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Lack of Persistence of Influenza Vaccine Antibody Titers in Patients with Heart Failure

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Abstract

Background: Patients with heart failure (HF) have lower initial antibody responses to the influenza vaccine compared to healthy individuals. Whether antibody titers wane faster in this population remains unknown.

Methods and Results: We studied 62 HF patients (18 ischemic, 44 idiopathic) and 40 healthy controls (HC) during the 2006/2007 and 2007/2008 influenza seasons. Antibody titers were measured before, and 2–4 weeks, and 11–12 months after vaccination. Serum antibody production was measured by hemagglutination inhibition assay, and antibody titers to individual vaccine viral strains between HF and HC were compared following the influenza season to measure persistence of antibody response. All participants demonstrated early antibody seroprotection (titers 40 hemagglutination inhibition units [HAU] to 1 strain). While antibody titers waned over time in both groups, titers to A/H3N2 and A/H1N1 strains decreased more in HF participants compared to HC ($p=0.004$ and $p=0.04$, respectively). Titers to the B-type strain decreased to below seroprotective levels in both groups.

Conclusions: Antibody titers to influenza A vaccine strains wane to below seroprotective levels in HF patients compared to HC, despite similar rates of initial seroprotection and seroconversion. These findings suggest that HF patients may remain at increased risk for influenza infection despite annual vaccination.

Keywords

Influenza; vaccine; antibodies

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DISCLOSURES

The authors of this study have no conflicts of interest to disclose.

INTRODUCTION

Influenza infection in patients with heart failure (HF) leads to increased rates of hospitalizations and other medical complications compared to healthy individuals.¹⁻³ Annual influenza vaccination has been shown to decrease acute HF exacerbations, hospitalizations, and all-cause mortality, making this a crucial preventative measure in HF patients.⁴

Despite widespread vaccination, rates of influenza-related hospital admissions and mortality are still on the rise.¹ Older adults and those with chronic conditions exhibit reduced immune responses to influenza vaccination. This could lead to increased susceptibility to influenza infection in these groups even with annual vaccination. We and others have shown a reduced humoral and altered cell-mediated response to the influenza vaccine in HF patients,^{5,6} but it is unknown whether initial vaccine-induced antibody titers to influenza antigens wane at a different rate in patients with HF compared to individuals without HF, which may leave these patients unprotected for part of the influenza season.

The objective of this study was to assess antibody titer levels to influenza antigens one year following influenza vaccination in patients with HF compared to healthy controls.

METHODS

Participants

Participants included in these analyses participated in previous studies during the 2006/2007 and 2007/2008 influenza seasons, evaluating immune responses to influenza vaccine.^{6,7} Eligibility criteria included: age greater than 18 years old, a diagnosis of heart failure, New York Heart Associated Functional Classes I through IV, and stable on guideline-based heart failure therapies for at least 30 days. Those with a documented history of allergic reaction to the influenza vaccine, a documented allergy to egg products, or moderate to severe acute febrile illness at baseline were excluded. The protocol was approved by the University of Wisconsin institutional review board. All participants provided written informed consent in accordance with established guidelines for the protection of human subjects.

Protocol

Data for these post-hoc analyses included 62 patients with HF (18 ischemic and 44 idiopathic) and 40 healthy individuals. Participants enrolled during the 2006/2007 influenza season (32 HF patients and 19 healthy controls) received one standard dose of the inactivated influenza vaccine intramuscularly during October or November of 2006. Phlebotomy was performed at baseline prior to vaccine administration, at 2-4 weeks, and at 11-12 months following vaccination to measure antibody titers. Baseline antibody titer data from additional participants enrolled during the 2007/2008 season (30 HF patients and 21 healthy controls) was used to test 11-12 month post-vaccine antibody titers from vaccine administered during the previous season. This additional cohort was enrolled to validate titer levels obtained from the 2006/2007 group.

The viral strain content in the influenza vaccine changes annually to include viruses anticipated to be the 3 most commonly circulating strains during the following year. The 3 types of virus strains included in the influenza vaccine are B type, H3N2, and H1N1 and each is further classified based on viral surface antigens. For the 2006/2007 influenza vaccination, the vaccine contained A/New Caledonia/20/99 (H1N1)-like virus, A/Wisconsin/67/2005 (H3N2)-like virus, and B/Malaysia/2506/2004-like virus.

The primary outcome measure was the difference in mean antibody titers to each of the three influenza vaccine strains between patients with HF and healthy individuals at 11-12 months

following vaccination. Antibody production was measured via hemagglutination inhibition assay (HIA), which measured serum influenza antibody concentrations. The hemagglutination inhibition assay was performed in duplicate using standard microtiter techniques.

