LETTER TO THE EDITOR

Reply to Vaz

Abigail S. L. Stickford, Jonathon L. Stickford, and Stephen M. Ratchford
Department of Health & Exercise Science, Appalachian State University, Boone, North Carolina

REPLY: We appreciate Dr. Vaz’s letter of interest (1) in our recently published Rapid Report on vascular impairments in healthy young adults recovering from the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Vaz suggests that we could have used individuals recovering from other respiratory viral infections like influenza, as opposed to healthy individuals, as a comparison group. Although we agree that comparisons with other disease states may provide more insight into the relative clinical significance of SARS-CoV-2 infection, we 1) were limited in our patient population due to university, regional, and national restrictions that impacted human research subject interactions; 2) collected a unique data set using specific equipment and protocols that could be difficult to appropriately compare with previously collected data from other laboratories; and 3) challenge the notion that a simple comparison with the influenza virus is the most appropriate first comparison to be made with this novel coronavirus.

Throughout the data collection process for this study, our campus, like many others around the world, was subject to modified stay-at-home orders, remote learning requirements, and restrictions on human subject research. As the current study was limited to otherwise healthy individuals who had recently contracted SARS-CoV-2, and, thus, presumably had temporary immunity (3), the project was uniquely designed to mitigate viral spread during an active pandemic. Research investigations involving non-SARS-CoV-2-infected persons were not permitted for safety concerns.

Furthermore, the novel coronavirus disease of 2019 (COVID-19) pandemic caused profound alterations in individual behavior and community mitigation efforts to reduce viral spread. Epidemiological evidence suggests substantially reduced rates of influenza, enterovirus, and pneumo-nia worldwide during the COVID-19 pandemic (4, 5), likely as a result of behavioral strategies such as wearing masks, hand hygiene, and social distancing and other interventions aimed to minimize SARS-CoV-2 transmission. However, this beneficial consequence of “lockdown” meant that there were very few cases of other viral diseases on whom to concomitantly collect comparative data, especially in the relatively smaller rural area where this study was conducted.

Given the aforementioned limitations, coupled with the fact that our group has not previously examined the vascular consequences of other respiratory viral infections, any comparisons to the current data set would have to be made with previously collected data from other laboratories. This presents additional concerns as there are distinct variations in assessment techniques, as well as interlaboratory variability in analyses and procedures, which could limit validity of the comparisons. For example, nuanced variations in flow-mediated dilation protocols alone could include, but are not limited to, cuff placement and inflation time, the make/model of the Doppler ultrasound equipment used, and data processing software (6).

Comparing SARS-CoV-2 infection with Middle East respiratory syndrome coronavirus (MERS) and/or severe acute respiratory syndrome coronavirus (SARS-CoV) may have revealed its unique consequences compared with other coronaviruses, but these diseases are now quite rare, and there is a lack of preexisting data assessing the same measures and time points following infection that we examined. Comparison with influenza would have exposed potential differences in endothelial function as a result of the two viruses, but the SARS-CoV-2 and influenza viruses are considerably different. SARS-CoV-2 has greater transmissibility, a larger prevalence of infected individuals requiring hospitalization, and a higher fatality rate as compared with influenza. Furthermore, SARS-CoV-2 and the influenza virus affect individuals across the age spectrum/distribution, race, body composition, and underlying health conditions differently from each other. In addition, differences in the precise mechanism for infection and viral replication would presumably warrant further comparisons with other viruses. For example, the influenza virus binds to sialic acid and engages with epidermal growth factor receptor (7), whereas the SARS-CoV-2 binds to the ACE2 receptor (8); these differences will likely impact the inflammatory response and subsequent endothelial and vascular function assessments. Finally, given the heterogeneity of viral variants, the explicit comparison between influenza and SARS-CoV-2 variants may be inadequate, opening a “viral can of worms” of potential comparisons within SARS-CoV-2 variants and across other viral variants. Although these are perhaps meaningful comparisons as well, these studies would nonetheless be designed to answer a different research question than the one we set out to answer.

We acknowledge that the influenza virus has been shown to acutely (e.g., within 3 days of positive test confirmation) reduce brachial flow-mediated vasodilation (9), and we observed similar functional decrements in our study. In addition, endothelial function has been shown to be at normal levels 3 months following influenza virus infection in a group of hospitalized patients (9). However, it is not known
when function may be restored after influenza infection, especially in a group of young adults who experience only mild symptoms (i.e., did not require hospitalization) akin to the subjects included in our study. In our investigation, the SARS-CoV-2 subjects were studied 3–4 weeks following positive test confirmation. Thus, our study suggests SARS-CoV-2 results in vascular dysfunction nearly 1 month after infection. That finding itself is clinically relevant, independent of whether it is different from, or similar to, the effects of contracting the influenza virus or another respiratory viral infection. We certainly can agree with Dr. Vaz that there was the potential to investigate SARS-CoV-2 in conjunction with influenza, and we may consider doing so in the future, but we believe our study design was the most appropriate starting place to shed light on the potential impact of SARS-CoV-2 infection on adult vascular health and allow for future studies to refine this critical area of research.

**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

A.S.L.S., J.L.S., and S.M.R. drafted manuscript; A.S.L.S., J.L.S., and S.M.R. edited and revised manuscript; A.S.L.S., J.L.S., and S.M.R. approved final version of manuscript.

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