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 with 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 control subjects (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 the HF and HC groups were compared after the influenza season to measure persistence of antibody response. All participants demonstrated early antibody seroprotection (titers 40 hemmaglutination inhibition units to 1 strain). Although antibody titers waned over time in both groups, titers to A/H3N2 and A/H1N1 strains decreased more in HF than in HC participants ($P = .004$ and $P = .04$, 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 with 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. (*J Cardiac Fail 2014;20:105−109*)

Key Words: Influenza, vaccine, antibodies.

Influenza infection in patients with heart failure (HF) leads to increased rates of hospitalizations and other medical complications compared with 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 with individuals without HF, which may leave patients unprotected for part of the influenza season.

The objective of the present study was to assess antibody titer levels to influenza antigens 1 year after influenza vaccination in patients with HF compared with healthy control subjects.

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

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See page 108 for disclosure information.

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criteria included: age > 18 years, a diagnosis of heart failure, New York Heart Association functional classes I−IV, and stable on guideline-based heart failure therapies for ≥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. Each participant 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 control subjects) received 1 standard dose of the inactivated influenza vaccine intramuscularly during October or November 2006. Phlebotomy was performed at baseline before vaccine administration and at 2−4 weeks and 11−12 months after 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-vaccination 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, A/H3N2, and A/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 median antibody titers to each of the 3 influenza vaccine strains between patients with HF and healthy individuals 11−12 months after vaccination. Antibody production was measured via hemagglutination inhibition assay (HIA), which measured serum influenza antibody concentrations. HIA was performed in duplicate with the use of 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 μL of 0.5% in phosphate-buffered saline solution) 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 with the use of *t* tests or Wilcoxon rank sum tests for continuous variables and with the use of chi-square tests for categoric variables, as appropriate.

For the primary study end point 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 3 influenza strains were compared with the use of a Wilcoxon rank 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 titer ≥1:40. Seroconversion was defined as a 4-fold increase in antibody concentrations to ≥1 vaccine strain.[8,9] Rates of seroprotection and seroconversion between groups 11−12 months after vaccination were assessed with the use of the chi-square test. Data were analyzed on the intention-to-treat principle. All analyses were conducted with Stata software (version 11; Statacorp, College Station, Texas).

Results

Participants

Data from 62 HF patients (43 male, 19 female) and 40 healthy control subjects (22 male, 18 female) were used in these analyses. Healthy control subjects were numerically younger than HF participants, but the difference was not significant (mean ages of 49 ± 9 and 57 ± 14 years for healthy control and HF groups, respectively; P = .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 after vaccination. Forty-five of the 62 HF participants (73%) and 29 of the 40 healthy control subjects (73%) exhibited seroconversion.

As previously reported, HF participants exhibited lower peak antibody titers compared with healthy control subjects for all 3 vaccine strains.[6] At 11−12 months after vaccination, antibody titers for the A/H3N2 strain were significantly lower in HF patients than in healthy control subjects (median antibody titers of 30 HAU [range 10−160] and 60 HAU [range 10−160] in HF and healthy control subjects, respectively; P = .04; Fig. 1). Median

Table 1. Participant Baseline Demographics

	Heart Failure Patients (n = 62)	Healthy Control Subjects (n = 40)
Age (y), mean ± SD*	57 ± 14	49 ± 9
Sex (M/F)*	43/19	22/18
HF etiology (ischemic/idiopathic)	18/44	
NYHA 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%)	
MRA	19/62 (31%)	

HF, heart failure; NYHA, New York Heart Association functional class; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

*P = not significant for comparison between groups.