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Re: Decreased immune responses to influenza vaccination in patients with heart failure

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We appreciate Dr. Shaw and colleagues' interest in our work. We agree that an improved understanding of immune responses in heart failure patients is of critical importance.

Regarding our finding of higher IL-10 concentrations in patients with heart failure (HF), while the source of IFN-γ and IL-10 in our culture model is not specific to only cytotoxic T-lymphocytes (CTL), a shift from Th1 (IFN-γ) to Th2 (IL-10) cytokines has been associated with reduced CTL activity.[1] Moreover, a previous study has shown that IFN-γ:IL-10 ratios measured in a cell culture model can be predictive of granzyme B levels (Grz B, a key enzyme in the viral clearing process), which also associate with CTL activity and vaccine effectiveness.[2, 3] The lower IFN-γ:IL-10 ratios in HF participants compared to controls reported in our study may suggest decreased CTL activity. The ratio of IFN-γ and IL-10 rather than just their sources may provide valuable insight into T-cell protection afforded by influenza vaccination.

We believe the Wilcoxon rank-sum test is a valid statistical approach to compare the continuous outcomes measures between the two treatment groups, and indeed, both the suggested Mann-Whitney U test and the Wilcoxon rank-sum test produce identical statistical results.[4] Dr. Shaw and colleagues also question the rationale for performing a log transformation when a non-parametric test was used and suggest that log-transformed data should be analyzed using a T-test. Though it is common for skewed data to be log-transformed *in order that* a T-test may be

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used, this is not the only reason to use the log transformation nor does a log transformation preclude use of a non-parametric test. We chose to present changes in log-transformed values from pre- to post-vaccination as this approach is more commonly employed;[2] a Wilcoxon rank-sum comparison of the percentage change from pre- to post-vaccination using untransformed values would have produced mathematically identical results.

We reported a trend toward better serologic responses to the A/H3N2 vaccine strain among HF participants taking carvedilol compared to those taking metoprolol (p=0.06). Both T-cells and B-cells express beta-2 adrenergic receptors (β2-AR).[5] Norepinephrine stimulation of β2-AR has been shown to reduce the ability of CD4+ T cells to produce cytokines necessary for cell expansion, a response not seen when cells were also cultured with a beta antagonist.[6, 7] Our lab also has data in support of reduced cytokine production when PBMCs are cultured with influenza antigens and the beta2-specific agonist salmeterol, and ongoing experiments in our laboratory confirm that adding carvedilol to culture reverses this effect. It is not unreasonable to hypothesize that beta antagonists with varying degrees of beta2 activity may differ in their ability to affect immune function to influenza vaccination in the setting of an overactive sympathetic nervous system. We acknowledge that our hypothesis generating findings require replication in a larger cohort.

While there were age differences between HF participants and controls in our study, and immune responses to influenza vaccine are reduced in older adults, the mean ages in both groups were well below age 65 years. Further, previous studies examining influenza vaccine responses by age compared groups with distinctly disparate ages.[8] Although different statistically, we do not feel the age differences in our study are clinically meaningful. Even so, we reanalyzed our data excluding results from the four participants in the HF group over the age of 65 years (ages 75, 77, 79, and 81) and found that the cytokine and serological response differences between the HF group and controls were the same as in the initial analysis (Table 1).

In light of the recent pandemic of the A/H1N1 (swine-type) influenza virus, examining vaccine immune responses in patients with HF who are at high risk for influenza-related complications is of paramount importance. Our study shows that patients with HF exhibit a different T-cell response phenotype compared to controls. We also noted a reduced humoral response to the A/H3N2 vaccine strain despite similar rates of overall seroprotection and seroconversion between groups, suggesting that responses by antigens may add important information about differing vaccine efficacy in patients with HF. These data underscore the importance of further study of immune responses in HF patients, and continuous evaluation of optimal vaccination strategies for high risk adults.

References

1. Hsu HC, Scott DK, Mountz JD. Impaired apoptosis and immune senescence - cause or effect? Immunol Rev Jun;2005 205:130–146. [PubMed: 15882350]
2. McElhaney JE, Herre JM, Lawson ML, Cole SK, Burke BL, Hooton JW. Effect of congestive heart failure on humoral and ex vivo cellular immune responses to influenza vaccination in older adults. Vaccine Jan 26;2004 22(5–6):681–688. [PubMed: 14741160]
3. McElhaney JE, Xie D, Hager WD, et al. T cell responses are better correlates of vaccine protection in the elderly. J Immunol May 15;2006 176(10):6333–6339. [PubMed: 16670345]
4. Cook, TD.; DeMets, DL. Introduction to statistical methods for clinical trials. Boca Raton: Chapman & Hall/CRC; 2008.
5. Kohm AP, Sanders VM. Norepinephrine and beta 2-adrenergic receptor stimulation regulate CD4+ T and B lymphocyte function in vitro and in vivo. Pharmacol Rev Dec;2001 53(4):487–525. [PubMed: 11734616]

6. Swanson MA, Lee WT, Sanders VM. IFN-gamma production by Th1 cells generated from naive CD4 + T cells exposed to norepinephrine. J Immunol Jan 1;2001 166(1):232–240. [PubMed: 11123297]

7. Ramer-Quinn DS, Swanson MA, Lee WT, Sanders VM. Cytokine production by naive and primary effector CD4+ T cells exposed to norepinephrine. Brain Behav Immun Dec;2000 14(4):239–255. [PubMed: 11120594]

8. Powers DC, Belshe RB. Effect of age on cytotoxic T lymphocyte memory as well as serum and local antibody responses elicited by inactivated influenza virus vaccine. J Infect Dis Mar;1993 167(3):584–592. [PubMed: 8440930]

Table 1

T-cell and Humoral Responses to Influenza Vaccine

	HF	Healthy Controls	P value**	P-value#
Interferon gamma (pg/mL)				
Pre-immunization	10.8	30.4	0.24	0.2
Post-immunization	94.5	119.4		
IL-10 (pg/mL)				
Pre-immunization	2.0	5.1	0.0004	0.0007
Post-immunization	22.5	12.2		
Seroprotection Ab > 40 HAU*	24/24	17/17	1	
Seroprotection 4-fold increase	14/24	14/17	0.11	
Antibody concentrations (HAU) H3N2 (A/Wisconsin)				
Pre-immunization	80	80	0.009	0.008
Post-immunization	160	320		
H1N1 (A/New Caledonia)				
Pre-immunization	20	80	0.9	0.95
Post-immunization	60	160		
B (Malaysia)				
Pre-immunization	10	10	0.08	0.05
Post-immunization	40	80		

*Seroprotection and seroconversion rate differences analyzed by chi-square

**Comparisons analyzed by Wilcoxon rank-sum test

#Comparisons analyzed by t-test