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Nitric Oxide Bioavailability and Adiponectin Production in Chronic Systolic Heart Failure: Relation to Severity of Cardiac Dysfunction

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Abstract

Adiponectin is an anti-inflammatory, anti-atherogenic adipokine elevated in heart failure (HF) that may protect against endothelial dysfunction by influencing underlying nitric oxide bioavailablity. In this study, we examine the relationship between plasma adiponectin levels and measures of nitric oxide bioavailability and myocardial performance in patients with chronic systolic HF. In 139 ambulatory patients with stable, chronic systolic HF (left ventricular [LV] ejection fraction 40%, New York Heart Association [NYHA] class I to IV), we measured plasma levels of adiponectin, asymmetric dimethylarginine (ADMA) and global arginine bioavailability (GABR), and performed comprehensive echocardiography with assessment of cardiac structure and performance. Adverse events (all-cause mortality or cardiac transplantation) were prospectively tracked for a median of 39 months. Plasma adiponectin levels directly correlated with plasma ADMA levels (Spearman's r=0.41, p<0.001) and NT-proBNP levels (r=0.55, p<0.001), inversely correlated with GABR (r= −0.39, p<0.001), and were not associated with hsCRP (p=0.81) or MPO (p=0.07). Interestingly, increased plasma adiponectin levels remained positively correlated with plasma ADMA levels only in patients with elevated NT-proBNP levels (r= 0.33, p=0.009). Higher

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plasma adiponectin levels were associated with worse LV diastolic dysfunction (rank sums p=0.002), RV systolic dysfunction (rank sums p=0.002), and RV diastolic dysfunction (rank sums p=0.011), but not after adjustment for plasma ADMA and NT-proBNP levels. Plasma adiponectin levels predicted increased risk of adverse clinical events (HR [95% CI]: 1.45 [1.02–2.07], p=0.038) but not after adjustment for plasma ADMA and NT-proBNP levels, or echocardiographic indices of diastolic or RV systolic dysfunction. In patients with chronic systolic HF, adiponectin production is more closely linked with nitric oxide bioavailability than inflammation, and appears to be more robust in the setting of cardiac dysfunction or elevated natriuretic peptide levels.

Keywords

Congestive heart failure; adiponectin; ADMA; natriuretic peptides; diastolic dysfunction

INTRODUCTION

Adiponectin is an adipocyte-derived hormone (or "adipokine") that plays a fundamental role in regulation of inflammation and energy homeostasis. Previous studies have identified adiponectin as a potent anti-inflammatory, anti-atherogenic, anti-oxidant and insulin-sensitizing cytokine reduced in the setting of cardiovascular disease, obesity, and diabetes mellitus.[1,2] Increasing mechanistic evidence supports a direct role for adiponectin as a protective factor against endothelial dysfunction. Low adiponectin levels have been linked to impaired endothelium-dependent vasodilation,[3] and adiponectin has been found to stimulate NO production via AMP-kinase-mediated endothelial nitric oxide synthase (NOS) phosphorylation.[4,5] Recent data have also reported that adiponectin inhibits endothelial cell accumulation of the endogenous NOS inhibitor, asymmetrical dimethylarginine (ADMA), through increased activity of the ADMA degrading enzyme dimethylarginine dimethylaminohydrolase.[6] In renal transplant recipients, low gene expression of adiponectin in visceral fat tissue was directly linked to increased plasma ADMA levels and development of endothelial dysfunction.[7] Recent reports have also linked low 25-hydroxyvitamin D_3 levels to elevated ADMA levels and endothelial dysfunction[8], while parallel reports have described low 25-hydroxyvitamin D_3 levels to be linked to low plasma adiponectin levels and postulate 1,25-dihydroxyvitamin D_3 positively regulates adiponectin gene expression [9,10].

We have previously reported that evidence of systemic inflammation and endothelial dysfunction were both associated with LV diastolic dysfunction, elevated natriuretic peptide levels, and adverse long-term clinical outcomes in patients with chronic systolic heart failure.[11,12] Recent data have revealed that natriuretic peptides directly enhance adipocyte adiponectin production[13–15] and that adiponectin may be synthesized by and released from the failing heart itself as a compensatory response in proportion to the extent of cardiac dysfunction.[16,17] We therefore hypothesize that in patients with chronic systolic heart failure, production of adiponectin may be closely associated with determinants of natriuretic peptide release (i.e. degree of left ventricular (LV) diastolic dysfunction or right ventricular (RV) systolic dysfunction). We aim to further explore the determinants of counter-regulatory responses mediated by adiponectin by examining the potential contributions of systemic inflammation (measured by C-reactive protein) and endothelial dysfunction (measured by ADMA) on adiponectin production in the setting of cardiac insufficiency.

