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Authors:

Andreas Kind, Dr. med. (Corresponding Author)
Daniela Zurkan, Ms (Co-author)
Alexandra Maria Chitroceanu, Dr. (Co-author)
Fabian Spinka, Dr. (Co-author)
Lucie Kretzler, Dr. (Co-author)
Alaeddine Slama, Dr. (Co-author)
Edwardo Reynolds, Dr. (Co-author)
Diana Bachran, Dr. (Co-author)
Kristina Franz, Dr. (Co-author)
Bianca Materne, Ms (Co-author)
Theresa Keller, Dr. (Co-author)
Alice Schneider, Dr. (Co-author)
Alessio Alogna, Dr. (Co-author)
Daniel Armando Morris, Dr. (Co-author)
Michael Gotthardt, Prof. Dr. med. (Co-author)
Frank Edelmann, Prof. Dr. (Co-author)

Right Ventricular Free Wall Strain Is Associated with Low-Grade Albuminuria in HFpEF: A Cross-Sectional Cohort Study

Authors

Andreas Kind^{1,2,3}, Daniela Zurkan^{1,2,3}, Alexandra Maria Chitroceanu^{1,2,3}, Fabian Spinka^{1,2,3}, Lucie Kretzler^{1,2,3}, Alaeddine Slama^{1,2}, Edwardo Reynolds^{1,2}, Diana Bachran^{1,2}, Kristina Franz^{1,2,3,4,5}, Bianca Materne^{2,6}, Theresa Keller^{2,6}, Alice Schneider^{2,6}, Alessio Alogna^{1,2,3}, Daniel Armando Morris^{1,2,3}, Michael Gotthardt^{1,2,3,5}, Frank Edelmann^{1,2,3}

Affiliations

¹ Deutsches Herzzentrum der Charité, Klinik für Kardiologie, Angiologie und Intensivmedizin, Augustenburger Platz 1, 13353 Berlin, Germany.

² Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany

³ DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany

⁴ Clinical Research Center, Charité University Medicine Berlin, Berlin, Germany

⁵ Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany

⁶ Institute for Biometry and Clinical Epidemiology (iBike) at Charité, Berlin, Germany

Short title: Right Ventricular Free Wall Strain is Associated with Albuminuria in HFpEF

Corresponding Author:

Andreas Kind, MD

Andreas.Kind@charite.de

+49 17621526466

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Abstract

Introduction

Heart failure with preserved ejection fraction (HFpEF) presents a major health burden worldwide. Up to 40% of HFpEF patients present with elevated urine-albumin-creatinine-ratio levels (UACR). In this subgroup, the risk for adverse cardiovascular (CV) outcomes is increased. Prior studies suggest a correlation between albuminuria and incident heart failure and adverse outcomes even at levels below current clinical thresholds and in the presence of preserved renal function and may mark early cardio-renal and endothelial dysfunction. Whether right ventricular (RV) systolic function, as measured by RV free wall strain (RVFWS), relates to albuminuria in heart failure with preserved ejection fraction (HFpEF) has not been characterized.

Methods

Patients with HFpEF (LVEF $\geq 50\%$, HFA-PEFF score ≥ 5 or invasively elevated filling pressures) and patients of a CKD comparator cohort (CKD $\geq G3$ or $>A1$ and ≥ 1 CV risk factor, without diagnosed HF) were pooled from two cross-sectional cohort studies for this analysis. All patients underwent comprehensive assessment including albuminuria and RVFWS measurement. Albuminuria was categorized by KDIGO stage (A1/A2/A3). RVD was defined by RVFWS $\geq -20\%$, RV FAC $<35\%$ or TAPSE <17 mm. We examined the association between RVFWS and albuminuria using a multivariate linear model with a cohort interaction term and cohort-specific models. Model robustness was assessed by elastic-net regression, bootstrap internal validation, E-value and by adding NT-proBNP, neutrophile count, pulmonary artery systolic pressure and urinary $\alpha 1$ -microglobulin individually in separate sensitivity models. Inter- and intra-observer reproducibility of RVFWS was quantified.

