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Autoantibodies Specifically Against β_1 Adrenergic Receptors and Adverse Clinical Outcome in Patients With Chronic Systolic Heart Failure in the β -Blocker Era: The Importance of Immunoglobulin G3 Subclass

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Abstract

Objective—To elucidate the prevalence and role of β_1 adrenergic receptor autoantibodies (β_1 AR-AAb) belonging to the immunoglobulin (Ig)G3 subclass in patients with heart failure (HF) treated with β -adrenergic blockers.

Background—Several cardiac AAbs have been reported to be present in sera from patients with dilated cardiomyopathy and other etiologies. Among AAbs, those recognizing β_1 AR-AAbs show agonist-like effects, have detrimental effects on cardiomyocytes, and may induce persistent myocardial damage.

Methods—We quantify total IgG and IgG3 subclass β_1 AR-AAb in subjects with chronic stable HF with long-term follow-up.

Results—In our study cohort of 121 subjects, non-IgG3- β_1 AR-AAb and IgG3- β_1 AR-AAb were found to be positive in 20 (17%) and 26 patients (21%), respectively. The positive rate of IgG3- β_1 AR-AAb was significantly higher for those with nonischemic compared with ischemic HF etiology (27% vs 8%, $P = .01$), but the positive rate for non-IgG3- β_1 AR-AAb was similar between the 2 groups (18% vs 16%, respectively, $P = \text{NS}$). There were no significant differences in clinical and echocardiographic measures among total β_1 AR-AAb negative, non-IgG3- β_1 AR-AAb positive, and IgG3- β_1 AR-AAb positive groups at baseline. During 2.2 ± 1.2 years of follow-up, we observed similar rates of the composite endpoint of all-cause mortality, cardiac transplantation, or hospitalization resulting from HF between total IgG- β_1 AR-AAb negative and positive patients. However, the composite endpoint events were significantly more common in the patients without than in those with IgG3- β_1 AR-AAb ($P = .048$, log-rank test).

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Disclosure

There are no relationships to disclose.

Conclusions—Presence of IgG3- β_1 AR-AAb, not total IgG, was associated with paradoxically more favorable outcomes in our cohort of patients with chronic systolic HF largely treated by β -blockers.

Keywords

Autoantibody; IgG3; β_1 -adrenergic receptor; β -blocker

There has been a longstanding belief that dysregulated autoimmune processes may lead to disease progression in heart failure (HF). Specifically, several cardiac autoantibodies (AAb) against specific cardiac antigens have been detected in sera from patients with dilated cardiomyopathy (DCM).^{1,2} In addition, immunization against the second extracellular loop peptide of the β_1 -adrenergic receptor (β_1 AR),³ muscarinic M2 receptor peptide,⁴ or troponin I peptide⁵ can generate AAbs and can lead to the development of DCM-like phenotypes in experimental models. Among the various anti-cardiac AAbs, autoantibodies against β_1 AR (β_1 AR-AAb) have been detected in 30–40% of DCM patients.^{6–10} Clinical studies conducted in the 1980s and 1990s (before the broad adoption of β -adrenergic blockers) demonstrated the associations between detectable β_1 AR-AAb and increased rates of mortality,⁸ fatal ventricular arrhythmias, and sudden death^{7,11} in patients with DCM. This finding suggests that certain β_1 AR-AAbs can be generated, at least in part, by cardiac loading or damage. Mechanistic studies have also demonstrated that β_1 AR-AAb may possess agonist-like properties,^{12–15} inducing receptor uncoupling,³ myocyte apoptosis,¹⁶ sustained calcium influx resulting in electric instability of the heart,¹⁷ and persistent myocardial damage.¹⁸ These potentially detrimental effects by the β_1 AR-AAb can be abolished by β -blockers in *in vitro*¹⁹ and *in vivo*³ experiments. Indeed, β_1 AR-AAb-positive HF patients have demonstrated a more favorable recovery of cardiac performance than β_1 AR-AAb-negative patients in response to β -adrenergic blocker therapy.^{9,20} Furthermore, immunoadsorption (IA) using columns specific for β_1 AR-AAb was effective in alleviating the cardiac dysfunction of an observational series of patients with DCM.²¹ Interestingly, in the analysis of weaned DCM patients who tested positive for β_1 AR-AAb before left ventricular assist device implantation, β_1 AR-AAb became undetectable after left ventricular unloading by mechanical circulatory assist support.²² Herein, the objective of our study is to determine the prevalence and clinical significance of specific β_1 AR-AAb in contemporary patients with chronic systolic HF predominantly treated with β -blockers.