METHODS

Study design and population

This analysis is part of the neurohormonal sub-study of Assessment of Doppler Echocardiography in Prognosis and Therapy (ADEPT) study, a single-center, prospective cohort study.[18] This study was approved by the Cleveland Clinic Institutional Review Board, and informed consent was obtained from all subjects. Briefly, 139 ambulatory subjects with stable, chronic systolic heart failure (LV ejection fraction 40%, NYHA functional class I-IV) underwent echocardiographic evaluation of systolic and diastolic performance with plasma sample collection. Glomerular filtration rate was calculated using the standard 4-variable Modification of Diet in Renal Disease equation.[19] Plasma NT-proBNP levels were assayed using a commercially available assay (Roche Elecsys® proBNP assay, Roche Diagnostics, Indianapolis IN). Plasma high-sensitivity C-reactive protein (hsCRP) was determined by the particle-enhanced immunonephelometry assay (Siemens Healthcare Diagnostics, Deerfield IL). Plasma myeloperoxidase (MPO) was determined by enzyme-linked immunosorbent assay (CardioMPO, Cleveland Heart Labs, Cleveland OH). The composite endpoint of clinical events (all-cause mortality or cardiac transplantation) was prospectively tracked for a median of 39 months by scheduled telephone calls as previously described.[18]

Transthoracic echocardiography

Comprehensive transthoracic echocardiography was performed using commercially available HDI 5000 (Phillips Medical Systems, N.A., Bothell, Washington) and Acuson Sequoia (Siemens Medical Solutions USA Inc., Malvern, Pennsylvania) machines. Two-dimensional and color Doppler imaging was performed in standard parasternal and apical views. Diastolic indices (including pulse-wave Doppler, color M-mode [CMM], and tissue Doppler imaging) were acquired over ten consecutive beats using sweep speeds of 50 and 100 cm/s using previously described techniques.[18,20] Classification of diastolic stage was determined as follows: (1) *Stage I (impaired relaxation)* consists of mitral E/A <1, deceleration time (DT) >220 ms, pulmonary vein S/D >1, color M-mode propagation velocity (Vp) <45 cm/s; (2) *Stage II (pseudonormal)* shows mitral E/A 1–2, pulmonary vein S/D <1, DT <220 ms, Vp <45 cm/s; (3) *Stage III (restrictive)* gives mitral E/A >2, pulmonary vein S/D <1, DT <150 ms, Vp <45 cm/s. The LV ejection fraction and cardiac volumes were measured using Simpson's biplane method. Right ventricular (RV) systolic dysfunction was qualitatively determined by visual assessment (on a scale of 0 to 4+). All ventricular volume measurements were indexed to body surface area. Measurements were averaged over three cycles (five cycles for atrial fibrillation), and measured by two experienced individuals prior to analyses of the neurohormonal data.

Plasma adiponectin and arginine metabolomic assays

All samples were collected using EDTA-plasma vacuum collecting tubes, processed and immediately frozen in aliquots at −80°C until analyzed. Plasma adiponectin levels were determined by the adiponectin sandwich enzyme-linked immunosorbent assay (Quantikine, R&D Systems). This assay demonstrated a minimum detection limit (as calculated by interpolation of the mean plus two standard deviations) of 0.025 μg/mL, with a within-run variation of 3.5%. Normal control values for plasma adiponectin have been reported to be 1.9–17 μg/mL.[21] Arginine metabolomic profiles were measured as previously described.[11] In brief, each sample solution was injected onto a HPLC column and ADMA, L-arginine, L-ornithine, and L-citrulline levels were quantified by LC/ESI/MS/MS analysis using an ABI 365 triple quadrupole mass spectrometer (Applied Biosystems Inc., Foster City, CA, USA) with Ionics EP 10+ redesigned source (Concord, Ontario, Canada) and electrospray ionization (ESI) needle connected to an Aria LX4 series multiplexed HPLC system with