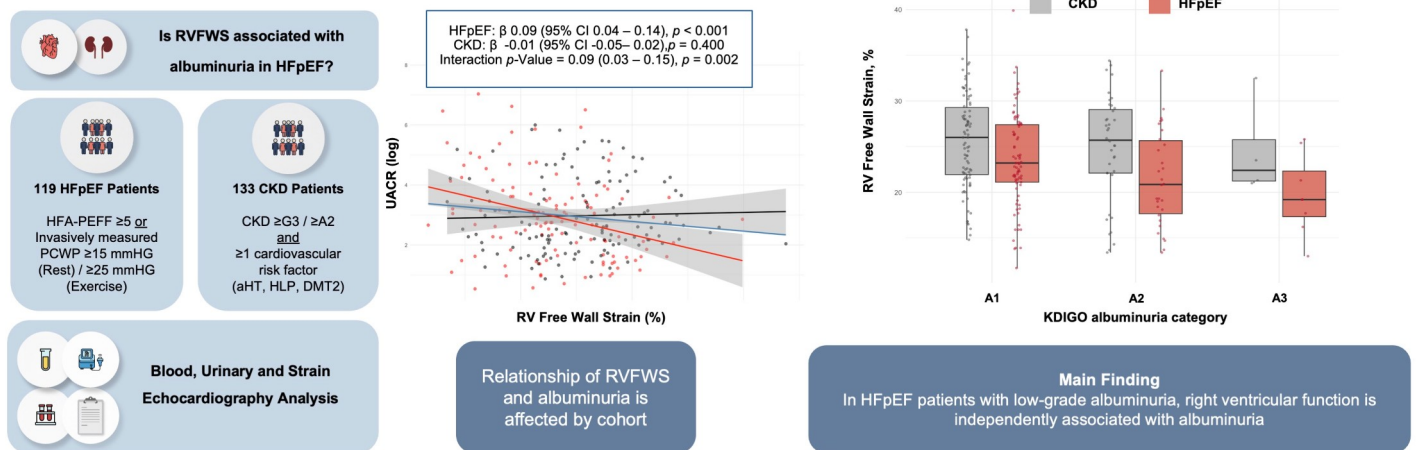
Results

In total, 119 HFpEF and 133 CKD patients were identified. In HFpEF, RVFWS was more impaired (-22.5% vs. -25.7% , $p < 0.001$) and RVD more prevalent (30% vs. 16%). Median UACR lay within the KDIGO A1 range in both cohorts. More impaired RVFWS was associated with higher UACR in HFpEF (adjusted UACR ratio 1.55 per 5% less-negative strain, 95% CI 1.17-2.04, $p=0.002$) but not in the CKD cohort ($p=0.380$), with a significant cohort interaction ($p=0.002$). The association persisted after adjustment in sensitivity models, and RVFWS was retained by penalized regression. Inter- and intra-observer agreement of RVFWS was moderate-to-good (ICC 0.71 and ICC 0.69, respectively).

Conclusion

In ambulatory HFpEF patients with predominantly low-grade albuminuria, RVFWS is associated with UACR independently of clinical confounders, an association not observed in a CKD cohort with CV risk factors and not attenuated after adjustment for estimated PASP.

Graphical Abstract



Introduction

Heart failure (HF) affects about 60 million people worldwide, half of which present with a preserved Ejection Fraction (HFpEF) [1,2]. Compared to heart failure with reduced ejection fraction (HFrEF), HFpEF portends a comparable prognosis for both mortality and risk of hospitalization [3]. However, the heterogeneous nature of HFpEF makes individual risk and prognosis assessment challenging. There is a need for simple, clinically available biomarkers to identify HFpEF patients at elevated risk and guide appropriate therapy.

In HFpEF up to 40% of patients present with albuminuria, with urine-albumin-creatinine-ratio (UACR) linked to congestion [4,5]. Importantly, albuminuria behaves as a continuous risk factor: even subtle increases below the conventional 30 mg/g threshold in patients with preserved glomerular filtration, demonstrated predictive value for incident heart failure, cardiovascular (CV) events and death [5–7]. This has led to the concept of albuminuria as an early, and frequently overlooked, marker of systemic cardio-renal and endothelial dysfunction [5–9]. Moreover, data from HFpEF, chronic kidney disease (CKD) and diabetes patients suggest that therapeutically lowering UACR leads to a decreased risk for adverse CV events [10,11]. Its simple acquisition, prognostic value, and therapeutic modifiability positions UACR as a clinically actionable biomarker for risk stratification and treatment guidance in HFpEF [10–12].

In HFpEF, albuminuria is hypothesized to arise through complex pathomechanisms including but not limited to a systemic pro-inflammatory state that induces microvascular endothelial dysfunction, which may lead to injury of the glomerular basement membrane and impaired albumin reuptake by proximal tubular damage and subsequent elevated activity of the renin-angiotensin-aldosterone system (RAAS) [5,13]. Furthermore,

hemodynamic considerations imply that a combined forward and backward cardiac failure in which venous congestion raises renal interstitial and tubular pressures, thereby lowering the net trans-glomerular filtration gradient [7,14,15]. In light of this, Katz et al. demonstrated a correlation between albuminuria and right ventricular dysfunction (RVD) measured by RV fractional area change (FAC) in HFpEF and further showed a prognostic value of albuminuria [16]. The relatively new deformation imaging analysis of the RV free wall strain (RVFWS), derived from speckle-tracking echocardiography (STE), is supposedly more sensitive in detecting subclinical RV dysfunction [17,18]. To our knowledge, the relationship between RVFWS and albuminuria in HFpEF has not been characterized yet [19]. Moreover, it is unknown whether the association of RVD and albuminuria is HFpEF-specific, or whether albuminuria occurs together with deteriorating RV function throughout CV, renal or metabolic disease.

To address these gaps in knowledge on cardio-renal interaction in HFpEF we investigated the relationship of UACR and RV function assessed by RVFWS in HFpEF patients and compared this to a CKD cohort with cardiovascular risk factors. Secondly, we probed whether this cardio-renal interaction is correlated with renal tubular injury in HFpEF.

Methods

Patient Cohort

Ambulatory patients from the ongoing Screen CardRen (NCT06272578) and CRC1470 (DRKS00032974) cohort studies at the German Heart Centre of Charité were pooled for this analysis. The CRC1470 cohort started in 2021 and included patients with signs and symptoms of HF, a left ventricular ejection fraction (LVEF) $\geq 50\%$, NT-proBNP levels ≥ 125 pg/mL (≥ 365 pg/mL in atrial fibrillation) and signs of functional and/or structural changes associated with

left ventricular diastolic dysfunction or elevated left ventricular filling pressures measured by echocardiography or invasive hemodynamics. Patients with infiltrative or genetic cardiomyopathy, constrictive pericarditis, pulmonary hypertension, severe anemia, end-stage renal disease, severe chronic obstructive pulmonary disease or severe valvular heart disease were excluded. To include unambiguous HFpEF cases from this cohort in our analysis, patients with an HFA-PEFF score ≥ 5 or invasively measured post-capillary wedge pressure (PCWP) ≥ 15 mmHg at rest or ≥ 25 mmHg during peak exertion were included in the HFpEF cohort of this analysis [20]. Patients in this cohort were invited for a baseline visit and followed up with structural telephone visits every 6 months and an in person visit at the clinic after 24 months.

This cohort was compared with a CKD comparator cohort consisting of patients from the cross-sectional Screen CardRen study which started in 2024. Here patients with chronic kidney disease (CKD) $\geq G3$ or $>A1$ and at least one CV risk factor (arterial hypertension, hyperlipidemia or diabetes mellitus) were included. Exclusion criteria comprised a prior diagnosis of HF or cardiomyopathy, implanted cardiac rhythm devices or end-stage renal disease. This cohort was selected as a clinically distinct comparator, in which albuminuria occurs in the context of CKD and CV risk factors. The specific cause of albuminuria was not ascertained in individual patients. Comparing HFpEF with such a cohort, rather than with healthy individuals, allows the RVFWS-albuminuria relationship to be examined against a background of comparable albuminuria arising outside diagnosed heart failure.

