HDL Protein Composition in Patients with Heart Failure with Preserved Ejection Fraction and End-Stage Renal Disease

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Background

Heart failure with preserved ejection fraction (HFpEF) is a pathophysiologically complex disease with intertwined contributing factors including systemic inflammation and metabolic disturbances such as dyslipidemia. Advanced disease stages are characterized by post-capillary pulmonary hypertension and often chronic kidney disease (CKD) further propagating the inflammatory state and disease progression. CKD and HFpEF may share pivotal pathophysiological pathways (both indicative and causally involved in these diseases) and the majority of patients with advanced CKD suffer from cardiac dysfunction. The protein composition of high-density lipoprotein (HDL) is severely altered in high cardiovascular risk diseases including end-stage renal disease (ESRD) and is associated with cardiovascular outcome in dialysis patients. Therefore, we assessed HDL quality by analysis of two critical HDL proteins, serum amyloid A (SAA) associated with systemic inflammation and surfactant protein B (SP-B) involved in pulmonary congestion that may reflect common diseases pathways of HFpEF and ESRD.

Methods

Serum from patients with HFpEF (n=145) diagnosed according to current ESC guidelines (1. signs and symptoms of heart failure, 2. left ventricular ejection fraction > 50% and 3. evidence of abnormal left ventricular relaxation, filling or diastolic stiffness) and ESRD patients on hemodialysis (CHD, n=85) was analyzed.

HDL-bound SAA and SP-B were quantified directly from serum by a novel ELISA assay developed in our laboratory. SAA and SP-B levels were then correlated with functional and clinical parameters of both patient cohorts and their association with a composite endpoint of cardiac events and/or mortality in the HFpEF cohort was assessed.

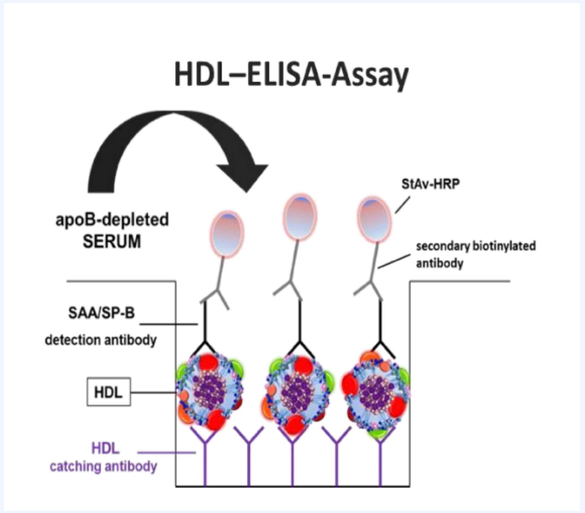


Figure 1: ELISA-Assay Principle.

Patient characteristics

Demographic and laboratory characteristics

	HFpEF patients	CHD patients	*p*
n	145	82	
Gender, n (% female)	96 (66.2%)	29 (35.4%)	
Age (years)	70.8 (8.7)	57.1 (17.2)	**<0.001**
BMI (kg/m2)	30.8 (6.1)	26.0 (4.6)	**<0.001**
RR systolic (mmHg)	140.0 (21.5)	140.0 (23.5)	0.997
RR diastolic (mmHg)	79.5 (12.9)	74.5 (15.3)	**0.003**
NT pro-BNP (pg/ml)	1066 [491-1971]	5383 [2127-18514]	**<0.001**
Serum creatinine (mg/dl)	1.3 (0.8)	9,2 (2,8)	**<0.001**
eGFR (ml/min/1.73m2)	58.8 (19.2)	6,4 (2,4)	**<0.001**
CRP (mg/dl)	0.92 (1.7)	1,2 (1,9)	**0.048**
Total Cholesterol (mg/dl)	173.0 (41.4)	162.0 (42.4)	**0.013**
Triglycerides (mg/dl)	138.0 (76.5)	161.0 (95.5)	**0.035**
HDL Cholesterol (mg/dl)	49.3 (15.5)	40.6 (16.3)	**<0.001**
LDL Cholesterol (mg/dl)	99.7 (37.6)	90.3 (34.2)	**0.018**
HbA1c (%)	6.2 (1.0)	5.3 (1.1)	**<0.001**

Data are shown in mean (SD) or median [IQR] if not indicated otherwise. BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RR, blood pressure.