Material and Methods

Study Population

One hundred and twenty one consecutive ambulatory and stable adult subjects (>18 years of age) with a clinical diagnosis of chronic systolic HF (left ventricular ejection fraction [LVEF] < 40%) who received longitudinal care at the Cleveland Clinic outpatient HF clinic were prospectively enrolled. Exclusion criteria consisted of a major cardiovascular event (myocardial infarction, unstable angina, stroke, transient ischemic attack, pulmonary embolism), having undergone major surgery, hospitalization, or emergency room visits for HF exacerbation, or the use of inotropic agents within the preceding 30 days. Written

informed consent was obtained from each of the patients before participation in the study, and the protocol was approved by the Cleveland Clinic Institutional Review Board.

Study Design

After informed consent and data collection, all patients underwent a blood draw and comprehensive transthoracic echocardiography evaluation using a Vivid 7 system (GE Vingmed Ultrasound, Horten, Norway). Two-dimensional grayscale and Doppler imaging were performed in standard parasternal and apical views. All subjects received guideline-directed medical therapy as tolerated, and their long-term outcomes (including all-cause mortality, cardiac transplantation, or hospitalization resulting from HF) were tracked by electronic medical record and determined by manual chart review. Ischemic cardiomyopathy (ICM) was defined as the presence of HF and angiographic evidence of coronary artery obstruction as contributing etiology.

β_1 AR-AAb Immunoassays

The presence of β_1 AR-AAb was determined by enzyme-linked immunoabsorbent assay using a synthetic peptide corresponding to the putative sequence of the second extracellular loop of human β_1 AR (amino acid sequence number, 197 to 222; H-W-W-R-A-E-S-D-E-A-R-R-C-Y-N-D-P-K-C-C-D-F-V-T-N-R) as an epitope peptide, as previously described.^{7,9,23} Anti-human immunoglobulin G (IgG) antibody or IgG3 antibody was used as a secondary antibody to detect β_1 AR-AAb belonging to IgG or IgG3 subclass. Positivity was defined as 2.5 times the background density as consistent with prior reports.^{7,9,23} IgG β_1 AR-AAb positive but IgG3 β_1 AR-AAb negative subjects were classified as “non-IgG3 β_1 AR-AAb positive” group.

Statistical Analysis

All values were expressed as the mean value $\pm$ SD. Differences between groups were compared using the non-paired *t* test or Mann-Whitney U rank-sum test for unpaired data and by the chi-square test for discrete variables. Kaplan-Meier survival curves for the composite endpoint of all-cause death, cardiac transplantation, or hospitalization due to the exacerbation of HF were calculated according to the presence or absence of IgG β_1 AR-AAb and/or IgG3 β_1 AR-AAb. Sensitivity analysis was performed by dividing the study cohort into 3 groups: (1) IgG3 β_1 AR-AAb positive; (2) non-IgG3 β_1 AR-AAb positive; and (3) β_1 AR-AAb negative groups. The differences among groups were analyzed by the log-rank test. Cox proportional hazards model was used to identify independent predictors of the composite endpoint of all-cause death, cardiac transplantation, and hospitalization resulting from exacerbation of HF. Heart rate (HR) at baseline, LVEF, estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula, and β_1 AR-AAb status were included in this model. A *P* value $< .05$ was considered statistically significant. All statistical analyses were performed in JMP 10.0.2 (SAS, Cary NC).