Our analysis compares data of the CRC1470 baseline visits with those of the Screen CardRen baseline visits that were available in October 2025.

Clinical and laboratory parameters

Baseline parameters such as patients' age, sex, smoking status, and body mass index (BMI), vital signs and medication were collected, along with a comprehensive medical history. Extensive analyses on blood samples were performed in all patients for creatinine, cystatin C, NT-proBNP, HbA1c, cholesterol levels, hemoglobin, erythrocyte count and leukocyte count. The estimated glomerular filtration rate (eGFR) was estimated based on creatinine levels according to recent guidelines [21]. Chronic kidney disease (CKD) was defined as eGFR <60 ml/min/1.73 m² or Albuminuria with an UACR of >30 mg/g at baseline measurement. In the CKD cohort, patients' clinical records were pre-screened for the same cut-offs, and CKD status was assessed during baseline measurement. Arterial hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at rest or current intake of anti-hypertensive medication. Diabetes mellitus (was defined as HbA1c ≥6.5% or current anti-diabetic medication. Obesity was defined based on a BMI cut-off of 30 kg/m². Anemia was defined as hemoglobin <12 g/dl for women or <13 g/dl for men. Spot urine specimens were used for analysis of urinary excretion of creatinine and albumin. UACR stage cut-offs for normal to mildly increased (<30 mg/g), moderately increased (30 – 300 mg/g) and severe albuminuria (>300 mg/g) are derived from recent guidelines [21]. In the HFpEF cohort data on urinary alpha-1-microglobulin excretion, a marker of tubular damage, were available. UACR and alpha-1-microglobulin values are displayed in milligrams per gram of creatinine.

Echocardiography

All patients underwent comprehensive echocardiographic imaging, including Doppler and tissue Doppler imaging using a commercially available ultrasound system (GE Vivid95, GE HealthCare Technologies, Chicago, USA) at the time of study inclusion. Structure and

function of both the left and right heart were analyzed as recommended by the American Society of Echocardiography [22]. RV size and volume were inferred from RV focused apical four-chamber views. Tricuspid annular plane systolic excursion (TAPSE) was measured on M-mode images of RV focused apical four-chamber views. RV fractional area change (FAC) was calculated using two-dimensional echocardiography of RV-focused apical four-chamber views. Pulmonary artery systolic pressure (PASP) was estimated as described previously [23]. Measurements were done offline using TomTec software (TomTec Version TTA2, TOMTEC Imaging Systems, Unterschleißheim, Germany) by experienced research sonographers (A.C., F.S., D.Z., L.K., A.K.) and supervised by senior investigators with expertise in echocardiographic imaging (F.E.).

Left ventricular global longitudinal strain was assessed from standard apical four-, three-, and two-chamber views and calculated as the average of the three values using TomTec. Left atrial reservoir strain was similarly assessed from apical four- and two-chamber views and calculated as the average of both values using the same software.

RV Free Wall Strain Measurement and RV Dysfunction

A two-dimensional, three-beat RV-focused apical four-chamber view was analyzed offline using TomTec software to infer RV function and strain. RV free wall strain (RVFWS) was assessed by A.C. and A.K. and acquired using TomTec software automatically tracing and averaging three segments (basal, mid, and apical) of the free wall with manual adjustments if necessary [22]. Imaging loops with low image quality or artifacts (i.e. reverberations) obstructing the RV free wall were excluded from analysis. RV dysfunction (RVD) was defined as RVFWS $\geq$ -20%, TAPSE <17 mm, or RV FAC <35% [22].

Statistical Methods

Categorical data are presented as counts (percentages) and continuous data as median $\pm$ interquartile range. Because UACR and NT-proBNP were right-skewed, both were log-transformed for all regression analyses. Albuminuria was categorized by Kidney Disease: Improving Global Outcomes (KDIGO) stage (A1: <30 , A2: $30 - 300$, A3: >300 mg/g) and chronic kidney disease (CKD) by KDIGO CKD-EPI G-classification.

The primary analysis used a pre-defined linear model regressing log-UACR on RVFWS with adjustment for confounding variables (age, sex, diabetes, arterial hypertension, body-mass index and cystatin C). This model was fitted to the full cohort with an RVFWS $\times$ cohort interaction term and separately within the HFpEF and CKD cohorts. Coefficients are reported with 95% confidence intervals, and effect sizes are expressed as adjusted geometric-mean UACR ratios per 5% and per standard-deviation change in RVFWS and for dichotomous RV dysfunction (RVFWS $\geq -20\%$).

Several sensitivity analyses addressed model stability and confounding. Penalized elastic-net regression ($\alpha = 0.5$, 10-fold cross-validation) was applied to a predefined covariate set to assess whether RVFWS was retained under variable selection. The covariate set included RVFWS, age, sex, bmi, arterial hypertension, diabetes mellitus, atrial fibrillation, Cystatin C levels, log-NT-proBNP, E/E' ratio, left atrial volume index, serum cholesterol levels and Neutrophile count. Bootstrap internal validation with 1000 resamples quantified optimism in the model R^2 and the calibration slope. An E-value quantified the strength of unmeasured confounding required to explain the primary association. Because exposure and outcome were both continuous, the E-value was obtained using the approximation of VanderWeele for continuous outcomes in R [24]. The regression coefficient for RVFWS was

standardized to represent a one-standard-deviation increase in RVFWS and divided by the residual standard deviation of log-UACR. This was approximately converted to a risk ratio, after which the E-value was calculated. The same procedure was applied to the confidence-limit estimate closest to the null. This approach assumes that the standardised mean difference approximates a log risk ratio for a dichotomisation of the outcome at an arbitrary threshold. The resulting E-value therefore provides an approximate sensitivity measure for unmeasured confounding and does not address other potential sources of bias, such as measurement error, selection bias, or model misspecification. As an ordinal corroboration, KDIGO albuminuria stage was modelled by proportional-odds logistic regression and the trend in RVFWS across stages tested by the Jonckheere-Terpstra test. The incremental value of RVFWS over the conventional clinical and biomarker base model was assessed for the dichotomous outcome of albuminuria $\geq$ A2 (UACR $\geq$ 30 mg/g) as change in the area under the receiver operating curve (AUC) with the DeLong test.