Flux pumps (Cohesive Technologies, Franklin, MA). Global arginine bioavailability ratio (GABR) was calculated as the quotient of L-arginine levels and the sum of L-ornithine plus L-citrulline levels. The imprecision of measurement for ADMA was 8.1%. The accuracy of measurement of ADMA was 99.2%.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation if normally distributed, and as median and interquartile range [IQR] if non-normally distributed. Normality was assessed by the Shapiro-Wilk W test. Spearman's rank correlation method was used as a nonparametric measure of association for correlations between plasma adiponectin levels and clinical and echocardiographic indices. For multiple regression analysis, a stepwise variable selection procedure was used to select variables significantly related with plasma adiponectin levels with a probability of 0.1 to enter or leave. Natural logarithmic transformations were applied to non-normally distributed variables. The Wilcoxon or Kruskal-Wallis (rank sums) tests were used to compare differences in plasma adiponectin levels across categorical variables. The Cox proportional hazards model was used to assess the clinical risk of all-cause mortality or cardiac transplantation associated with increasing continuous standardized increments of natural logarithm-transformed plasma adiponectin levels. The proportional hazards assumption was verified with log(time) vs. long[−log(survival)] plots. All-cause mortality and cardiac transplantation were followed for a median of 39 months. All p-values reported are from two-sided tests and a p-value <0.05 was considered statistically significant. For multiple hypothesis testing correction, we recommend considering Bonferroni correction with a significance level of α/n, but note the increased risk for type II error. Statistical analyses were performed using JMP 9.0.0 (SAS Institute, Cary, NC).

RESULTS

Plasma Adiponectin Levels in Study Population

In our study cohort, the mean and median plasma adiponectin levels were 14 ± 13 μg/mL and 10.4 [5.6, 18.1] μg/mL respectively, in similar ranges as previously reported.[22,23] Mean and median plasma ADMA levels were 0.47 ± 0.15 μM and 0.45 [0.36, 0.56] μM, respectively (Table 1). In our overall study cohort, plasma adiponectin levels were inversely correlated with BMI (Spearman's r = −0.32, p<0.001) and eGFR (r = −0.25, p=0.004), and directly associated with increasing age (r = 0.29, p<0.001) and plasma NT-proBNP levels (r = 0.55, p<0.0001). Plasma adiponectin levels were not associated with gender (p=0.34). Plasma adiponectin levels were significantly higher in patients with ischemic versus non-ischemic heart failure etiology (12.5 [7.6, 20.4] versus 9.2 [4.4, 16.8] μg/mL, p=0.034). Plasma adiponectin levels were also significantly lower in patients on beta-blocker therapy (8.2 [5.3, 14.6] versus 13.6 [8.0, 24.1] μg/mL, p=0.006), but this association was not significant after adjustment for NT-proBNP levels or echocardiographic indices of cardiac performance (p>0.10).

Plasma Adiponectin Levels in Myocardial Structure and Performance

Table 2 presents the relationship between plasma adiponectin levels and echocardiographic indices of cardiac structure and function. There were no statistically significant correlations between plasma adiponectin levels and cardiac structure and LV ejection fraction. In contrast, plasma adiponectin levels were directly correlated with indices of left ventricular diastolic dysfunction, including mitral inflow E/A ratio (r = 0.19, p = 0.027), mitral E/septal Ea ratio (r = 0.27, p = 0.002), and large left atrial volume index (r = 0.27, p=0.006) (Table 2). Higher plasma adiponectin levels were also directly associated with overall increasing LV diastolic dysfunction stage (rank sums p=0.002). Increasing plasma adiponectin levels

were also associated with echocardiographic indices of right-sided dysfunction, including high RV systolic dysfunction stage (rank sums p=0.002), high RV diastolic dysfunction stage (rank sums p=0.011), high pulmonary artery systolic pressure (r = 0.22, p=0.031), large right atrial volume index (r = 0.42, p<0.0001), large tricuspid regurgitant jet area (r = 0.33, p <0.001), tricuspid E/A ratio (r = 0.19, p=0.032), tricuspid DT (r = −0.20, p=0.028), and low hepatic vein S/D ratio (r = −0.35, p<0.001).