Results

Patient Characteristics

Baseline characteristics of the study population based on the β_1 AR-AAb status is shown in Table 1. There were no significant differences in age, gender, heart rate, LVEF, or plasma B-type natriuretic peptide levels among the 3 groups. In addition, there were no significant differences in medication or in the proportion of patients who underwent implantable cardioverter defibrillator implantation among the 3 groups. Of note, the large majority of patients (97%) were treated with β -adrenergic blockers in this ambulatory, stable HF population.

Prevalence of Detectable β_1 AR-AAb in Study Cohort

Among 121 subjects, we observed 46 patients with detectable β_1 AR-AAb (38%); 26 patients (21%) tested positive for belonging to the IgG3 subclass (IgG3- β_1 AR-AAb) and 20 patients (17%) tested positive for β_1 AR-AAb belonging to other IgG subclasses. The remaining 75 patients (62%) were deemed negative. The positive rate of IgG3 β_1 AR-AAb was significantly higher in patients with DCM vs ICM (27% vs 8%, $P = .01$), though the positive rates of non-IgG3 β_1 AR-AAb did not differ between the different HF etiologies (18% vs 16% respectively, $P = \text{NS}$).

Clinical Events Based on the β_1 AR-AAb Status

Figure 1 shows the Kaplan-Meier curves based on β_1 AR-AAb status. During 2.2 ± 1.2 years of follow-up, there was no significant difference in the composite endpoint of all-cause death, cardiac transplantation, and hospitalization resulting from HF between total IgG β_1 AR-AAb positive and negative groups (Fig. 1A). However, when the study population was divided into 2 groups based on IgG3 β_1 AR-AAb positivity, we observed that the composite endpoint was more common in the IgG3 negative group than in the positive group ($P = .048$, log-rank test, Fig. 1B). Furthermore, when study subjects were divided into 3 groups based on the presence or absence of both β_1 AR-AAb and IgG3 subclass (β_1 AR-AAb negative, non-IgG3 β_1 AR-AAb positive, and IgG3 β_1 AR-AAb positive), subjects with IgG3 β_1 AR-AAb had the lowest rate of adverse clinical events compared with the other 2 groups (Fig. 1C). Specifically within the β_1 AR-AAb positive cohort, the difference in adverse event rates between IgG3 positive and negative groups was statistically significant ($P < .01$, log-rank test). As seen in Table 2, univariate analysis showed that HR at baseline, LVEF, and β_1 AR-AAb status were associated with the occurrence of the composite endpoint. Multivariate analysis demonstrated that both HR at baseline and β_1 AR-AAb status were independent predictors of the composite endpoint.

Discussion

In our single-center study cohort with contemporary HF therapy including broad β -blocker use, we report that β_1 AR-AAb is detectable in excess of 1 of 3 patients, which is consistent with previous reports from Germany^{6,8,24,26} and Japan.^{7,9,10,20} Interestingly, the positive rate of the IgG3 subclass of β_1 AR-AAb was significantly higher in DCM compared with ICM patients, whereas the positive rate of non-IgG3 β_1 AR-AAb was similar between

different HF etiologies. Contrary to prior reports, we observed significantly lower adverse clinical event rates in those with detectable IgG3 β_1 AR-AAb positive vs negative patients in this patient cohort with 97% β -blocker use. Taken together, these hypothesis-generating findings imply the possibility that β_1 AR-AAb IgG subclasses might play differential roles in the pathophysiology of cardiomyopathies. Specifically, it is conceivable that IgG3 β_1 AR-AAb may exert a more direct pathologic effect related to a primary autoimmune process, such as failure of self-tolerance, than other non-IgG3 β_1 AR-AAbs that are more dependent on secondary autoimmune responses to self-antigens released as a result of cardiac damage.