To evaluate potential effect mediators, NT-proBNP, neutrophil count, as an index of inflammation, PASP and urinary α 1-microglobulin-to-creatinine ratio (A1MCR) were each added separately, in individual models, to the primary HFpEF model. These sensitivity analyses did not constitute formal causal mediation analysis. Because PASP could not be estimated in a proportion of patients (0.8% in HFpEF, 31.6% in CKD), the PASP-adjusted analysis was performed within the HFpEF cohort as a complete-case analysis. An RVFWS-PASP interaction was tested to assess effect modification by estimated pulmonary artery pressure. Statistical significance was defined at a two-sided p -value $\leq$ 0.05. Analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria).

Reproducibility of RVFWS was assessed in randomly selected cases. F.S. was blinded to the primary measurement and re-measured RVFWS for inter-observer agreement. For intra-observer agreement, a primary observer (A.K.) repeated measurements at least two weeks apart from the primary measurement. Agreement was quantified by the intraclass correlation coefficient (ICC (2,1), two-way random effects, absolute agreement, single measures) and Bland-Altman analysis.

Results

Baseline Characteristics

At the time of analysis N = 123 HFpEF and N = 136 CKD patients were identified. In N = 119 (96.7%) HFpEF and N = 133 (97.8%) CKD patients TTE imaging of the right ventricle eligible for free wall strain analysis was available. Of these patients 53% and 54% were female, respectively. Clinical and laboratory parameters stratified by cohort are presented in Table 1. Median UACR levels were within the KDIGO A1 range in both cohorts and albuminuria stages did not differ significantly (HFpEF: A1 = 68%, A2 = 25%, A3 = 7%; CKD: A1 = 68%, A2 = 29%, A3 = 3%). Patients in the CKD comparator cohort demonstrated lower eGFR and higher cystatin C levels despite comparable UACR. HFpEF patients were older and had a higher prevalence of atrial fibrillation and higher NT-proBNP and were treated more frequently with beta blockers and loop diuretics (Table 1).

Echocardiographic Parameters

Echocardiographic measurements for both cohorts are summarized in Table 2, while echocardiographic parameters by albuminuria stage are displayed in Table 2b. HFpEF was associated with signs of LV hypertrophy such as higher LV mass, increased relative wall

thickness as well as LV dilation (i.e. LV end diastolic volume). While LVEF was preserved in all patients, LV systolic function parameters (e.g. LVEF and LV global longitudinal strain) were worse in HFpEF patients. Furthermore, in HFpEF left atrial (LA) dilation and functional impairment (i.e. LA strain) was more prevalent. Similarly, LV diastolic function (i.e. E wave and lateral e' velocities, E/E' ratio) was more impaired and PASP was higher in patients with HFpEF.

RV basal diameter did not differ between groups, but right atrial area was larger in HFpEF (19.9 cm² vs. 16.3 cm²). RVFWS was more positive (i.e. worse) in HFpEF patients compared to CKD comparator patients (-22.5% vs. -25.7%, $p < 0.001$), while RV FAC and TAPSE did not vary meaningfully between both cohorts. In 30% of HFpEF and 16% of CKD patients, RVFWS identified RVD (Table 2). In contrast, RVD prevalence defined by TAPSE or FAC did not vary between groups.

Inter-observer agreement of RVFWS in a random 40-case sample was moderate-to-good (ICC 0.71, 95% CI 0.51 – 0.83, concordance 0.70), with Bland-Altman limits of agreement of -8.3% to +10.5%. Intra-observer agreement in 50 re-measured cases was likewise moderate-to-good (ICC 0.69, 95% CI 0.51 – 0.81, limits of agreement -7.7% to +7.9%).

Relationship of Right Ventricular Free Wall Strain and Albuminuria

In the primary model, more impaired RVFWS was associated with higher log-UACR in HFpEF ($\beta = 0.09$ per 1% less-negative strain, 95% CI 0.04 – 0.14, $p = 0.002$, Table 3 and Figure 1B), corresponding to a 54.6% higher adjusted geometric-mean UACR per 5% change (ratio 1.55, 95% CI 1.17 – 2.04) and a 58.3% higher UACR per standard deviation. Dichotomous RV

dysfunction by RVFWS was associated with a 2.56-fold higher adjusted geometric-mean UACR (95% CI 1.31 – 5.00, $p = 0.007$). In contrast, no such association was present in CKD patients ($\beta = -0.01$, 95% CI -0.05 – 0.02, $p = 0.380$, Table 3). The interaction term for RVFWS and the cohort was significant ($\beta = 0.09$, 95% CI 0.04 – 0.15, $p = 0.002$, Table 3).

Across KDIGO albuminuria stages within HFpEF, median RVFWS became progressively less negative (A1 -23.2%, A2 -20.9%, A3 -19.2%, Jonckheere–Terpstra trend $p = 0.008$, Table 2b and Figure 1A). This trend was not statistically significant in CKD patients ($p = 0.584$). In proportional-odds regression, more impaired RVFWS was associated with higher odds of a higher KDIGO albuminuria stage (OR 1.71 per 5% change, 95% CI 1.13-2.58, $p = 0.011$).

