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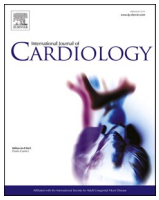

Inflammasome pathway component expressions in myocardial samples of advanced heart failure patients treated with novel heart failure pharmacotherapies

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ABSTRACT

Background: The inflammasome pathway has been implicated in the progression of heart failure (HF). Preclinical studies suggest that angiotensin receptor–neprilysin inhibitor (ARNi) and sodium–glucose cotransporter-2 inhibitor (SGLT2i) therapies may attenuate inflammasome activation, yet evidence in the failing human myocardium remains sparse. Hence, we evaluated the associations between ARNi and SGLT2i therapies and myocardial priming of inflammasome pathway components in explanted hearts from heart transplantation (HTX) recipients.

Methods: Biobank samples from the left ventricular myocardium of 104 HTX recipients were analyzed. The mRNA and protein expression of inflammasome-related targets (absent in melanoma 2 [AIM2], NLR family pyrin domain containing 3 [NLRP3], caspase-1, gasdermin D, and nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB]) were quantified using qRT-PCR and Western blotting. Multivariable linear regression models were applied to assess the relationships between inflammasome component expression and clinical variables, including treatment with ARNi and SGLT2i.

Results: ARNi and SGLT2i therapies were associated with lower mRNA expression of AIM2, NLRP3, caspase-1, and NF-κB in univariate analyses. However, after adjustment for clinical covariates, these associations with inflammasome-related transcripts were no longer statistically significant. In multivariable models, only female sex, diabetes, time since heart transplantation, and serum potassium concentration remained associated with myocardial inflammasome pathway expression.

Conclusions: In myocardial samples from patients with advanced HF, no clear differences in the expression of selected inflammasome priming-related targets were observed between treatment eras before and after the introduction of ARNi and SGLT2i therapies, despite their experimentally suggested anti-inflammatory effects, warranting further investigation.

1. Introduction

Growing evidence implicates the inflammasome pathway as an important mediator in heart failure (HF) development, suggesting new, yet still investigational treatment opportunities. In patients with HF and reduced ejection fraction (EF), angiotensin receptor-neprilysin inhibitor (ARNi) and sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapies reduce the risk of cardiovascular death and HF events compared with earlier regimens [1,2]. Emerging experimental data suggest that attenuation of inflammasome signaling may contribute to these clinical benefits [3,4]. However, evidence from human myocardial tissue confirming these pathways remains limited. Therefore, we examined the

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association between inflammasome pathway component expression and contemporary pharmacotherapy in myocardial samples from patients with HF.

2. Methods

The investigation conformed to the Declaration of Helsinki and was approved by institutional and national ethics committees (ETT TUKEB 7891/2012/EKU (119/PI/12) for collection/storage; ETT TUKEB IV/10161–1/2020 for processing). Written informed consent was obtained from all patients. Human left ventricular (LV) tissue samples (standardly taken from the anterior region) from advanced HF patients undergoing heart transplantation (HTX) were obtained from the Transplantation Biobank of the Heart and Vascular Center, Semmelweis University, Budapest [5]. Samples were snap-frozen in liquid nitrogen and stored at −80 °C immediately after explantation. Clinical data were retrieved from the Biobank database.

Patients receiving uninterrupted guideline-directed medical therapy (GDMT) of HF (ARNi or angiotensin-converting enzyme inhibitor (ACEi), beta blocker, mineralocorticoid receptor antagonist in all patients and SGLT2i in a subset after its introduction into HF management) for ≥3 months pre-HTX at target or maximally tolerated doses were included. Exclusion criteria were mechanical or pharmacological circulatory support ≥3 months pre-HTX; non-viable anterior LV region in patient history; diseases causing myocardial deposits, systemic inflammation, fibrosis; documented non-compliance; investigational drugs.

Our molecular targets included two inflammasome sensors expressed in the heart, NLR family pyrin domain containing 3 (NLRP3) and absent in melanoma 2 (AIM2) [6]; common inflammasomal effector proteins, caspase-1 and gasdermin D (GSDMD); and an upstream activator, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB, P65/*RELA* subunit). Both mRNA and protein expressions were measured. Briefly, following RNA isolation, RNA quality control and cDNA library construction from frozen LV samples (Qiagen, Germany), qRT-PCR analysis was conducted (TaqMan Gene Expression Assay, Applied Biosystems, USA) per manufacturer instructions and a previously described protocol [5]. mRNA expressions were calculated using the CT comparative method, normalized to GAPDH and a positive calibrator, and expressed as $2^{-\Delta\Delta CT}$. Protein expressions were assessed with Western blot (Bio-Rad system, USA; antibodies from Cell Signaling Technology, USA), according to the distributor's protocol, as reported previously [7]. Optical densities of targets were normalized to GAPDH as a loading control, and relative expression levels were further normalized to the mean of a reference group of samples without ARNi or SGLT2i treatment included on each membrane.