Briefly, influenza virus-induced agglutination of guinea pig red blood cells was inhibited by antibodies present in the human serum. Serial dilutions of the human sera were made. Titrated influenza antigen was incubated with the serum dilutions for 30 minutes. Guinea pig red blood cells (50 *micro*L of 0.5% in phosphate-buffered saline) were added and incubated for 45 minutes. The dilution of serum that no longer inhibits hemagglutination (HA) was the influenza antibody titre.⁶

Statistical Analyses

Baseline characteristics of healthy individuals and HF participants were compared using t-tests or Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables, as appropriate.

For the primary study endpoint of differences in antibody titers to the vaccine viral strains between the HF and healthy control groups, the median antibody titers for each of the three influenza strains were compared using a Wilcoxon ranked-sum test. Correlation analyses were performed to examine associations between 11-12 month antibody titers for each vaccine antigen and age (as a continuous variable)

Seroprotection, a protective antibody response to the influenza vaccine, was defined as an antibody titre 1:40. Seroconversion, was defined as a four-fold increase in antibody concentrations to at least one vaccine strain.^{8,9} Rates of seroprotection and seroconversion between groups at 11-12 months post vaccination were assessed using the chi-square test. Data were analyzed on the intent-to-treat principle. All analyses were conducted with STATA (version 11, StataCorp, College Station, Texas).

RESULTS

Participants

Data from 62 HF patients (43 males, 19 females) and 40 healthy controls (22 males, 18 females) were used in these analyses. Healthy controls were numerically younger compared to HF participants, but the difference was not significant (mean age of 49 ± 9 and 57 ± 14 years for healthy control and HF groups, respectively, $p=0.07$). The majority (94%) of HF patients were New York Heart Association functional classes I or II and 29% had an ischemic etiology. Participants in the HF group were well optimized on guideline-based therapies. Baseline characteristics are summarized in Table 1.

Antibody Responses to Influenza Vaccine

All participants demonstrated seroprotection to influenza vaccine when measured 2-4 weeks post vaccination. Forty-five of the 62 HF participants (73%) and 29 of the 40 healthy controls (73%) exhibited seroconversion.

As previously reported, HF participants exhibited lower peak antibody titers compared to healthy controls for all three vaccine strains.⁶ At 11-12 months following vaccination, antibody titers for the A/H3N2 strain were significantly lower in HF patients compared to healthy controls (median antibody titers of 30 HAU [range 10-160] and 60 HAU [range 10-160] in HF and healthy controls, respectively; $p = 0.04$) (Figure 1). Median antibody titers dropped below 40 HAU in 29% of HF participants, indicating a loss of seroprotection,

while a larger proportion of healthy controls remained seroprotected to the A/H3N2 strain; only 9% of healthy controls exhibited post-season titers below 40 HAU. Post-season median antibody titers to the A/H1N1 strain were also significantly lower in HF patients compared to healthy controls (median titers of 30 HAU [range 10-160] and 80 HAU [range 10-640] in HF and healthy controls, respectively; $p = 0.004$) (Figure 2), and levels in 61% of HF participants dropped below seroprotective levels, compared to 24% of healthy controls. Significant differences were not noted between groups to the B/Malaysia strain (post-vaccination antibody titers of 20 HAU in both HF [range 10-160 HAU] and healthy controls [range 10-80 HAU], $p > 0.05$) (Figure 3). Seroprotection to the B-strain was lost in 48% and 47% of HF and healthy control participants. There were no differences in antibody titers within HF and healthy control groups of different seasons (enrollees from 2006/2007 and 2007/2008 seasons, data not shown). Correlation analyses did not reveal associations between 11-12 month antibody titer levels and age (A/H1N1 correlation coefficient = -0.18 [p -value = 0.20], A/H3N2 = 0.19 [p -value = 0.16], B-type = 0.24 [p -value = 0.10]).

DISCUSSION

We found that following influenza vaccination, mean antibody titers to both the A/H3N2 and A/H1N1 influenza strains were significantly lower in HF patients compared to healthy controls at 11-12 months post-vaccination, while mean antibody titers to the B-type influenza strain were not significantly different between HF patients and healthy controls post-season. Importantly, antibody titers in participants with HF decreased to below seroprotective levels for both A-type antigens, while antibody titers remained at protective levels in healthy controls at approximately one year after vaccine administration.

Our findings are consistent with other studies showing reduced long-term antibody titers to influenza vaccine antigens in patients with chronic conditions. Individuals aged 50-64 with comorbid diabetes, liver cirrhosis, chronic renal failure, malignancy or chronic steroid use have been shown to exhibit reduced immunogenicity to the influenza vaccine at 6 and 12 months post-vaccination compared to younger, healthy adults aged 18-49.¹⁰ Persons experiencing chronic stress, as observed in caregivers of patients with aggressive dementia, have also exhibited significantly reduced antibody titers to influenza vaccine 6 months post-vaccination compared to healthy controls.¹¹ Conversely, solid organ transplant recipients and those with chronic lung disease did not exhibit reduced antibody titers compared to healthy individuals post-vaccination.^{12,13} These studies suggest that some chronic medical conditions, but not necessarily use of immunosuppressing medications, may be associated with immune function dysregulation, which could potentially affect response to vaccines. Our findings of waning antibody titers suggest that those with HF may not be adequately protected throughout the entire influenza season.

