tidal breathing protocol [12]. The patients were asked to inhale the methacholine solution for 5 min in serial concentrations (0.0625, 0.25, 1, 4, and 16 mg/mL) using nebulizer. After each nebulization spirometry was performed. When the FEV1 fell less than 20% from the baseline, next highest concentration of methacholine was put into nebulizer for subsequent inhalation. If the FEV1 fell more than 20% from baseline, the test was stopped, salbutamol was administrated and the final spirometry measurement was performed 10 min later. The cumulative methacholine concentration used was calculated (provocative concentration causing a 20% fall in FEV1 values = PC₂₀). When the highest methacholine concentration was given without substantial FEV1 decrease, the test was negative (PC₂₀ < 16mg/ml). PC₂₀ ≤ 16mg/ml defined airway responsiveness.

Conventional echocardiography and two-dimensional speckle-tracking analysis

Transthoracic echocardiography was performed using a commercially available ultrasound equipment with a 2,5-MHz phased array transducer (Vivid 7, General Electric Medical Health, Waukesha, Wisconsin, United States; iE 33 Philips Medical Systems, Koninklijke N.V.), according to the recommendations of the American Society of Echocardiography [13]. Parasternal, apical and subcostal views were acquired. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method from apical four-chamber view. Diastolic function was determined by

the measurements of the peak early (E) and late (A) mitral inflow velocity by the pulsed-wave Doppler and of the peak early (E') and late (A') diastolic velocity of the septal and lateral mitral valve annuli by the pulsed-wave tissue Doppler. Based on the guidelines of the American Society of Echocardiography [13], the diastolic function was classified as follows: grade 0 (normal) if E/A ratio > 0.8 and average E/E' ratio < 10 , grade I if E/A ratio ≤ 0.8 and average E/E' ratio < 10 , grade II if E/A ratio > 0.8 to < 2.0 and average E/E' ratio = 10-14 and grade III if E/A ratio ≥ 2.0 and average E/E' ratio > 14 . Right ventricular systolic function was assessed as the tricuspid annular plane systolic excursion (TAPSE) in the apical four-chamber view. TAPSE < 20 mm determined right ventricular systolic dysfunction. The systolic pulmonary artery pressure (sPAP) was calculated using the tricuspid regurgitation peak velocity measured by the continuous wave Doppler. sPAP > 30 mmHg was defined as pulmonary hypertension.

For the offline two-dimensional speckle-tracking analysis two consecutive cardiac cycles were acquired and transferred to a workstation with dedicated software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany), as previously described [14,15]. On the basis of a grayscale apical four-chamber view, left ventricular and right free wall endocardial borders at the end-systolic frame were manually traced. The region of interest (ROI) was adjusted to include the entire myocardial wall. In order to determine regional longitudinal ventricular strains left ventricle and right ventricular free wall were divided into six (basal, medial and apical for septal and lateral wall) and three segments (basal, medial and apical), resp. For each segment longitudinal strain curves were generated by the software. Negative systolic peak was detected on each strain curve and expressed as percentage. Global longitudinal left and right ventricular strains were calculated by averaging the six and three segmental values, resp. The more negative the strain value was, the better the ventricular function was. The term "reduced longitudinal strain" used in the present manuscript indicates lower absolute values corresponding to the more impaired systolic cardiac function.

Blood markers

C-reactive protein (CRP), differential blood count, immunoglobulin E (IgE) and NT-pro-brain natriuretic peptide (NT-pro-BNP) were assessed in the blood of all study participants at the time of enrollment into the study.

Statistical analysis

Parametric values were expressed as means $\pm$ standard error of the mean (SEM). The means between all three groups were compared by the one-way ANOVA test, whereas potential differences in means between two groups were assessed by the Student's t-test. Comparisons between categorical data were performed by using the chi-square test. Univariate and multiple linear regression analyses were conducted to estimate an association between the predictors and responses. $P < 0.05$ was considered as statistically significant. Statistical calculations were carried out by means of the SPSS software, version 22.0 (SPSS Inc.).