Associations between marker expression levels (mRNA and protein) and selected clinical parameters – including age, sex, body mass index (BMI), diabetes, hypertension, ischemic etiology of HF, atrial fibrillation, 'time since HTX' (interval between HTX and sample analysis, used as a proxy for treatment era to capture the time-dependent improvement in HF care), implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy, New York Heart Association (NYHA) functional class, LV end-diastolic diameter, LVEF, and the following laboratory parameters: white blood cell count (WBC), C-reactive protein (CRP), potassium, bilirubin, and creatinine – as well as treatment with ARNi and SGLT2 inhibitors, were evaluated using linear regression. First, associations were examined in univariable linear regression models, with each clinical parameter as the independent variable and the respective inflammasome marker (mRNA or protein) as the dependent variable. Subsequently, multivariable linear regression models were constructed including prespecified covariates based on prior knowledge (sex, BMI, diabetes, hypertension, ischemic etiology of HF, atrial fibrillation, NYHA class, WBC, CRP, creatinine), with additional variables demonstrating an association at $P \leq 0.15$ in univariable analyses. Inflammasome markers were log-transformed before analysis. In all models, we performed complete case analysis, as missing data were minimal, confined to total bilirubin (4/104, 3.8%), serum potassium (7/104, 6.7%), and LV end-diastolic diameter (3/104, 2.9%). Residuals were inspected for linearity using residual-versus-fitted plots. Confidence intervals for regression coefficients were derived from a nonparametric case-resampling bootstrap with 1000 repetitions, with a fixed random-number seed to ensure reproducibility. No relevant multicollinearity was detected (variance inflation factor < 5). $P < 0.05$ (two-sided) was considered statistically significant. Analyses were performed using Stata, version 18 (StataCorp, USA).

3. Results

Among 542 patients who underwent HTX between January 16, 2013, and November 22, 2024, 104 met the eligibility criteria for this study. Median age was 54 years, 70 patients (67%) were male. Most patients had nonischemic HF etiology (83%) with a median LVEF of 23%. 49 patients (47%) were treated with ARNi, the remaining 55 received ACEi. On top of triple GDMT, 34 (33%) patients received SGLT2i. Among these patients, 30 (88%) were treated with ARNi and 4 (12%) with ACEis. Median CRP was 2.5 mg/L, median WBC was 8.2 × 10^9/L and median procalcitonin was 0.04 μg/L (Table 1).

In univariable analyses, lower mRNA expressions of AIM2, NLRP3 (with borderline significance for ARNi), caspase-1, and NF-κB were associated with both ARNi and SGLT2i therapies, whereas higher GSDMD and lower NLRP3 protein expression were associated with ARNi

Table 1
Patient characteristics.

	Patients
n	104
Age – Yr	54 (47–61)
Female sex – No. (%)	34 (33)
Body mass index	27 (24–30)
Etiology of heart failure – No. (%)	
Ischemic cardiomyopathy	18 (17)
Non-ischemic	86 (83)
NYHA functional class – No. (%)	
I	1 (1)
II	13 (13)
III	76 (73)
IV	14 (13)
Hypertension– No. (%)	55 (53)
Diabetes mellitus – No. (%)	23 (22)
ICD – No. (%)	88 (85)
CRT – No. (%)	44 (42)
ACEi treatment – No. (%)	55 (53)
ARNi treatment – No. (%)	49 (47)
SGLT2i treatment – No. (%)	34 (33)
BB treatment – No. (%)	104 (100)
MRA treatment – No. (%)	104 (100)
LVEF – %	23 (19–28)
LVEDD – mm	71 (62–79)
Potassium – mmol/L	4.3 (4.1–4.6)
Total bilirubin – mmol/L	11.0 (6.7–16.1)
Creatinine – mmol/L	103 (90–133)
Estimated GFR – mL/min/1.73m^2	63 (51–76)
CRP – mg/L	2.5 (1.1–5.4)
WBC – x10^9/L	8.2 (6.4–9.5)
Procalcitonin – mg/L	0.04 (0.02–0.07)
Time since HTX – Yr	3.9 (1.1–5.3)

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HTX, heart transplantation; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter 2 inhibitor; WBC, white blood cell count.
Values are median (IQR). No missing data were present, except for total bilirubin (4/104, 3.8%), potassium (7/104, 6.7%), and LVEDD (3/104, 2.9%).

therapy (Table 2). After adjustment for clinically and statistically relevant covariates in multivariable linear regression models, none of these associations remained significant (Table 2). Other independent predictors of higher inflammasome expression were female sex (NLRP3 mRNA, AIM2 and caspase-1 protein expressions), time since HTX (AIM2, caspase-1 and NF-κB mRNA expressions), serum potassium level (AIM2, caspase-1, GSDMD, NLRP3 and NF-κB mRNA expressions) and diabetes (caspase-1 mRNA expression) (Table 2).