Echocardiographic parameters

	HFpEF patients	CHD patients	*p*
n	145	82	
Ultrasound parameters			
Left atrial diameter (mm)	62.2 (7.5)	57.6 (8.7)	**<0.001**
Left ventricular diameter (mm)	44.0 (5.6)	47.4 (5.9)	**<0.001**
Right atrial diameter (mm)	62.5 (9.1)	56.6 (8.3)	**<0.001**
Right ventricular diameter (mm)	36.4 (8.0)	31.6 (5.7)	**<0.001**
Left ventricular ejection fraction (%)	59.2 (7.0)	/	
IVS (mm)	12.9 (2.4)	14.8 (2.9)	**<0.001**
sPAP (mmHg)	58.7 (17.7)	41.6 (11.5)	**<0.001**

Data are given in means (SD). IVS, intraventricular septum; sPAP, systolic pulmonary arterial pressure.

Body composition

	HFpEF patients	CHD patients	*p*
n	145	82	
BCM measurement			
Overhydration (l)	0.8 (1.5)	2.4 (2.0)	**<0.001**
Overhydration (% ECW)	3.9 (7.5)	12.5 (9.7)	**<0.001**
Overhydration post HD (l)	/	0.3 (2.4)	
Overhydration post HD (% ECW)	/	1.1 (12.6)	
Total body water (l)	37.4 (8.0)	38.5 (7.5)	0.335
Extracellular water (l)	18.3 (3.9)	18.6 (3.3)	0.403
Intracellular water (l)	19.3 (4.3)	19.8 (4.7)	0.492
Lean tissue mass (kg)	37.0 (10.4)	41.2 (12.2)	0.037
Adipose tissue mass (kg)	45.1 (16.6)	31.6 (15.5)	**<0.001**

Data are given in means (SD). ECW, extracellular water; HD, hemodialysis.

HDL proteins in HFpEF and ESRD patients

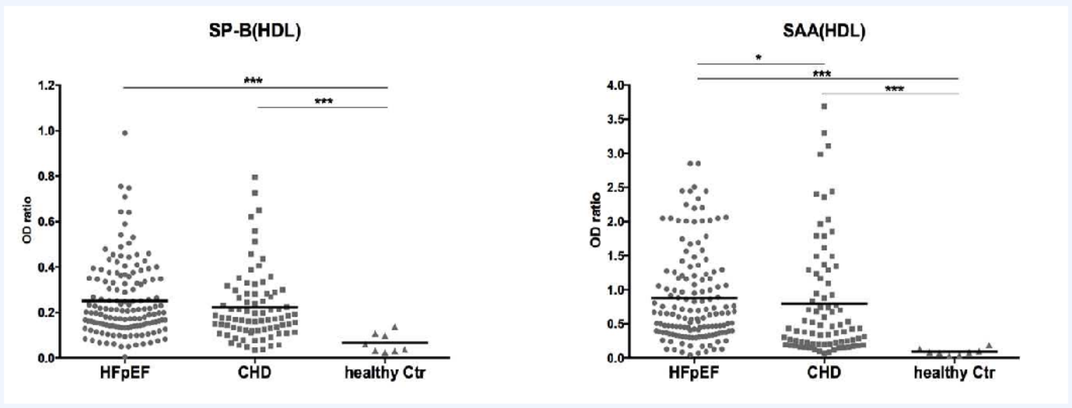


Figure 2: HDL-associated SP-B and SAA are elevated in HFPEF and ESRD patients. The levels of (A) SP-B and (B) SAA on HDL of HFpEF patients (n=145), ESRD patients (n=85) and healthy controls (n=8) were measured by a newly developed ELISA.