Results:

As the main finding of the present study, we observed a relevant reduction in global longitudinal left ventricular (LV) and right ventricular (RV) strains in severe asthma ($-12.91 \pm 0.84\%$, $-10.35 \pm 1.04\%$, resp., $p < 0.05$ for both vs. control) compared to the matched control ($-16.55 \pm 0.49\%$, $-18.48 \pm 1.90\%$, resp., Fig. 1). In mild-to-moderate asthma LV strain was also significantly decreased ($-13.92 \pm 1.55\%$), while there was a tendency towards lower RV strain ($-13.85 \pm 1.05\%$) versus control. Analysis of regional dysfunction showed that regional LV strains were reduced in asthma collective, especially in severe asthma versus control (mild-to-moderate asthma: septal apical: $-15.93 \pm 1.09\%$, $p < 0.05$ vs. control; severe asthma: septal basal: $-10.05 \pm 0.85\%$, septal apical: $-16.83 \pm 1.16\%$, lateral apical: $-8.27 \pm 0.80\%$, $p < 0.05$ for all vs. control, Fig. 2i and 2ii). Similarly, RV strains were decreased in the basal areas in mild-to-moderate ($-18.92 \pm 2.89\%$, $p < 0.05$ vs. control) and in the medial and basal areas in

severe asthma ($-12.06 \pm 1.31\%$, $-15.93 \pm 1.62\%$; resp., $p < 0.05$ for both vs. control) in comparison with the control group (RV strains: medial areas: $-20.28 \pm 2.52\%$, basal areas: $-29.49 \pm 3.95\%$; resp., Fig. 2iii).

In the subgroups of patients with LABA and inhaled but no oral cortisone treatment with (1a) vs. without (1b) additional omalizumab therapy, the statistical interpretation of ventricular strains demonstrated no significant differences in cardiac strains between both subgroups despite the tendency towards slightly improved LV strain and more impaired RV strain in 1a compared to 1b (Fig. 3i). In contrast, an analogous analysis of ventricular strains in the subgroups of patients with LABA, inhaled cortisone and omalizumab treatment with (2a) vs. without (2b) additional oral cortisone therapy showed a clear trend towards reduced global LV strain ($p = 0.053$) and even statistically significantly decreased some regional LV strains in 2a (septal basal LV strain, septal medial LV strain, septal apical LV strain and lateral basal LV strain) compared to 2b (Fig. 3ii). No relevant differences in RV strains between the subgroups 2a and 2b were observed (Fig. 3ii).

Of note, lung function was significantly impaired in subgroup 2a (FEV_1 (% predicted) = 68.34 ± 6.32) vs. 2b (FEV_1 (% predicted) = 85.93 ± 3.86), whereas there were no such differences between subgroups 1a and 1b.

In contrast to the cardiac strains, no differences in standard echocardiographic parameters were detected between asthma and control populations (table 2).

An analysis of blood parameters showed significant elevated CRP and IgE values in both asthma groups compared to control (table 3). Leukocyte numbers were relevantly higher only in the group of severe asthma as compared to control, while the percentage of lymphocytes was significantly decreased and that of eosinophils was significantly increased in both asthma groups versus control. Interestingly, blood levels of NT-pro-BNP were similar across the groups. Of note, only IgE values and leukocyte numbers differed significantly between mild-to-moderate and severe asthma. In the asthma subgroups 1 and 2, merely IgE values were significantly different between the subgroups 1a (1034.07 ± 187.33 IU/ml) and 1b (299.13 ± 130.58 IU/ml) as well as IgE values, leukocyte numbers and

the percentages of lymphocytes, neutrophils and basophils were relevantly different between 2a (382.34±104.52 IU/ml; 9.40±0.92 G/l; 20.54±2.79 %; 68.17±3.81 %; 0.59±0.07 %, resp.) and 2b (1034.07±187.33 IU/ml; 7.17±0.26 G/l; 28.49±1.34 %; 58.79±1.80 %; 0.86±0.06 %, resp.).

An univariate regression analysis for global longitudinal ventricular strains with independent values such as age, BMI, FEV1%, RV%, Rtot%, CRP, IgE, leukocytes, lymphocytes, eosinophils, NT-pro-BNP and global longitudinal ventricular strains (LV strain for RV strain and RV strain for LV strain) revealed that age and global longitudinal RV strain had relevant influence on global longitudinal LV strain. The same analysis showed that BMI and global longitudinal LV strain were significantly linked to global longitudinal RV strain. An analogical multivariate analysis for the same predictors demonstrated that only global longitudinal LV strain had influence on the global longitudinal RV strain, and inversely global longitudinal RV strain correlated with global longitudinal LV strain.