Inflammation and Arginine Bioavailability as Determinants of Plasma Adiponectin Levels

Overall, plasma adiponectin levels were positively correlated with plasma ADMA levels (Spearman's r = 0.41, p<0.0001) and inversely correlated with GABR (Spearman's r = −0.39, p<0.0001), including after adjustment for age, BMI, gender, eGFR, diabetic status, and heart failure etiology (Standardized [Std] β = 0.37, p<0.0001, and Std β = −0.36, p<0.001, respectively). After adjustment for plasma NT-proBNP, plasma adiponectin levels were not associated with plasma ADMA (Std β = 0.09, p=0.280) and only modestly associated with GABR (Std β = −0.17, p=0.050). In stepwise multiple regression analysis, plasma NT-proBNP and BMI were independently associated with plasma adiponectin levels (p<0.0001 and p=0.004, respectively; Table 2).

Figure 1 presents the relationship between plasma adiponectin and ADMA levels in our overall study cohort and subgroups stratified by median NT-proBNP. Plasma adiponectin levels remained significantly associated with plasma ADMA levels in patients with high (above median levels of) plasma NT-proBNP (r = 0.33, p=0.009) but not low plasma NT-proBNP (r=0.21, p=0.096). Plasma levels of adiponectin remained associated with ADMA in patients with preserved renal function (eGFR 60 ml/min/1.73 m^2); (r = 0.047, p<0.001). This was similar when stratified according to diastolic dysfunction (Figure 2). In contrast, overall plasma adiponectin levels did not demonstrate any clear relationships with hsCRP (r = −0.02, p = 0.81) or MPO (r= 0.16, p=0.07).

Plasma Adiponectin Levels and Prognosis

In Cox proportional hazard analysis, natural logarithm-transformed adiponectin demonstrated increased risk for adverse clinical events (unadjusted HR 1.45, 95% CI: 1.02 – 2.07, p=0.038). In multivariate Cox proportional hazard analysis, natural logarithm-transformed plasma adiponectin predicted risk independent of age, BMI and diabetic status (HR 1.55, 95% CI: 1.08 – 2.23, p = 0.038). However, plasma adiponectin levels did not demonstrate independent prognostic value when adjusted for echocardiographic indices of LV diastolic function, indices of RV systolic or diastolic function, plasma NT-proBNP levels, or plasma ADMA levels (Table 3).

DISCUSSION

Over the past decade, there has been a growing understanding of the role of metabolic factors, in particular adipokines, in the pathophysiology of heart failure. In this study, we report a direct association between higher plasma levels of adiponectin and greater impairment of diastolic dysfunction and right ventricular systolic dysfunction in patients with chronic systolic heart failure. Furthermore, we observed a link between circulating adiponectin levels and the degree of underlying nitric oxide bioavailability (either in the form of substrate-product balance as measured by GABR, or the presence of endogenous NO synthase inhibitor as measured by ADMA) rather than with measures of systemic inflammation (as measured by MPO or hsCRP) in the setting of cardiac insufficiency. Remarkably, these correlations were stronger with increasing disease severity as indicated by higher NT-proBNP levels. These findings support the potential role of adiponectin as a

counter-regulatory response to cardiac insufficiency rather than a metabolic mediator of disease progression.

The relationship between adiponectin levels and cardiac dysfunction is complex. Adiponectin has been found to be present in damaged cardiomyocytes,[16] and is thought to be upregulated in response to signals of local inflammatory and oxidative stress[24] as well as sensors of energy imbalance.[25,26] Recent reports have also revealed that adiponectin may be synthesized by and released from the failing heart itself in proportion to the extent of LV dysfunction[16,17] and that natriuretic peptides enhance adipocyte adiponectin synthesis.[13–15]

In our overall study cohort, plasma adiponectin also was directly associated with increasing overall LV diastolic dysfunction stage and with individual echocardiographic indices of diastolic dysfunction, as has been previously reported. These findings confirm previous reports of a direct association between plasma adiponectin and NT-proBNP levels, and corroborate recent findings of a direct association between increased plasma adiponectin levels and echocardiographic indices of LV diastolic dysfunction in patients with hypertrophic cardiomyopathy.[27] In addition, we demonstrate for the first time new associations between increased plasma adiponectin levels and echocardiographic estimates of right ventricular systolic and diastolic dysfunction, including RAVi, hepatic vein S/D ratio, tricuspid E/A ratio, and tricuspid DT. RAVi, as a measure of the chronicity of RV diastolic function over time,[28] was associated with plasma adiponectin levels independent of plasma NT-proBNP levels. Hepatic congestion secondary to right-sided failure may increase plasma adiponectin levels independent of plasma natriuretic peptide levels as the liver is the primary site of clearance of adiponectin.[29] In addition, plasma adiponectin levels may be independently raised in response to metabolic derangements. Tricuspid regurgitation and increased estimated pulmonary arterial systolic pressure are known to correlate with hepatic congestion and malnutrition.[30] In fact, tricuspid regurgitation itself may be an accentuating and accelerating risk factor for cardiac cachexia on account of a greater hypoalbuminemia and hyponatremia, which presumably results from the associated protein-losing enteropathy.[31]