Variables associated with HDL proteins

Variables associated with SAA(HDL)

	HFpEF patients (n = 145)	CHD patients (n = 82)
SAA(HDL)	0.66 [0.38-1.2]	0.43 [0.21-1.18]
Age		
r	-0.08	0.26
p	0.335	**0.019**
eGFR		
r	-0.19	-0.16
p	**0.026**	0.889
CRP		
r	0.43	0.43
p	**<0.001**	**<0.001**
HbA1c		
r	0.06	0,23
p	0.496	**0,039**
Intraventricular septum thickness		
r	-0.12	0,26
p	0.145	**0,023**

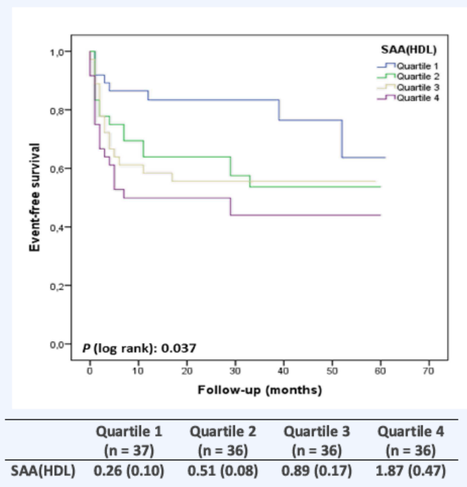
r, Spearman correlation coefficient. SAA(HDL) values are shown as median [IQR]. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

Variables associated with SP-B(HDL)

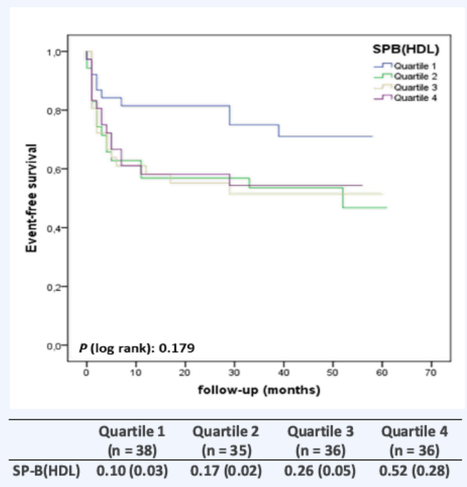
	HFpEF patients (n = 145)	CHD patients (n = 82)
SP-B(HDL)	0.21 [0.14-0.35]	0.18 [0.12-0.28]
Age		
r	0.12	**0.50**
p	0.168	**<0.001**
Body mass index		
r	**-0.17**	0.12
p	**0.04**	0.306
Left atrial diameter		
r	-0.06	**0.48**
p	0.490	**<0.001**
Right atrial diameter		
r	-0.04	0.39
p	0.638	**0.001**
Right ventricular diameter		
r	-0.03	0.29
p	0.749	**0.012**
Systolic pulmonary arterial pressure		
r	-0.01	**0.53**
p	0.904	**0.003**

r, Spearman correlation coefficient. SP-B(HDL) is shown as median [IQR].

SAA(HDL) and SP-B(HDL):predictive of CV outcome in HFpEF



	Quartile 1 (n = 37)	Quartile 2 (n = 36)	Quartile 3 (n = 36)	Quartile 4 (n = 36)
SAA(HDL)	0.26 (0.10)	0.51 (0.08)	0.89 (0.17)	1.87 (0.47)



	Quartile 1 (n = 38)	Quartile 2 (n = 35)	Quartile 3 (n = 36)	Quartile 4 (n = 36)
SP-B(HDL)	0.10 (0.03)	0.17 (0.02)	0.26 (0.05)	0.52 (0.28)

Figure 3: Prognostic effect of HDL-bound Serum Amyloid A [SAA(HDL)] or Surfactant protein B [SP-B(HDL)] on a composite of cardiac hospitalization and/or cardiac death. Kaplan-Meier Curves according to quartiles of SAA(HDL) or SP-B(HDL) across the entire study population. SAA(HDL) and SP-B(HDL) were divided into quartiles based on ratios normalized values. Data are shown as mean (SD)

CONCLUSION

SP-B(HDL) and SAA(HDL) are predictive of CV outcome in HFpEF

HDL quality reflects pathophysiological changes in HFpEF, comparable to ESRD

SAA(HDL) emerges as potential predictor of CKD progression in HFpEF

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