NT-proBNP, estimated PASP, neutrophile count and A1MCR were each added separately to the primary HFpEF model (Table S2). The RVFWS coefficient for albuminuria remained unchanged after addition of log-A1MCR ($\beta = 0.090$, $p < 0.001$) and PASP ($\beta = 0.09$, $p = 0.002$), with no RVFWS-PASP interaction ($p = 0.350$, Table S1). Addition of neutrophile count increased the RVFWS effect by around 10% ($\beta = 0.10$, $p < 0.001$). Finally, after addition of log-NT-proBNP the coefficient was 22% smaller ($\beta = 0.068$, $p = 0.024$).

RVFWS was retained alongside cystatin C, log-NT-proBNP and neutrophil count in cross-validated elastic-net regression over the full prespecified candidate set. Bootstrap internal validation indicated modest optimism (apparent R^2 0.17, optimism-corrected 0.06, calibration slope 0.81), consistent with the sample size. On the approximate risk-ratio scale corresponding to a one-standard-deviation change in RVFWS (RR 1.34), the E-value was 2.02, and 1.48 for the confidence limit nearer the null. An unmeasured confounder would need to be associated with both RVFWS and UACR by at least a risk ratio of this magnitude, beyond the measured covariates, to explain the association. Multivariable logistic regression showed

an association of RVFWS with higher odds of UACR elevation above 30 mg/g (Albuminuria $\geq$ A2) in the HFpEF cohort (OR 1.12 (95% CI 1.02 – 1.24), $p = 0.013$, Table 4). This did not translate to improved discrimination for the dichotomous threshold UACR ≥ 30 mg/g over the baseline model without RVFWS (Δ AUC 0.68 $\rightarrow$ 0.71; DeLong $p = 0.364$).

Discussion

This cross-sectional analysis examined the relationship between RV systolic function measured by RVFWS and albuminuria in ambulatory HFpEF patients and a CKD cohort with CV risk factors. In HFpEF patients with predominantly low-grade albuminuria, more impaired RVFWS was associated with higher UACR independently of standard clinical confounders, which was not observed in CKD patients. The difference between cohorts was supported by a significant interaction.

Our regression models demonstrated divergent correlates of elevated UACR in the two cohorts. In CKD patients, diabetes and impaired glomerular function were correlated with albuminuria, consistent with prior studies demonstrating that hyperglycemia induces glomerular hyperfiltration, leading to progressive glomerular damage and subsequent albuminuria [25]. In these patients, RV function was not associated with UACR, despite similarly elevated albuminuria levels. Conversely, more impaired RVFWS was associated with higher UACR in HFpEF patients. This effect modification, supported by a significant RVFWS-cohort interaction, indicates that the correlates of albuminuria differ between an established HFpEF phenotype and a cohort in which albuminuria arises in the context of hypertension and diabetes. Because the CKD cohort was chosen as a comparator cohort with cardiovascular risk factors rather than a matched control and comparability of baseline characteristics was limited, this observation is hypothesis-generating. Furthermore, when comparing renal function and albuminuria levels between both cohorts, we noticed worse glomerular-filtration markers (cystatin C) in the CKD cohort despite comparable albuminuria levels. This may suggest that low-grade albuminuria reflects congestion and endothelial dysfunction rather than chronic kidney disease in HFpEF.

Our findings align with and extend the work of Katz et al., who described an association between RV function assessed by fractional area change and albuminuria and its prognostic relevance in HFpEF [16]. We show that subtle changes in RV systolic function, captured by deformation-based RVFWS, are associated with UACR in HFpEF, and that this association persisted after adjustment for a urinary tubular-injury marker. Comparing HFpEF with a CKD cohort of similar albuminuria allowed the correlates of albuminuria to be characterised across the cardio-renal disease spectrum. Taken together, these findings are consistent with recent evidence that RVFWS tracks disease severity in HFpEF [26].

Mechanistically, renal venous congestion is a recognized determinant of albuminuria, as demonstrated in experimental models, where renal vein ligation increases venous pressure and disrupts glomerular barrier integrity [7,27]. The resulting reduction in trans glomerular filtration pressure promotes RAAS activation, which may induce endothelial and tubular injury [7,28]. In HFpEF, chronically elevated right-sided filling pressures and impaired RV systolic function may promote backward transmission of venous pressure to the kidneys. In this scenario RVFWS represents a plausible surrogate for this hemodynamic axis. Contrary to this expectation, the association was neither attenuated by adjustment for estimated PASP nor modified by it (interaction $p = 0.350$). This should be interpreted cautiously and does not establish independence from backward pressure transmission. PASP reflects pulmonary rather than systemic venous pressure, whereas renal congestion is driven more directly by right atrial and central venous pressure, which were not measured invasively. Consistent with an incomplete hemodynamic explanation, atrial fibrillation did not influence the RVFWS-UACR relationship, despite its known hemodynamic effects.

Beyond hemodynamics, the cardio-renal interaction leading to albuminuria may involve inflammatory and neurohormonal processes, as well as glomerular and tubular cross-talk. Under normal conditions the small amount of albumin filtered across the glomerular filtration barrier is reabsorbed in the early proximal tubule through endocytosis and returned to the circulation. In this way albuminuria reflects the balance between filtration-barrier integrity and tubular resorptive capacity [29]. When the barrier is disrupted or tubular reabsorption is overwhelmed, increased albumin handling promotes intrarenal inflammation, tubular injury, and activation of the renin-angiotensin-aldosterone system with sodium and water retention that further aggravates congestion [29]. In heart failure these pathways may converge. Retrograde transmission of elevated central venous pressure increases renal interstitial hydrostatic pressure and, together with endothelial dysfunction and comorbidity-related inflammation, produces the glomerular-tubular injury described as congestive nephropathy. Low-grade albuminuria in HFpEF may thus integrate glomerular, tubular, inflammatory and hemodynamic contributions rather than marking a single mechanism.