Often referred to as “cardiodepressant” AAbs, certain types of AAbs purified from patients with DCM have been found to induce a negative inotropy and reduction of calcium transients *in vitro*^{27,29} and *ex vivo*. Interestingly, patients with cardiodepressant AAbs demonstrate an acute increase in cardiac index and LVEF after immunoadsorption (IA) therapy, whereas those without cardio-depressant AAbs do not show significant changes.^{27,29} Staudt and colleagues have reported that the cardio-depressant effects of these AAbs are unlikely to be induced by either the F(ab')₂ or Fc fragment alone. They showed that reconstitution of the antibody Fc portion by incubating cardiomyocytes with DCM-F(ab')₂ fragments followed by goat-anti-human-F(ab')₂-IgG can still induce reduction of cell shortening and calcium transients.³⁰ Therefore, AAb requires Fc fragment binding to Fc receptors as well as F(ab')₂ fragments binding to their epitope peptide to exert its pathological effect, and therefore the effects of the AAb may vary depending on the structure of the Fc fragment.

Immunoglobulin G has 4 subclasses (IgG1, 2, 3, and 4) according to the structure of the Fc fragment. IgG antibody subclasses 1 and 3 are most likely to trigger effector function and be involved in immunoregulatory activities. IgG1 and IgG3 both act by binding to and activating the Fc γ receptor and complement.^{28,31} IgG3 AAbs against some cardiac proteins can be detected in patients with DCM, and their presence has been shown to be an independent predictor of the presence of cardiodepressant AAb.¹⁰ Also, indices of hemodynamic dysfunction were correlated with anti-myosin AAb titer belonging to IgG3, but not total IgG, in patients with DCM.³² The importance of IgG3 AAbs was further supported when IA via anti-human IgG columns (high affinity for all IgG subclasses) resulted in additional improvement of cardiac function compared with using protein A (high affinity for IgG1, 2, and 4, but low affinity for IgG3).³³ Similarly, anti-IgG column eluent of DCM patients, but not protein A column eluent, has been observed to exert cardiodepressant effects on rat cardiomyocytes that were abolished after subsequent removal of IgG3 subclass from the eluent of the anti-IgG column.³⁴ In humans, IA using protein A columns with a modified protocol to effectively eliminate IgG3 subclass has also demonstrated better hemodynamic improvement in patients with DCM.³⁵ Alternatively, using the tryptophan column, IgG3 subclass was eliminated effectively by IA and to a greater extent than other subclasses.²³ The increase in LVEF after IA was better correlated with AAb titers belonging to the IgG3 subclass than total IgG, which also suggests that the removal of IgG3-AAb is important to maximize the effect of IA for patients with DCM.²⁹

There is an emerging appreciation that only a subset of β_1 AR-AAbs may be functionally active.^{36,37} The notion that IgG3 β_1 AR-AAbs may serve as a potential pathogenic factor that

can be counteracted with β -blockers raises an exciting possibility that their detection in patients who are at risk for developing cardiomyopathies may serve as potential indication for preventive β -blocker therapy. Further investigations into the presence of IgG3 β_1 AR-AAbs in at-risk patients are warranted.

Limitations

We note the following limitations in the present study. Although we evaluated β_1 AR-AAb status at baseline by enzyme-linked immunoabsorbent assay and examined clinical endpoints in our cohort, the mechanism that differentiated IgG3 and non-IgG3 β_1 AR-AAb was beyond our scope of investigation. In addition, although the administration of β -blockers is speculated as a mechanism that might have yielded more favorable outcomes in patients with IgG3 β_1 AR-AAb, the observational nature of our study did not allow further clarifications regarding the interrelationship between β -blockers and IgG3 β_1 AR-AAb.

Conclusions

The presence of IgG3 subclass of β_1 AR-AAb was paradoxically associated with favorable long-term outcomes in our HF patients compared with those without detectable IgG3 β_1 AR-AAb. Future investigations will be necessary to better elucidate the detailed mechanisms that differentiate the effects of IgG3 and non-IgG3 β_1 AR-AAb.