4. Discussion

To the best of our knowledge, this is the first study to examine the myocardial expression of inflammasome pathway components in relation to novel pharmacotherapies of HF in real-world patients. In our previous work, we found significant associations between ARNi and SGLT2i therapies and myocardial fibrosis in a similar patient cohort of advanced HF patients undergoing HTX, even after adjusting for relevant clinical variables [5]. Beyond their antifibrotic effects, both ARNi and SGLT2i therapies are also postulated to inhibit the inflammasome pathway, which, according to recent evidence, plays a crucial role in the pathogenesis of HF [3,4,6]. Nevertheless, our study could not confirm that the introduction of newer HF pharmacotherapies with anti-remodeling properties may translate into meaningful modulation of myocardial inflammasome priming, while not ruling out anti-inflammatory effects through unassessed mechanisms. Still, the need for inflammation-targeted HF therapies remains unmet, ongoing studies are already evaluating inflammasome-directed strategies, including those focused on the well-characterized NLRP3 pathway and the more recently implicated AIM2 sensor protein [8,9]. In addition, shared pathway components such as caspase-1, gasdermin D, and the upstream regulator NF-κB are being explored as potential therapeutic targets [10–12].

Among the clinical variables, aside from ARNi and SGLT2i treatment, only female sex, higher serum potassium levels, diabetes and a longer interval between HTX and sample analysis (“time since HTX”) were independently associated with increased expression of inflammasome-related targets. Each of these associations is biologically plausible. Sex differences in inflammatory signaling are well documented, including in inflammasome pathways [13,14]. The role of inflammasomes is also well established in diabetes-associated cardiovascular disease [15]. Multiple mechanisms may underlie the relationship with serum potassium. Potassium efflux is a known trigger of NLRP3 activation [16,17], although our data capture inflammasome priming rather than activation. Worsening renal function also emerges as a correlate but is unlikely to fully explain this finding given the lack of association with creatinine, and the stable use of MRAs and RAAS inhibitors argues against potassium simply serving as a surrogate for background therapy. Taken together, the coexistence of elevated serum potassium and increased inflammasome component expression likely reflects a severe, catabolic heart failure phenotype characterized by pronounced neurohormonal and inflammatory overactivation.

A longer time since HTX implies that patients were transplanted in an earlier era of HF management; therefore, the lower levels of myocardial inflammation observed in more recently transplanted patients may plausibly reflect advances in contemporary HF care and guideline-directed therapies. No technical factors are likely to account for these differences, as sampling and storage protocols remained unchanged over time.

5. Limitations

Transplantation biobanks provide a unique opportunity to analyze myocardial tissue from patients with advanced HF, but this study design is accompanied by several important limitations. First, our findings cannot be generalized to earlier HF stages. Second, this nonrandomized cohort represents a highly selected patient population without matched positive or negative control groups, preventing the determination of the extent and nature of inflammatory activation in the studied tissue specimens. We sought to mitigate these limitations by applying strict selection criteria, enrolling a relatively large sample, and using multivariable statistical models. Third, we assessed only a limited set of molecular targets within the broader inflammasome pathway, and changes in their expression predominantly reflect pathway priming rather than definitive activation. Therefore, further studies across the HF spectrum, incorporating direct measures of inflammasome activation and a broader panel of targets, are needed to better define the anti-inflammasome effects of ARNi and SGLT2i therapies.

6. Conclusion

In myocardial samples from patients with advanced HF undergoing HTX, ARNi and SGLT2i therapies were not independently associated with lower expression of the inflammasome pathway-associated proteins AIM2, NLRP3, gasdermin D, caspase-1, or NF-κB after adjustment for statistically and clinically relevant covariates in multivariable regression analyses.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used *ChatGPT (OpenAI, version current as of March 2026)* for language editing. After using this tool the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Dávid Nagy: Writing – original draft, Visualization, Project administration, Investigation, Data curation. **Zsófia Onódi:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrea Kovács:** Investigation, Data curation. **Tímea Bálint:** Writing – review & editing, Validation, Supervision, Methodology. **Zoltán Horváth:** Writing – review & editing, Project administration, Investigation, Data curation. **Attila Oláh:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Alex Ali Sayour:** Writing – review & editing, Validation, Supervision, Software, Methodology, Conceptualization. **Bálint András Barta:** Visualization, Validation, Software, Formal analysis. **Péter Ferdinandy:** Validation, Supervision, Resources, Funding acquisition. **Tamás Radovits:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Béla Merkely:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition. **Zoltán Varga:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Mihály Ruppert:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Table 2
Linear regression analysis for inflammasome pathway protein expressions and clinical parameters.