To probe these pathways, candidate markers were added individually to the HFpEF model (Table S2). The RVFWS–UACR association was essentially unchanged after adjustment for A1MCR and estimated PASP. The coefficient was 22% smaller after adjustment for log-NT-proBNP, and increased moderately by 10% after adjustment for neutrophile count. Therefore NT-proBNP, as a marker for congestion, was correlated with a moderately attenuated RVFWS-UACR association, while the fairly low increase of this relation by neutrophile count might resemble statistical noise rather than a biological correlation. It is important to note is that, such analyses cannot quantify the contribution of an individual mechanistic pathway. Also, these markers are nonspecific and may be influenced by outside

effectors not accounted for in our models and single-variable adjustment cannot separate direct from indirect effects or exclude mediator-outcome confounding, and we did not undertake formal causal mediation. We therefore interpret these results only as the association not being fully explained by any single marker. Systemic inflammation, indexed by neutrophil count, was an independent correlate of albuminuria in HFpEF but was not associated with RVFWS and did not attenuate the RVFWS-UACR association. RV dysfunction and inflammation therefore appear to be separate correlates of albuminuria rather than sharing a similar pathomechanism, in keeping with the comorbidity-inflammation paradigm in HFpEF [13,30].

In our analysis, RVFWS classified RVD more frequently than TAPSE or FAC in the HFpEF cohort, consistent with the proposed greater sensitivity of deformation imaging to subclinical RV dysfunction reported previously [17]. However, in the absence of an independent reference standard for RV function, we cannot exclude that the higher detection rate partly reflects measurement variability rather than true sensitivity. Several features of RVFWS reinforce this caution and currently limit its clinical applicability. The proposed cut-offs of -20% used here, was conceived as a pragmatic consensus-based threshold for RVD rather than from pathophysiological or outcome-based anchors, and the generalisability is uncertain [22]. Strain estimates also depend on vendor-specific software and are influenced by the ultrasound system, image quality and patient factors. Consistent with these concerns, reproducibility in our study was moderate-to-good (inter-observer ICC 0.71, intra-observer ICC 0.69). Because the readers were blinded to albuminuria, this measurement error is expected to be non-differential and to bias the RVFWS-UACR association toward the null. Nonetheless, with reproducibility that was only moderate-to-good, measurement variability may affect both the magnitude and the precision of the

estimated association, and its direction cannot be assumed in a sample of this size. Individual RVFWS values, particularly those close to the -20% cut-off, should therefore be interpreted with caution, and reliance on any single measurement or threshold is not warranted.

Because both RVD and albuminuria are established prognostic markers in HFpEF, a better understanding of their relationship may ultimately help characterise cardio-renal risk, although our cross-sectional data do not support clinical risk stratification. Some evidence suggests that albuminuria-lowering therapy improves renal and, to a lesser extent, cardiovascular endpoints [11,31], but these data derive from CKD and type 2 diabetes populations. Therefore, the effect of albuminuria reduction in HFpEF remains to be studied. Longitudinal studies relating the RVFWS–UACR association to disease severity and heart-failure outcomes are needed to clarify a mechanism linking RV mechanics and albuminuria.

Limitations

Several limitations should be noted. First, the cross-sectional, exploratory design precludes causal inference and outcome association and render our findings as hypothesis-generating. Second, the CKD cohort, although free of diagnosed heart failure, already carried substantial CV and renal disease burden, elevated natriuretic peptides and subclinical RV changes, and may include pre-HFpEF (stage A/B) phenotypes. Since our study did not include HFrEF, HFmrEF, pulmonary-hypertension or alternative congestive comparators, the specificity of the association to HFpEF cannot be firmly established. CKD was, moreover, ascertained from baseline assessments that did not match KDIGO criteria for chronicity in both cohorts. Because persistence beyond three months could not be documented, the KDIGO G- and A-categories reported here reflect a single time point and may misclassify transient reductions in eGFR or transient albuminuria. Third, albuminuria was assessed from

a single spot UACR, which is known to be subject to substantial within-individual variability. Our estimates should be interpreted accordingly. Fourth, PASP could be estimated non-invasively in only part of the CKD cohort, so the pulmonary-pressure analysis was confined to HFpEF. Fifth, as discussed previously, RVFWS is technically demanding, is influenced by the vendor and software used and its reproducibility was only moderate-to-good, particularly near the RV-dysfunction cutoff. Finally, the sample size, relative to the number of candidate covariates and the low prevalence of higher albuminuria stages, limits precision despite penalized and bootstrap validation. Larger, longitudinal studies are needed to confirm these findings.

Conclusion

In ambulatory HFpEF patients with predominantly low-grade albuminuria, more impaired RV free wall strain was associated with higher urinary albumin excretion independently of standard clinical confounders. This association was not observed in a cardiovascular/CKD comparator cohort and furthermore was not attenuated after adjustment for PASP. These hypothesis-generating findings identify RV systolic function as a candidate correlate of early cardio-renal dysfunction in HFpEF that warrants confirmation in larger, longitudinal cohorts.

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Statement of Ethics

Both studies were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants at study inclusion for participation and pseudonymized data analysis. Both studies were approved by the Ethics Committee of Charité University Medicine Berlin (Screen CardRen: EA4/257/23; SFB1470: EA1/224/21).

Conflict of Interest Statement

A.K. declares honoraria for lectures from AstraZeneca GmbH. All other authors declare no conflicts of interest.

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Author Contributions

A.K.: Conceptualization, Data Curation, Formal Analysis, Methodology, Investigation, Resources, Visualization, Writing – Original Draft, Writing – Review & Editing. D.Z.: Conceptualization, Investigation, Project Administration. A.M.C.: Conceptualization, Investigation. F.S.: Investigation, Formal Analysis, Writing – Review & Editing. L.K.: Investigation, Formal Analysis, Writing – Review & Editing. A.Slama: Investigation, Formal Analysis, Writing – Review & Editing. E.R.: Data Curation, Methodology. D.B.: Project Administration, Writing – Review & Editing. K.F.: Project Administration, Writing – Review & Editing. B.M.: Data Curation, Methodology. T.K.: Data Curation, Methodology. A.Schneider: Data Curation, Methodology. A.A.: Supervision, Writing – Review & Editing. D.A.M.: Supervision, Writing – Review & Editing. M.G.: Supervision, Writing – Review & Editing. F.E.: Supervision, Funding Acquisition, Writing – Review & Editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to legal and ethical restrictions (patient privacy, institutional data governance, and the terms of ethics approval). Anonymized data may be made available upon reasonable request to the corresponding author, subject to approval by the Ethics Committee of Charité University Medicine Berlin and applicable data protection regulations.