In direct contrast to previous reports of an inverse correlation between plasma adiponectin and ADMA levels in the non-heart failure setting, our data indicate a direct correlation between plasma adiponectin and ADMA levels. Since increased adiponectin levels have been reported to attenuate the TNFα-mediated decrease in the activity of the ADMA degrading enzyme, dimethylarginine dimethylaminohydrolase,[6,7] our data imply that natriuretic peptide enhanced upregulation of adipocyte adiponectin production is a counter-regulatory effect in response to underlying endothelial dysfunction that is likely contributing to or associated with cardiac insufficiency. In support of this possible mechanistic link, the positive association we observed between plasma adiponectin and ADMA levels in this study population was not independent of plasma NT-proBNP levels, and in subgroup analysis, was preserved only in patients with above-median NT-proBNP levels alone. Furthermore, plasma adiponectin levels were not predictive of long-term clinical outcomes independent of plasma NT-proBNP levels, plasma ADMA levels, or echocardiographic indices of diastolic dysfunction. In contrast, no such relationships were observed between plasma adiponectin levels and C-reactive protein, a marker of systemic inflammation shown to provide independent prognostic value in heart failure.[12]

Study Limitations

Different isoforms of adiponectin, including low-, middle-, and high-molecular weight forms were not separately determined. Alternate methods of assessing endothelial function, including assessment of flow-mediated dilation by strain-gauge venous occlusion plethysmography, were not performed. Estimates of diastolic dysfunction were derived from

non-invasive echocardiographic assessment as opposed to direct invasive measurements of intracardiac pressures. Due to the cross-sectional nature of this study, any causal relationship between adiponectin levels and plasma ADMA, GABR and echocardiographic indices will require further investigation. Nevertheless, our data report for the first time a positive association between plasma adiponectin and ADMA levels (a finding opposite to that observed in non-heart failure populations) as well as a negative association between plasma adiponectin and GABR, especially in patients with chronic systolic heart failure. In addition, we confirm recent reports of a direct association between increased plasma adiponectin levels and echocardiographic indices of LV diastolic dysfunction, and demonstrate for the first time novel associations between plasma adiponectin levels and RV systolic and diastolic dysfunction. Further studies are needed to determine in which heart failure subgroups increased plasma adiponectin levels are protective, and, in subgroups where increased adiponectin levels mark worse prognosis, whether adiponectin is simply a marker of a failed counter-regulatory response or an active contributor to worsening heart failure progression. Finally, the potential risks and benefit of therapeutic strategies that directly raise plasma adiponectin levels need to be examined carefully in the setting of chronic systolic heart failure.

CONCLUSIONS

In our cohort of symptomatic patients with chronic systolic heart failure, higher adiponectin levels were associated with lower nitric oxide bioavailability as well as more impaired diastolic performance and right (but not left) ventricular systolic dysfunction. Our observations also support one of the notions that adiponectin is more likely generated in response to endothelial dysfunction than to systemic inflammation.

Acknowledgments

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Brief Commentary

Background

Adiponectin is an anti-inflammatory, anti-atherogenic adipokine elevated in heart failure and previously associated with poor prognosis. Recent mechanistic data report natriuretic peptides enhance adiponectin production, and suggest adiponectin may increase catabolism of asymmetric dimethylarginine (ADMA).

Translational Significance

We observe that plasma adiponectin levels, as previously reported to have prognostic value in heart failure, were not predictive of long-term clinical outcomes independent of plasma natriuretic peptide or ADMA levels, or diastolic dysfunction. Hence, natriuretic peptide-enhanced upregulation of adiponectin may constitute a compensatory (and potentially favorable) response to endothelial dysfunction, and rather than deleterious effects associated with systemic inflammation.