Discussion:

The present study demonstrates subclinical systolic biventricular heart dysfunction measured by an ultrasound-based speckle-tracking method in severe allergic asthma patients. In our work, severe asthma was characterized by a relevant airway obstruction measured in the pulmonary function test compared to control. In other study, it has been shown that even clinically inapparent lung function impairment was related to a manifest heart failure [16]. In the British Regional Heart Study, reduced FEV1 reflecting airflow obstruction was associated with cardiac dysfunction [17] and an increase risk of incident heart failure compared to the asthma-free referent group [7]. Asthma correlated modestly with the diagnosis of different cardiovascular diseases, among them heart failure [18]. Asthma patients who were cigarette smokers reported more often a concurrent diagnosis of congestive heart failure than smokers without asthma [19].

The reason for higher coexistence of asthma and heart dysfunction is probably multifactorial. In our study, we have detected an elevated inflammatory level in blood with increased CRP, IgE and eosinophils in asthma individuals and a higher absolute leukocyte number in severe asthma patients compared to the control ones. Similarly, increased CRP concentrations have also been detected in symptomatic asthma adults [20]. Higher CRP and leukocyte levels have been shown to be associated with increased risk of heart failure, independent of traditional risk factors [21]. Higher IgE concentrations may promote atherosclerosis due to activation of inflammatory cells [22]. Moreover, total serum IgEs is significantly increased in patients with ischemic heart disease and often correlates with the prognosis [23]. In allergic disorders, such as asthma, enhanced atherosclerosis associated with elevated IgE levels was documented [24]. Eosinophilia and positive skin tests, especially in combination with other risk factors predict cardiovascular mortality [8]. Chronic eosinophilic inflammation may cause endomyocardial fibrosis and in consequence heart failure [25].

In the present univariate regression analysis BMI was a predictor for global longitudinal RV strain. It is known that obesity correlates with measures of asthma severity [26]. On the other hand, increased BMI values are strongly associated with the development of heart failure [27]. Therefore, obesity is a common risk factor for the onset of asthma and heart failure. Likewise, age was a risk factor for the global longitudinal LV strain reduction in our work. It has been shown that aging predisposes to the manifestation of heart failure [28]. However, pathomechanisms underlying asthma-related preclinical cardiac dysfunction are much more complex and exceed the single effect of obesity or aging, since the control group in our study was, among others, also BMI- and age-matched. In our multivariate analysis both LV and RV strains influenced each other. Left and right ventricle work as one functional unit, so that the dysfunction of one of them causes impairment in contractility of the other one via activation of multiple mechanisms [29]. Although NT-pro-BNP is a sensitive biomarker of heart failure and inversely correlates with global longitudinal cardiac strain [30], we have not

observed such a relationship in our study. This could have been due to the relatively low number of study participants which may have limited the statistical significance.

Another interesting finding of our study was that there were no significant differences in LV and RV strains in asthmatics under inhaled therapy with (1a) versus without (1b) omalizumab treatment. In contrast, an addition of oral cortisone to the inhaled and omalizumab therapy was associated with relevantly reduced regional, especially septal, LV strains (2a versus 2b).

The impact of the antiasthmatic therapy on heart function is generally not clear. Several studies demonstrate an increase in risk for heart failure hospitalization and mortality in patients receiving LABA [31,32]. However, these studies were concerning already preexisting heart failure in patients with COPD. In another study no relationship was found between mortality and use of LABA when adjusted for BNP, clinical, demographic and medication data [33]. LABA therapy was not associated with incident heart failure in COPD [31] or development of idiopathic dilated cardiomyopathy in asthma patients [34]. Inhaled corticosteroids seem to have rather protective effects on cardiovascular outcome by reducing the risk of myocardial infarction and cardiovascular and all-cause mortality in asthma patients [35,36]. In our study almost all asthma patients were under inhaled LABA and cortisone therapy so that a statistically meaningful comparison with non-LABA/non-inhaled cortisone asthma individuals was not possible. In terms of potential interactions between omalizumab and heart function there are only scarce data. Iribarren et al. showed a higher incidence rate of cardiovascular and cerebrovascular events, among others heart failure, in asthma patients with omalizumab therapy versus non-omalizumab group [37]. In our present work, there were no differences in cardiac strains between omalizumab (1a) and non-omalizumab (1b) collectives. However, baseline characteristics in both groups did not differ from each other, whereas in the study of Iribarren et al. the severity of asthma was more pronounced with more frequent use of oral cortisone in the omalizumab compared to the non-omalizumab group. Oral glucocorticoids have been identified as risk factor for heart failure in the mixed collective of patients, predominantly