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Figures

Figure 1 Caption: A) Box plots for right ventricular free wall strain stratified by KDIGO albuminuria category in each cohort and B) scatter plot with univariate linear regression of log-UACR and RV free wall strain for the full cohort with and by cohort

Figure 1 Legend: Abbreviation: CI = Confidence Interval, RV = right ventricle, HFpEF = Heart Failure with preserved Ejection Fraction

Table 1. Patient and Laboratory Parameters

Characteristic	CKD Cohort N = 133 ¹	HFpEF Cohort N = 119 ¹	p-value ²
Age (years)	73 ± 11	76 ± 7	0.018
Female	72 (54%)	63 (53%)	0.8
Body Mass Index (kg/m ²)	26.7 ± 5.0	26.9 ± 5.8	0.6
Coronary Artery Disease	44 (35%)	53 (45%)	0.11
Atrial Fibrillation	22 (17%)	75 (63%)	<0.001
Myocardial Infarction	20 (15%)	26 (22%)	0.2
Stroke	11 (8.3%)	19 (16%)	0.063
Anemia	27 (20%)	23 (19%)	0.8
Myocardial Infarction	20 (15%)	26 (22%)	0.2
Obese	35 (26%)	35 (29%)	0.6
Arterial Hypertension	113 (86%)	96 (81%)	0.3
Hyperlipidemia	104 (80%)	92 (77%)	0.6
Diabetes Mellitus	50 (38%)	31 (26%)	0.037
Active Smoker	18 (14%)	13 (11%)	0.5
Angiotensin Receptor Inhibitor	58 (44%)	54 (45%)	0.8
Angiotensin Converting Enzyme Inhibitor	30 (23%)	23 (19%)	0.5
Calcium Antagonist	46 (35%)	43 (36%)	0.8
Mineralocorticoid Receptor Antagonist	8 (6.0%)	5 (4.2%)	0.5
Beta Blocker	68 (51%)	93 (78%)	<0.001
Loop Diuretic	22 (17%)	37 (31%)	0.006
NT-proBNP (ng/L)	195 ± 734	473 ± 515	<0.001
HbA1c (%)	6.00 ± 1.08	5.80 ± 0.81	0.073
Cystatin C (mg/L)	1.30 ± 0.54	1.07 ± 0.28	<0.001
Creatinine (mg/dL)	1.17 ± 8.20	0.89 ± 0.29	<0.001
eGFR (mL/min/1.73m ²)	54 ± 16	69 ± 17	<0.001
Urine Albumin/Creatinine Ratio (mg/g)	14 ± 178	16 ± 330	0.9
KDIGO Albuminuria Category			0.3
A1	90 (68%)	81 (68%)	
A2	39 (29%)	30 (25%)	
A3	4 (3.0%)	8 (6.7%)	
KDIGO CKD GFR Category			<0.001
G5	0 (0%)	0 (0%)	
G4	4 (3.0%)	2 (1.7%)	
G3b	26 (20%)	9 (7.6%)	
G3a	66 (50%)	21 (18%)	
G2	32 (24%)	74 (62%)	
G1	5 (3.8%)	13 (11%)	
¹ Values are shown as median ± SD or n (%), as appropriate. Units are provided in parentheses.			
² Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test			

Table 2a: Echocardiographic parameters by cohort

Characteristic	HFpEF Cohort N = 119¹	At-Risk Cohort N = 133¹	p-value²
Left Ventricular Ejection Fraction (%)	56.0 (52.1 - 60.0)	58.1 (54.2 - 61.6)	0.036
LV Internal Diameter in Diastole (mm)	47.9 (44.0 - 53.0)	47.9 (44.3 - 52.7)	0.8
Interventricular Septal Thickness in Diastole (mm)	13.00 (11.69 - 15.00)	11.01 (9.77 - 12.20)	<0.001
Posterior Wall Thickness in Diastole (mm)	11.00 (9.90 - 13.00)	7.00 (6.00 - 8.65)	<0.001
Relative Wall Thickness	0.46 (0.38 - 0.55)	0.30 (0.25 - 0.35)	<0.001
LV Mass (Devereux Formula) (g)	221 (185 - 269)	152 (123 - 186)	<0.001
LV Mass Index (g/m ²)	114 (101 - 130)	80 (67 - 95)	<0.001
LV End-Diastolic Volume (mL)	109 (89 - 130)	99 (81 - 118)	0.003
LV End-Diastolic Volume Index (mL/m ²)	58 (46 - 68)	52 (45 - 61)	0.005
LV Global Longitudinal Strain (%)	-16.8 (-18.7 - -14.8)	-18.2 (-20.1 - -16.1)	<0.001
Left Atrial Diameter (mm)	43 (40 - 48)	35 (32 - 38)	<0.001
Left Atrial Volume Index (mL/m ²)	46 (39 - 55)	29 (22 - 36)	<0.001
Left Atrial Reservoir Strain (%)	18 (11 - 22)	29 (22 - 36)	<0.001
Mitral E Wave Velocity (cm/s)	82 (69 - 96)	66 (53 - 79)	<0.001
Mitral A Wave Velocity (cm/s)	66 (43 - 84)	71 (57 - 85)	0.2
Mitral e' Septal (cm/s)	6.16 (5.00 - 8.00)	6.54 (5.30 - 8.01)	0.8
Mitral e' Lateral (cm/s)	7.30 (6.00 - 9.00)	8.41 (6.80 - 10.80)	0.003
E/e' Ratio	11.4 (9.2 - 13.7)	9.0 (7.3 - 11.1)	<0.001
Tricuspid Regurgitation Vmax (m/s)	2.74 (2.42 - 2.97)	2.46 (1.96 - 2.67)	<0.001
Pulmonary Artery Systolic Pressure (mmHg)	34 (28 - 40)	27 (19 - 33)	<0.001
Right Atrial Pressure (mmHg)	3 (3 - 8)	3 (3 - 3)	0.2
RV Basal Diameter (mm)	38 (35 - 43)	37 (35 - 42)	0.15
Right Atrial Area (cm ²)	19.9 (16.3 - 23.0)	16.0 (12.8 - 19.4)	<0.001
RV Free Wall Longitudinal Strain (%)	-22.5 (-27.2 - -19.1)	-25.7 (-29.2 - -21.9)	<0.001
Tricuspid Annular Plane Systolic Excursion (mm)	23.0 (20.0 - 26.8)	22.2 (20.4 - 24.9)	0.2
RV Fractional Area Change (%)	43 (37 - 47)	43 (39 - 46)	0.4
RV Dysfunction by RVFWS	36 (30%)	21 (16%)	0.006
RV Dysfunction by TAPSE	10 (8.4%)	13 (10%)	0.6
RV Dysfunction by RV FAC	16 (16%)	11 (10%)	0.2
¹ Values are shown as median (interquartile range), as appropriate. Units are provided in parentheses.			
² Wilcoxon rank sum test; Pearson's Chi-squared test			

