To conclude that BNT162b2 does not worsen echocardiographic indices, well-powered multicenter studies are required

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DEAR EDITOR,

We read with interest Hsu et al's[1] article on the echocardiographic findings in 25 adolescent vaccinees who received the second dose of the BNT162b2 vaccine. Serial echocardiographic examinations were performed on days –7, 2, 7, 14, and 28 before/after vaccination.[1] Ejection fraction increased from 73.8% at baseline to 77.8 on day 28.[1] Likewise, fractional shortening increased from 42.4% at baseline to 46.7% on day 28 postvaccination.[1] In females (n = 11), left ventricular assist devices (LVIDs) decreased from baseline to day 2 postvaccination.[1] It was concluded that adolescents vaccinated with BNT162b2 often experience transient discomfort after the second dose, but serial echocardiography does not detect significant deterioration until day 28 postvaccination.[1] The study is impressive, but some points require discussion.

The major limitation of the study is the small group size. Because cardiac complications following severe, acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) vaccinations are reported to be rare,[2] it would be imperative to convert the design to multicenter and international to increase the group size and increase the likelihood that some of the included vaccinees will become manifest with cardiac side effects. No final conclusions can be drawn before expanding the study cohort.

A second limitation is that there is no comprehensible explanation as to why systolic function increased steadily from baseline to day 28 postvaccination.[1] Was the increase in systolic function a compensatory mechanism for myocardial damage not visible on echocardiography or due to increased sympathetic tone? In a study of isolated rat cardiomyocytes, both messenger ribunucleic acid (mRNA)-1273 (Moderna) and BNT162b2 led to the expression of the spike protein in cardiomyocytes 48 hours after vaccination, mRNA-1273 induced arrhythmic and completely irregular contractions associated with irregular and localized calcium transients, suggesting dysfunction of the cardiac ryanodine receptor (RyR2), and BNT162b2 increased cardiomyocyte contractility via increased protein kinase-A (PKA) activity on the cellular level.[3]

A third limitation is that autonomic function was not included in the analysis. Because systolic function depends on the balance between sympathetic and parasympathetic drive, we should know how the level of sympathetic activation was measured and included in the assessment. Vaccinees in whom sympathetic tone predominates may have higher systolic function than vaccines in whom parasympathetic tone predominates. Were urinary catecholamines or serum norepinephrine levels measured before echocardiography was performed?[4]

A fourth limitation is that the decreased LVIDs in females on day 2 were not adequately explained. Were the decreased LVIDs in females attributable to the significantly increased LVID at baseline in males compared to women?

How was chest pain within 2 days of vaccination explained in "most vaccinees"? Was there elevated blood pressure, coronary spams, pulmonary embolism, or systolic dysfunction on the first-day postvaccination that could not be detected in the study because the first echocardiography was not performed until the second day after vaccination?

In conclusion, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Before concluding that echocardiographic parameters do not worsen after vaccination with BNT162b2, well-powered multicenter studies must be performed.

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