with rheumatoid arthritis and COPD [38]. In our study, patients under oral cortisone therapy (2a) showed significantly decreased some regional LV strains compared to the asthma group without oral cortisone therapy (2b). The explanation for this result could be cortisone-related side-effects, known as Cushing's syndrome which increase cardiovascular morbidity and mortality [38]. However, there were no relevant differences in cardiovascular risk factors between oral cortisone (2a) and non-oral cortisone (2b) in our study, so that potential deleterious effects of cortisone were not mediated by the traditional cortisone-side effects. Since the oral cortisone group (2a) was characterized by a worse lung function compared to the non-cortisone patients (2b), it is difficult to distinguish between effects of disease activity, treatment or both on heart function.

Conclusions:

In summary, severe allergic asthma was associated with an increased occurrence of subclinical biventricular heart dysfunction measured by reduced cardiac strain. Decreased lung function, enhanced systemic inflammation and possibly administration of oral cortisone seem to be the underlying pathomechanisms. Therefore, an echocardiographic screening, including the use of a speckle-tracking method may be helpful to identify individuals with asthma who are at risk for developing heart failure.

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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List of abbreviations:

BMI	body mass index
CRP	C-reactive protein
FEV1	forced expiratory volume in 1 second
GLLVS	global longitudinal left ventricular strain
GLRVS	global longitudinal right ventricular strain
IgE	immunoglobulin E
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
NT-pro-BNP	NT-pro-brain natriuretic peptide
ROI	region of interest
Rtot	dynamic total pulmonary resistance
RV	residual volume
SABA	short-acting beta-2 agonist
sPAP	systolic pulmonary artery pressure
TAPSE	tricuspid annular plane systolic excursion
TLC	total lung capacity

Figure legends:

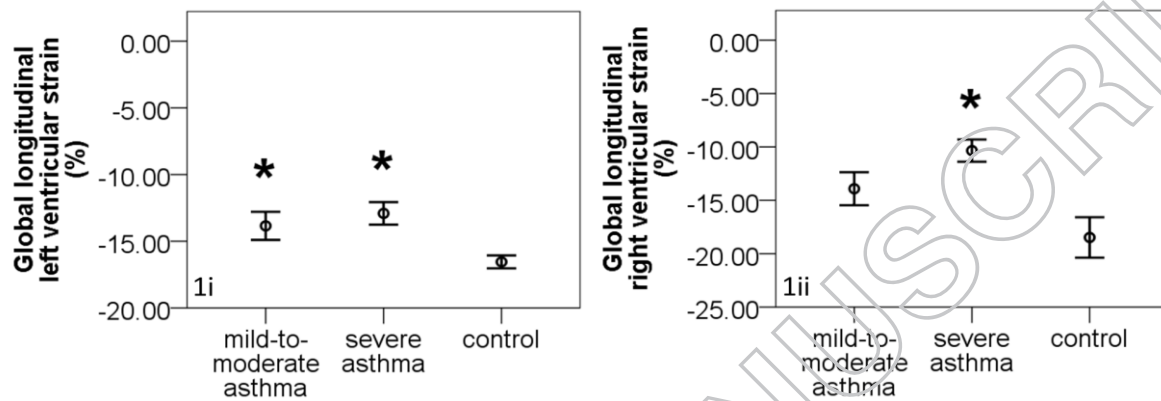
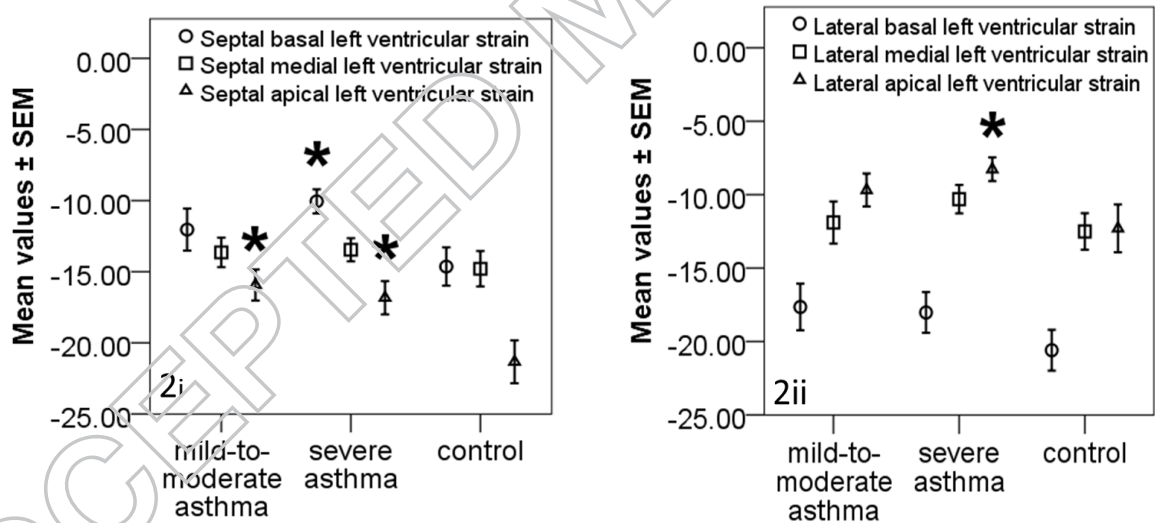