In this study, both groups exhibited a lack of persistence of antibody titers to the B-type viral strain when measured 11-12 months post-vaccination. The reasons for reduced antibody titers one year following vaccination among healthy controls to the B strain are unclear. Initial antibody titers to the B strain were higher in healthy subjects compared to individuals with heart failure, however titers waned similarly in both groups. In general, antibody responses to the B-strain have been shown to be less consistent, with reduced titers produced compared to the A-strains.^{14,15}

There are several potential reasons for reduced antibody titers to A/H1N1 and A/H3N2 in HF patients observed in this study. Activation of the sympathetic nervous system results in detrimental effects on the myocardium, but may play a role in the reduced response to influenza vaccine in HF patients.¹⁶ Beta-2 adrenergic receptors are expressed on both T and B lymphocytes, suggesting an overlap between the SNS and immune function.¹⁷ Although

short-term elevated norepinephrine levels lead to the activation of cytotoxic T-cells and natural killer cells, chronic administration has been shown to have inhibitory effects on antibody production, explaining decreased immune responses in HF patients.¹⁸ While antibody titers decreased from initial measurement to post-season in both HF and healthy control groups, titers among those with HF decreased to below seroprotective levels. This may be partially due to the lower peak antibody response exhibited in HF participants compared to healthy controls. It is possible that higher initial post-vaccination titer levels would prevent a loss of seroprotection in patients with HF.

Our study had several limitations. First, the sample size is small and therefore has limited power to detect differences in antibody titers between groups. Moreover, the study was retrospective in nature and thus is subject to confounding. Mean ages between HF participants and healthy controls differed numerically, but not statistically. However, these differences in age have unclear clinical relevance, as studies showing reduced vaccine responses in older adults included individuals over age 65.^{19,20} The majority of our participants were under age 65. Although post-season antibody titers were different between HF and control groups, titers were not measured at other times during the influenza season. As such, we cannot exclude the possibility that titer levels during winter or spring months were similar between groups. The 11-12 month titers are still useful, as they signify the duration of potential protection afforded by the vaccine. Moreover, re-exposure to the same vaccine antigens in the following year's vaccine typically yields less pronounced changes in antibody titers compared to first time exposure. In this study, lower baseline titers in patients with heart failure may reduce the likelihood of achieving seroprotective levels with the next year's vaccine. Nonetheless, additional titer levels during the influenza season would help inform whether alternative vaccination strategies should be utilized for individuals with reduced responses to vaccination. Lastly, data were not available to examine associations between antibody titer levels and clinical outcomes, specifically among individuals with waning titer amounts. Future studies should examine effects of initial, mid-season, and post-season antibody titers on clinical protection conferred from influenza vaccine.

In summary, influenza vaccine antibody titers waned more significantly among HF patients post-season compared to healthy individuals, resulting in a loss of seroprotection in two of the three influenza vaccine strains. As such, it is possible that HF patients may be at an increased risk for influenza infection despite annual vaccination, but this should be explored prospectively. Alternative vaccination strategies to standard dose vaccine administration in HF patients should be investigated to offset waning antibody titers. A previous study has shown administration of a double dose influenza vaccine results in increased antibody-mediated responses 2-4 weeks post-vaccination in patients with HF.²¹ A more pronounced initial antibody response to influenza vaccine may prevent loss of seroprotection, and further studies should be conducted to assess antibody titers throughout the season after administration of a higher influenza vaccine doses in HF patients.

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Figure 1. Median antibody titers to A/H3N2 at 2-4 weeks and 11-12 months post-vaccination. $P=0.04$ for comparison of post-season median antibody titers between HF and healthy control groups

Figure 2. Median antibody titers to A/H1N1 at 2-4 weeks and 11-12 months post-vaccination. $P=0.004$ for comparison of post-season median antibody titers between HF and healthy control groups

Figure 3.

Median antibody titers to B-type at 2-4 weeks and 11-12 months post-vaccination. P=not significant for comparison of post-season median antibody titers between HF and healthy control groups

Table 1

Participant Baseline Demographics

	Heart Failure (N=62)	Healthy Controls (N=40)
Age (yrs) *	57 ± 14 [†]	49 ± 9
Sex (M / F) *	43 / 19	22 / 18
HF Etiology (Ischemic / idiopathic)	18 / 44	
NYHA FC I / II / III	37 / 21 / 4	
ACE inhibitor / ARB	60 / 62 (97%)	
Beta blocker	57 / 62 (92%)	
Diuretic	35 / 62 (56%)	
Digoxin	19 / 62 (31%)	
Mineralocorticoid receptor antagonist	19 / 62 (31%)	

* p=not significant for comparison between groups

[†] Mean ± SD