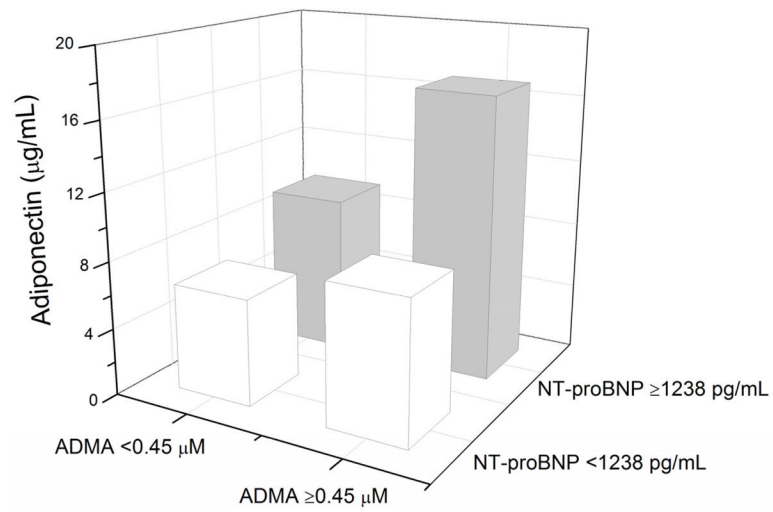**Figure 1.**
Median plasma adiponectin levels stratified by median plasma ADMA (0.45 μM) and median plasma NT-proBNP (1,238 pg/mL) levels.
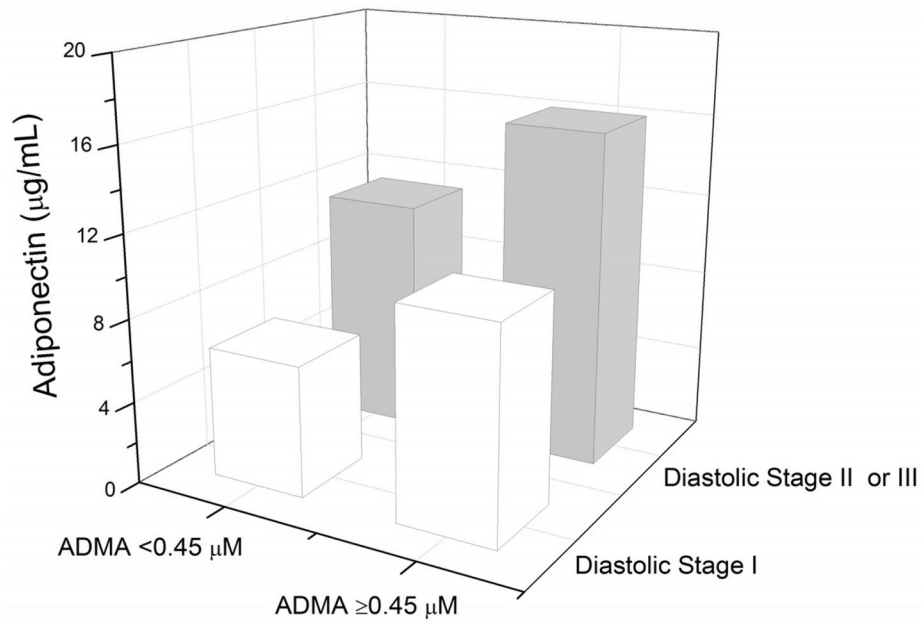
Figure 2.
Median plasma adiponectin levels stratified by median plasma ADMA level (0.45 μM) and diastolic dysfunction stages.

Table 1

Subject Characteristics (n=139)

Variable	Value
Age (years)	58 ± 13
Male gender (%)	107 (77%)
Heart failure history:	
NYHA class III or IV (%)	45 (33%)
Ischemic etiology (%)	57 (42%)
Co-morbid Conditions:	
Hypertension (%)	77 (57%)
Diabetes mellitus (%)	41 (30%)
Body mass index (kg/m^2)	28 ± 5
Medications:	
ACE inhibitors/ARB (%)	127 (94%)
Beta-blockers (%)	81 (60%)
Spironolactone (%)	36 (28%)
Loop diuretics (%)	106 (78%)
Digoxin (%)	77 (60%)
Echocardiographic indices:	
LV ejection fraction (%)	26 ± 6
LVED volume index (mL/m^2)	112 ± 35
LV Diastolic stage II or III (%)	76 (62%)
Mitral annular septal E/Ea	16.6 [12.0, 24.0]
eGFR (mL/min/1.73 m^2)	71 ± 24
Laboratory Data	
NT-proBNP (pg/mL)	1,238 [517, 3318]
Adiponectin (μg/mL)	10.4 [5.6, 18.1]
ADMA (μM)	0.45 [0.36, 0.56]
hsCRP (mg/L)	3.23 [1.42, 7.17]

Abbreviations: NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LV, left ventricular; LVED, left ventricular end-diastolic; eGFR, estimated glomerular filtration rate; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; ADMA, asymmetric dimethylarginine; hsCRP, high-sensitivity C-reactive protein.