Fig. 1. Reduced global longitudinal left (1i) and right (1ii) ventricular strains in asthma patients compared to control. Asterisk = $p < 0.05$ vs. control.



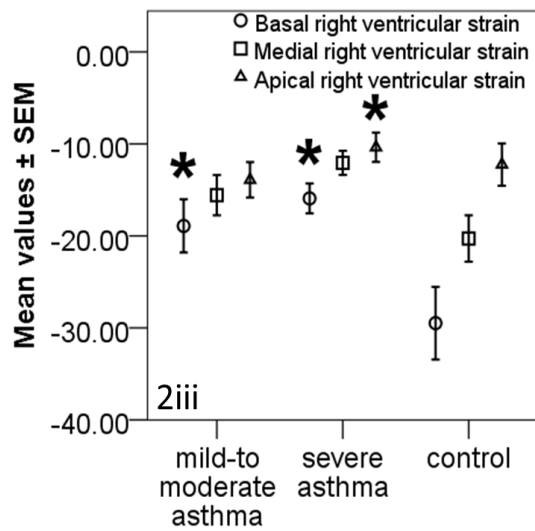
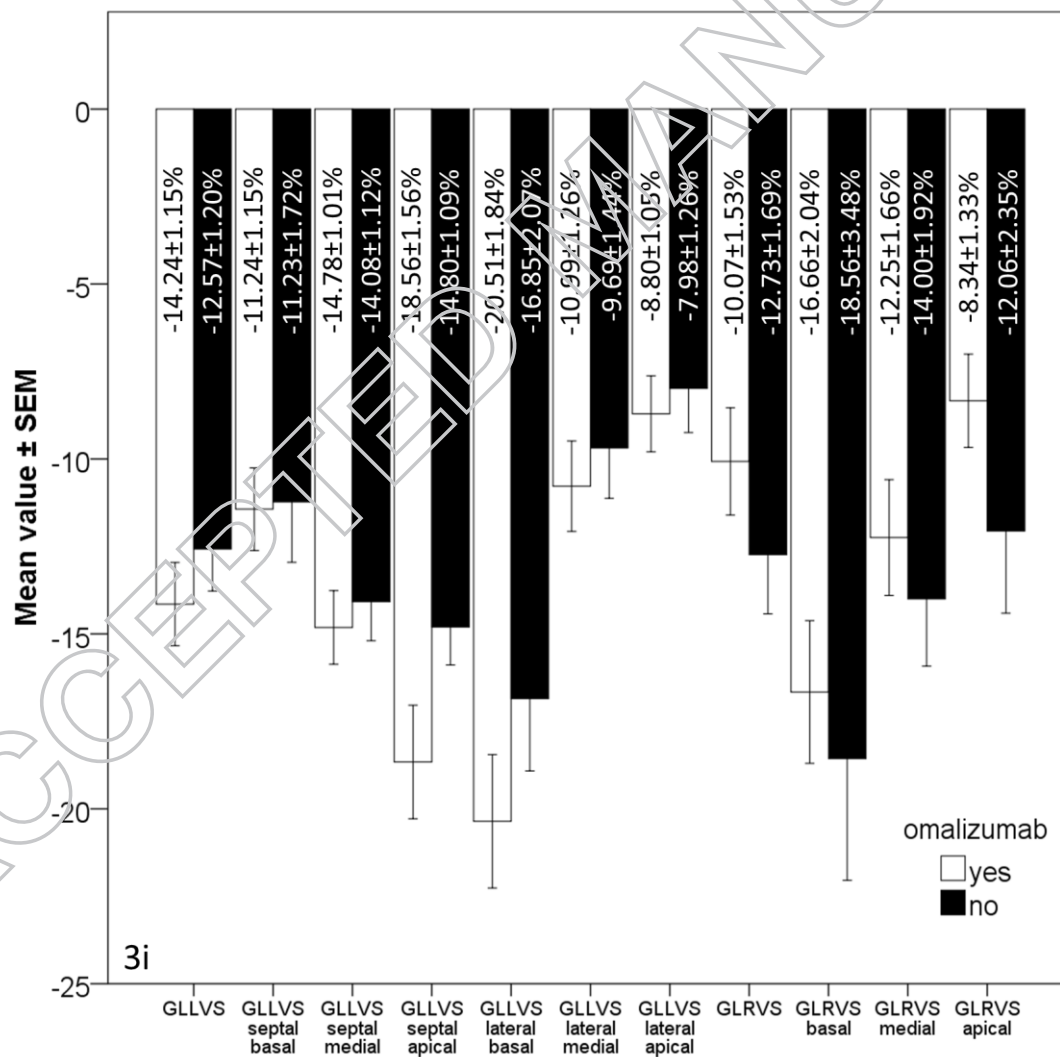