Table 2b. Echocardiographic Parameters by KDIGO Albuminuria Stage

Characteristic	Cohort	A1 ¹	A2 ¹	A3 ¹	p-value ²
Right Ventricular Free Wall Strain (%)	HFpEF	-23.2 ± 5.2	-20.9 ± 5.2	-19.2 ± 4.4	0.008
	CKD	-26.0 ± 5.5	-25.7 ± 5.8	22.4 ± 5.4	0.584
Fractional Area Change (%)	HFpEF	44 ± 8	44 ± 9	36 ± 7	0.227
	CKD	42 ± 7	41 ± 8	50 ± 4	0.751
TAPSE (mm)	HFpEF	23.0 ± 4.0	23.0 ± 4.2	20.8 ± 6.4	0.5812
	CKD	22.6 ± 3.7	21.7 ± 4.7	22.0 ± 4.0	0.209
TAPSE/PASP Ratio	HFpEF	0.70 ± 0.27	0.60 ± 0.25	0.65 ± 0.19	0.152
	CKD	0.84 ± 0.84	0.99 ± 1.07	0.73 ± 0.60	0.596
Pulmonary Artery Systolic Pressure (mmHg)	HFpEF	32 ± 12	36 ± 9	35 ± 11	0.155
	CKD	28 ± 10	23 ± 14	33 ± 15	0.287
TR Vmax (m/s)	HFpEF	2.67 ± 0.51	2.85 ± 0.33	2.74 ± 0.41	0.065
	CKD	2.50 ± 0.61	2.26 ± 0.76	2.75 ± 0.99	0.495
E/E' Ratio	HFpEF	10.9 ± 4.2	11.9 ± 3.4	12.0 ± 3.0	0.340
	CKD	8.57 ± 3.14	9.77 ± 4.49	10.60 ± 1.98	0.020
Left Atrial Volume Index (mL/m ²)	HFpEF	46 ± 16	44 ± 15	43 ± 11	0.999
	CKD	28 ± 9	30 ± 8	37 ± 9	0.122
Left Atrial Strain (%)	HFpEF	20 ± 9	12 ± 11	20 ± 8	0.291
	CKD	30 ± 9	27 ± 1	24 ± 14	0.340
Right Atrial Area (cm ²)	HFpEF	19.8 ± 5.6	20.0 ± 7.4	18.6 ± 5.4	0.803
	CKD	16.3 ± 4.5	15.5 ± 6.2	18.9 ± 5.1	0.798
¹ Values are shown as median ± SD or n (%), as appropriate. Units are provided in parentheses.					
² Jonckheere-Terpstra-Test					

Table 3. Multivariable linear regression for log-UACR

	Full cohort (interaction)			HFpEF Model			CKD Model		
Characteristic	Beta ¹	95% CI	p-value	Beta ¹	95% CI	p-value	Beta ¹	95% CI	p-value
RV Free Wall Strain (%)	-0.01	-0.05, 0.03	0.6	0.09** *	0.04, 0.14	<0.001	-0.01	-0.05, 0.02	0.4
HFpEF	2.6***	1.1, 4.0	<0.001						
Age (years)	0.00	-0.02, 0.02	0.8	-0.01	-0.05, 0.03	0.7	0.00	-0.02, 0.02	>0.9
Male	-0.28	-0.60, 0.04	0.083	-0.35	-0.91, 0.21	0.2	-0.25	-0.63, 0.14	0.2
Diabetes Mellitus	0.60***	0.25, 0.95	<0.001	0.25	-0.40, 0.89	0.5	0.84***	0.45, 1.2	<0.001
Arterial Hypertension	0.23	-0.33, 0.78	0.4	0.19	-0.65, 1.0	0.6	0.35	-0.43, 1.1	0.4
Body Mass Index (kg/m ²)	-0.04*	-0.07, -0.01	0.013	-0.04	-0.09, 0.02	0.2	-0.04	-0.07, 0.00	0.067
Cystatin C (mg/L)	1.2***	0.83, 1.6	<0.001	1.4**	0.37, 2.4	0.008	1.2***	0.80, 1.5	<0.001
RV Free Wall Strain (%) X HFpEF	0.09**	0.03, 0.15	0.002						
¹ p<0.05; **p<0.01; ***p<0.001									
Abbreviations: *p<0.05; **p<0.01; ***p<0.001. CI = confidence interval; RV = right ventricle., CI = Confidence Interval, HFpEF = Heart Failure with preserved Ejection Fraction,									

Figure 1