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Fig. 1.

Kaplan-Meier survival curves for the composite endpoint of all-cause death, cardiac transplantation, or hospitalization resulting from the exacerbation of heart failure. Kaplan-Meier curve based on immunoglobulin (Ig)G- β_1 adrenergic receptor autoantibody (β_1 AR-AAb) (A) and IgG3- β_1 AR-AAb status (B) and Kaplan-Meier curve of the 3 groups β_1 AR-AAb negative, non-IgG3- β_1 AR-AAb positive and IgG3- β_1 AR-AAb (C). * $P < .05$ vs β_1 AR-AAb negative group; ‡ $P < .01$ vs non-IgG3- β_1 AR-AAb positive group.

Table 1Baseline Characteristics Based on the β_1 AR-AAb Status

	β_1 AR-AAb		
	(-) (n = 75)	Non-IgG3 (+) (n = 20)	IgG3 (+) (n = 26)
Age	56 $\pm$ 10	53 $\pm$ 9	55 $\pm$ 15
Male sex	71% (53)	60% (12)	62% (16)
Systolic blood pressure (mmHg)	114 $\pm$ 17	119 $\pm$ 22	119 $\pm$ 21
Heart rate (bpm)	73 $\pm$ 12	75 $\pm$ 13	78 $\pm$ 16
LVEF (%)	31 $\pm$ 12	31 $\pm$ 15	34 $\pm$ 14
BNP (pg/mL)	262.8 $\pm$ 362.8	174.4 $\pm$ 164.2	269.2 $\pm$ 426.4
eGFR (mL/min)	78 $\pm$ 23	78 $\pm$ 28	82 $\pm$ 26
Sodium (mEq/L)	139 $\pm$ 3	139 $\pm$ 3	138 $\pm$ 3
Hemoglobin (g/dL)	13.6 $\pm$ 1.8	13.1 $\pm$ 1.5	13.3 $\pm$ 1.7
Medication			
ACEi or ARB	89% (65/73)	75% (15/20)	92% (22/24)
β blocker	96% (70/73)	100% (19/19)	96% (23/24)
Digoxin	40% (29/73)	40% (8/20)	17% (4/24)
Loop diuretics	67% (49/73)	60% (12/20)	67% (16/24)
Aldosterone antagonist	45% (33/73)	70% (14/20)	42% (10/24)
ICD	64% (47/73)	65% (13/20)	54% (13/24)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; β_1 AR-AAb, autoantibody against β_1 -adrenergic receptor; eGFR, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease formula; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction.

Table 2**Cox Proportional Hazards Model for Composite Endpoint**

	Univariate					Multivariate				
	n/N	Hazard Ratio (Unit)	Lower 95%	Higher 95%	P value	n/N	Hazard Ratio (Unit)	Lower 95%	Higher 95%	P value
eGFR (mL/min)	34/113	0.990	0.976	1.004	.171	29/104	0.997	0.981	1.013	.726
HR (bpm)	34/119	1.029	1.003	1.053	.030	29/104	1.042	1.010	1.074	.011
LVEF (%)	31/114	0.943	0.905	0.980	.002	29/104	0.969	0.930	1.004	.083
β_1 AR-AAb status (neg./non-IgG3/IgG3)	35/120				.038	29/104				.021
Non-IgG3(+) vs neg.		1.751	0.764	3.682	.175		2.180	0.913	4.873	.078
IgG3(+) vs neg.		0.412	0.120	1.080	.07		0.358	0.080	1.123	.081
IgG3(+) vs non-IgG3(+)		0.236	0.064	0.725	.011		0.164	0.034	0.597	.005

β_1 AR-AAb, autoantibody against β_1 -adrenergic receptor; eGFR, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease formula; HR, heart rate; LVEF, left ventricular ejection fraction; n, number of patients with endpoints; N, number patients with baseline condition.