Fig. 2. Regional longitudinal septal (2i) and lateral (2ii) left as well as right (2iii) ventricular strains in asthma and control. Asterisk = $p < 0.05$ vs. control.



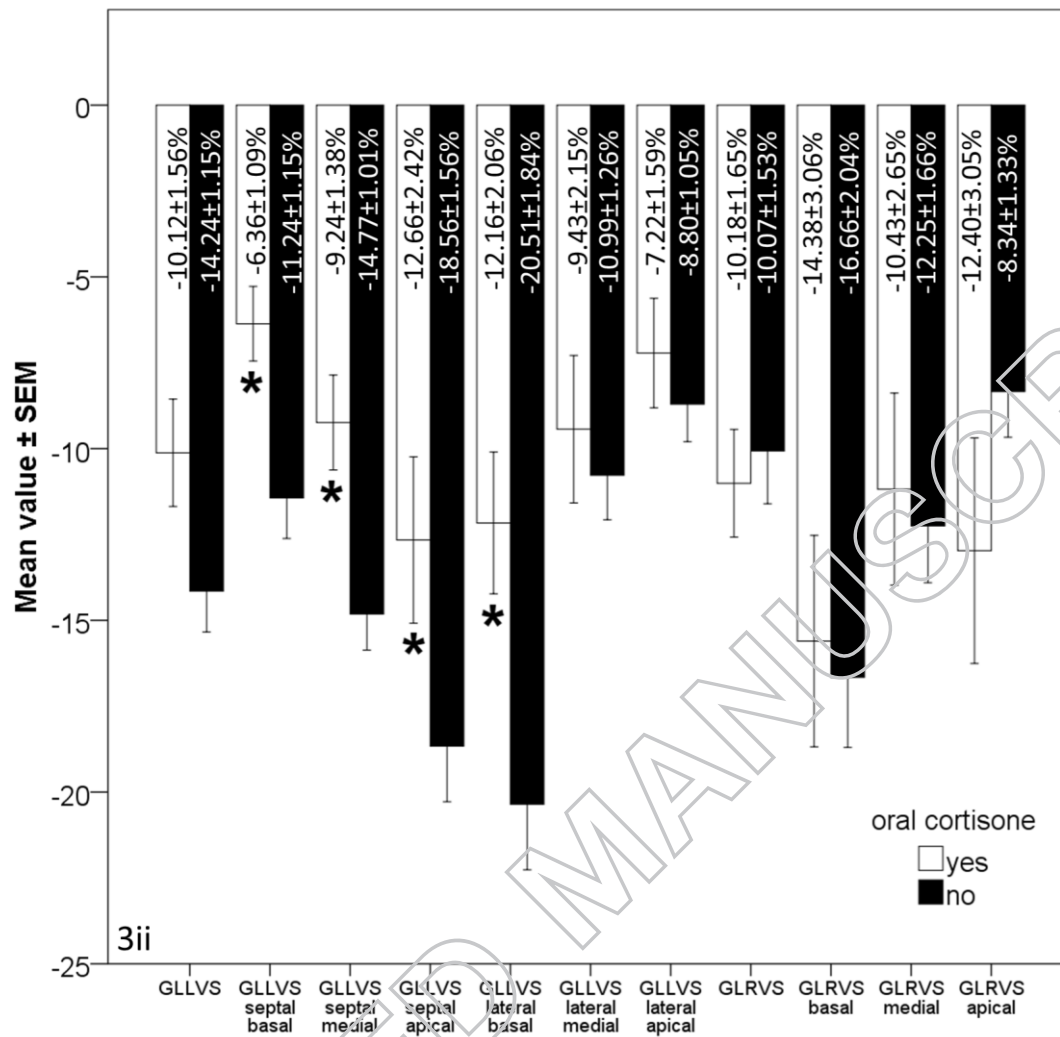


Fig. 3. Longitudinal left and right ventricular strains in asthma individuals under inhaled therapy but no oral cortisone with or without omalizumab treatment (3i). Longitudinal left and right ventricular strains in asthma patients under inhaled therapy and omalizumab treatment with or without oral cortisone (3ii). GLLVS = global longitudinal left ventricular strain. GLRVS = global longitudinal right ventricular strain. Asterisk = $p < 0.05$ between compared groups.

Tables:

Table 1. Baseline characteristics of asthma and control groups. Except for a worse lung function and specific medication in asthma patients, there were no significant differences between the collectives. LAMA = Tiotropium (5µg/day). BMI = body mass index. FEV1 = forced expiratory volume in 1 second, TLC = total lung capacity, RV = residual volume, Rtot = total airway resistance. Data are presented as a mean ± standard error of the mean (SEM) or n (%). P value < 0.05 = significant.

	Mild-to-moderate asthma, n=25	Severe asthma, n=47	No asthma=Control, n=20	P value
Sex, male, n (%)	6 (24.0)	18 (38.3)	6 (30.0)	non significant
Age, years	45.0±2.3	51.1±1.9	45.6±3.2	non significant