	mRNA expression										Protein expression									
	AIM2		Caspase-1		Gasdermin D		NF-κB		NLRP3		AIM2		Caspase-1		Gasdermin D		NF-κB		NLRP3	
	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Univariate linear regression																				
ARNi therapy	−0.37 (−0.63 to −0.11)	0.005	−0.44 (−0.67 to −0.21)	<0.001	0.12 (−0.13 to 0.37)	0.338	−0.24 (−0.46 to −0.02)	0.033	−0.19 (−0.40 to 0.01)	0.058	−0.01 (−0.04 to 0.03)	0.787	−0.05 (−0.12 to 0.01)	0.110	0.11 (0.02 to 0.20)	0.019	0.01 (−0.10 to 0.13)	0.796	−0.06 (−0.12 to −0.01)	0.022
SGLT2i therapy	−0.30 (−0.56 to −0.03)	0.030	−0.43 (−0.66 to −0.20)	<0.001	0.02 (−0.17 to 0.21)	0.811	−0.18 (−0.37 to −0.00)	0.052	−0.25 (−0.46 to −0.04)	0.023	−0.02 (−0.06 to 0.02)	0.257	−0.07 (−0.15 to 0.01)	0.104	0.03 (−0.06 to 0.13)	0.510	−0.07 (−0.20 to 0.07)	0.331	−0.04 (−0.11 to 0.02)	0.153
Multivariable linear regression																				
ARNi therapy	0.03 (−0.41 to 0.46)	0.906	−0.04 (−0.46 to 0.37)	0.837	0.19 (−0.28 to 0.66)	0.434	0.06 (−0.37 to 0.50)	0.771	0.24 (−0.13 to 0.60)	0.200	0.03 (−0.02 to 0.07)	0.247	−0.02 (−0.10 to 0.07)	0.710	0.03 (−0.12 to 0.17)	0.735	0.07 (−0.10 to 0.23)	0.434	−0.06 (−0.13 to 0.02)	0.142
SGLT2i therapy	0.16 (−0.33 to 0.64)	0.526	0.07 (−0.31 to 0.44)	0.728	−0.03 (−0.53 to 0.46)	0.892	0.25 (−0.18 to 0.68)	0.253	−0.08 (−0.44 to 0.29)	0.683	−0.05 (−0.10 to 0.01)	0.119	0.01 (−0.09 to 0.11)	0.884	−0.07 (−0.24 to 0.10)	0.413	−0.09 (−0.27 to 0.09)	0.320	0.03 (−0.08 to 0.13)	0.595
Sex (male)									−0.34 (−0.59 to −0.08)	0.009	−0.05 (−0.09 to −0.01)	0.027	−0.07 (−0.13 to −0.00)	0.038						
Time since HTX (per 1 year change)	0.13 (0.04 to 0.21)	0.004	0.12 (0.04 to 0.20)	0.003			0.10 (0.02 to 0.19)	0.014												
Potassium (per 1 mmol/L change)	0.42 (0.06 to 0.78)	0.022	0.34 (0.05 to 0.63)	0.022	0.46 (0.07 to 0.86)	0.021	0.43 (0.10 to 0.76)	0.010	0.48 (0.16 to 0.80)	0.003										
Diabetes mellitus			0.35 (0.01 to 0.68)	0.041																

AIM2, absent in melanoma 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; ARNi, angiotensin receptor-neprilysin inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; HTX, heart transplantation. n = 104. Outcome variables were base-10 logarithmically transformed prior to analysis. The β parameter (depicted with 95% confidence interval) represents both the direction and magnitude of the change in the outcome variable in the linear regression model, resulting from a one-unit increase in the predictor variable. Each multivariable model contained clinically relevant parameters (sex, body mass index, diabetes, hypertension, ischemic heart disease, atrial fibrillation, New York Heart Association stage, serum creatinine and C-reactive protein, white blood cell count), as well as parameters with a $P \leq 0.15$ significance in the univariate analyses.
For clarity, only the associations with pharmacotherapies and the significant associations with other clinical parameters in the multivariable analyses are shown in the table.

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Declaration of competing interest

The authors have nothing to declare.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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