Table 2

Univariable and multivariable correlations between plasma adiponectin levels and clinical and echocardiographic indices.

Variable	Univariable analysis		Multivariable analysis	
	Spearman's r	p-value	Standardized β	p-value
Age (years)	0.29	<0.001	--	---
Body mass index (kg/m^2)	−0.32	<0.001	−0.23	0.004
Echocardiographic indices:				
LV ejection fraction (%)	−0.14	0.108	--	---
LVED volume index (mL/m^2)	−0.02	0.834	--	---
Mitral E/A ratio	0.19	0.027	--	---
Mitral DT (ms)	−0.17	0.062	--	---
PV S/D ratio	−0.15	0.088	--	---
E/Septal Ea ratio	0.27	0.002	--	---
Tricuspid regurgitant jet area (cm^2)	0.33	<0.001	--	---
PA systolic pressure (mmHg)	0.22	0.031	--	---
LAVi (ml/m^2)	0.27	0.006	--	---
RAVi (ml/m^2)	0.42	<0.0001	--	---
eGFR (mL/min/1.73 m^2)	−0.25	0.004	--	---
NT-proBNP (pg/mL)	0.55	<0.0001	0.51	<0.0001
ADMA (μM)	0.41	<0.0001	--	---
GABR	−0.39	<0.0001	--	---
hsCRP (mg/L)	−0.02	0.812	--	--

Abbreviations: LV, left ventricular; LVED, left ventricular end-diastolic; DT, deceleration time; PV, pulmonary vein; PA, pulmonary artery; LAVi, left atrial volume index; RAVi, right atrial volume index; eGFR, estimated glomerular filtration rate; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; ADMA, asymmetric dimethylarginine; hsCRP, high-sensitivity C-reactive protein.

Table 3

Multivariable Cox proportional hazard analyses of adverse clinical events.

Variable	Hazard ratio (95% CI)	p-value
Model 1 (32 events)		
Ln Adiponectin (µg/mL) [*]	1.45 (1.02 – 2.07)	0.038
Model 2 (28 events)		
Ln Adiponectin (µg/mL) [*]	1.55 (1.08 – 2.23)	0.019
Age (years) [*]	0.87 (0.60 – 1.28)	0.461
Body Mass Index (kg/m^2) [*]	0.98 (0.63 – 1.49)	0.927
Diabetes mellitus	2.27 (1.04 – 4.93)	0.040
Model 3 (30 events)		
Ln Adiponectin (µg/mL) [*]	1.26 (0.85 – 1.89)	0.250
Ln E/Septal Ea ratio [*]	1.69 (1.13 – 2.56)	0.010
Model 4 (32 events)		
Ln Adiponectin (µg/mL) [*]	1.25 (0.85 – 1.83)	0.255
RV systolic dysfunction class [†]	1.44 (1.10 – 1.89)	0.007
Model 5 (30 events)		
Ln Adiponectin (µg/mL) [*]	1.13 (0.73 – 1.71)	0.577
Ln NT-proBNP (pg/mL) [*]	1.73 (1.17 – 2.52)	0.006
Model 6 (32 events)		
Ln Adiponectin (µg/mL) [*]	1.26 (0.85 – 1.85)	0.248
Ln ADMA (µM) [*]	1.53 (1.04 – 2.27)	0.030

[*] Hazard ratios per 1 standard deviation (SD) increments (1 SD for Ln Adiponectin = 0.81 µg/mL; 1 SD for Age = 13.5 years; 1 SD for BMI = 4.87 kg/m^2; 1 SD for Ln ADMA = 0.30 µM; 1 SD for Ln LV ejection fraction = 0.25 (%); 1 SD for Ln E/Septal Ea ratio = 0.56; 1 SD for Ln NT-proBNP = 1.34 pg/mL).

[†] Hazard ratios per +1 increments

Abbreviations: Ln, natural log; RV, right ventricular; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; ADMA, asymmetric dimethylarginine; SD = standard deviation.