BMI, kg/m ²	26.0±0.8	27.0±0.8	24.9±0.7	non significant
Arterial hypertonus, n (%)	7 (28.0)	16 (34.0)	6 (30.0)	non significant
Hypercholesterolemia, n (%)	5 (20.0)	4 (8.5)	2 (10.0)	non significant
Diabetes mellitus, n (%)	3 (12.0)	4 (8.5)	2 (10.0)	non significant
Current nicotine abuse, n (%)	5 (20.0)	1 (2.1)	3 (15.0)	non significant
Former nicotine abuse, n (%)	4 (16.0)	11 (23.4)	4 (20.0)	non significant
Nicotine abuse, packyears	4.4±1.9	3.9±1.3	2.6±1.3	non significant
History of coronary heart disease, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	non significant
History of peripheral arterial disease, n (%)	5 (20.0)	7 (14.9)	2 (10.0)	non significant
Therapy				
- Inhaled glucocorticoids, n (%)	22 (88.0)	47 (100.0)	0 (0.0)	significant
Fluticasone propionate (1000µg/day), n (%)	4 (18.2)	40 (85.1)	0 (0.0)	
Fluticasone propionate (500µg/day), n (%)	5 (22.7)	0 (0.0)	0 (0.0)	
Fluticasone furoate (200µg/day), n (%)	0 (0.0)	2 (4.3)	0 (0.0)	
Budesonide (800µg/day), n (%)	3 (13.6)	2 (4.3)	0 (0.0)	
Budesonide (400µg/day), n (%)	4 (18.2)	0 (0.0)	0 (0.0)	
Beclometasone dipropionate (400µg/day), n (%)	3 (13.6)	3 (6.4)	0 (0.0)	
Beclometasone dipropionate (200µg/day), n (%)	3 (13.6)	0 (0.0)	0 (0.0)	
- Long acting beta-2 agonists = LABA, n (%)	17 (68.0)	47 (100.0)	0 (0.0)	significant
- Salmeterol (100µg/day), n (%)	9 (52.9)	40 (85.1)	0 (0.0)	
- Vilanterol (25µg/day), n (%)	0 (0.0)	2 (4.3)	0 (0.0)	

- Formoterol (24µg/day), n (%)	4 (23.5)	5 (10.6)	0 (0.0)	
- Formoterol (12µg/day), n (%)	4 (23.5)	0 (0.0)	0 (0.0)	
- Long-acting muscarinic antagonists = LAMA, n (%)	6 (24.0)	29 (61.7)	0 (0.0)	significant
- Oral glucocorticoids, n (%)	0 (0.0)	15 (31.9)	0 (0.0)	significant
- Prednisolone, doses, mg/day (range)	0 (0)	7.3±1.0 (2.5-20)	0 (0)	
- Omalizumab, current, n (%)	0 (0.0)	40 (85.1)	0 (0.0)	significant
- Omalizumab, current, mg/month (range)	0	671.1±53.2 (150-1200)	0	
- Omalizumab, former, n (%)	0 (0.0)	4 (4.3)	0 (0.0)	significant
- Omalizumab, former, mg/month (range)	-	525.0±143.6 (300-900)	-	
Lung function				
- TLC (l)	5.6±0.3	6.0±0.2	6.4±0.4	non significant
- TLC (% predicted)	100.8±3.3	101.7±2.0	108.3±3.9	non significant
- FEV1 (l)	2.7±0.2	2.4±0.1	3.4±0.3	significant
- FEV1 (% predicted)	90.5±4.3	78.6±3.1	104.6±4.3	significant
- RV (l)	2.0±0.2	2.6±0.1	2.6±0.1	significant
- RV (% predicted)	113.0±7.6	133.3±6.1	133.3±6.1	non significant
- Rtot (l*kPa/s)	0.3±0.0	0.4±0.0	0.4±0.2	non significant
- Rtot (% predicted)	104.7±12.8	118.2±11.9	62.4±4.8	significant

Table 2. No relevant differences in classical echocardiographic parameters between asthma and control groups. P value < 0.05 = significant. LV = left ventricular. RV = right ventricular.

	Mild to-moderate asthma, n=25	Severe asthma, n=47	No asthma= Control, n=20	P value
LV systolic dysfunction	0 (0.0%)	0 (0.0%)	0 (0.0%)	non significant
LV diastolic dysfunction				
grade 0	18 (72.0%)	24 (51.1%)	16 (80.0%)	non significant
grade I	7 (28.0%)	21 (44.7%)	4 (20.0%)	non significant
grade II	0 (0.0%)	2 (4.3%)	0 (0.0%)	non significant
grade III	0 (0.0%)	0 (0.0%)	0 (0.0%)	non significant
RV dysfunction	0 (0.0%)	1 (2.1%)	0 (0.0%)	non significant
Pulmonary hypertension	1 (4.0%)	2 (4.3%)	1 (5.0%)	non significant
Aortic valve insufficiency	2 (8.0%)	3 (6.4%)	0 (0.0%)	non significant

(grades I+II)				
Mitral valve insufficiency (grades I+II)	12 (48.0%)	26 (55.3%)	14 (70.0%)	non significant
Tricuspidal valve insufficiency (grades I+II)	8 (40.0%)	9 (36.0%)	24 (51.1%)	non significant
Pericardial effusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	non significant

Table 3. Blood levels of asthma- and heart dysfunction-associated markers in asthma and control groups. CRP = C-reactive protein, IgE = immunoglobulin E, NT-pro-BNP = NT-pro-brain natriuretic peptide. P value < 0.05 = significant across the groups (ANOVA).

	Mild-to-moderate asthma, n=25	Severe asthma, n=47	No asthma=Control, n=20	P value
CRP (mg/dl)	2.85±0.50	3.39±0.46	1.21±0.37	significant
IgE (IU/ml)	212.06±60.17	795.20±130.26	34.54±16.64	significant
Leukocytes (G/l)	6.72±0.30	7.84±0.32	6.24±0.26	significant
Lymphocytes (%)	27.38±1.08	26.70±1.25	32.15±2.16	significant
Eosinophils (%)	4.07±0.69	3.86±0.43	1.67±0.27	significant
NT-pro-BNP (pg/ml)	50.52±6.28	110.81±28.45	77.85±17.49	non significant