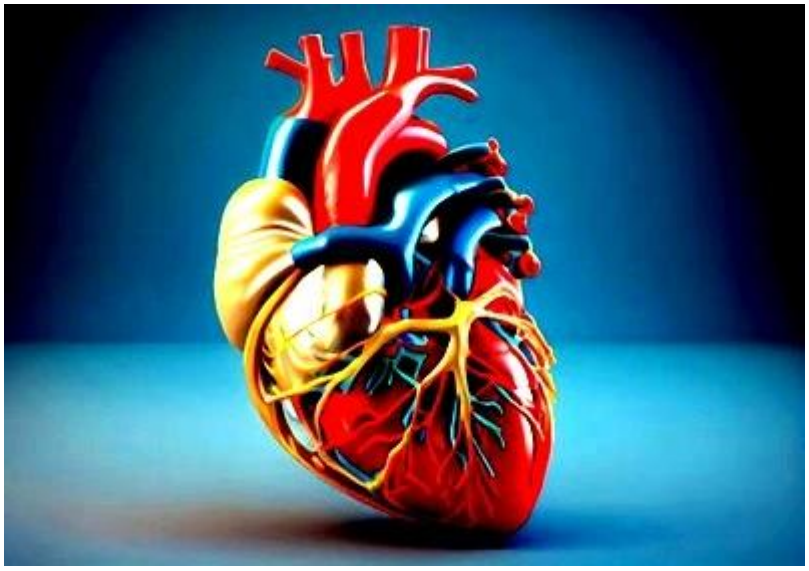
Desmosomes are specialized and highly ordered membrane domains that mediate cell-cell contact and strong adhesion. Adhesive interactions at the desmosome are coupled to the intermediate filament cytoskeleton. By mediating strong cell-cell adhesion and cytoskeletal linkages, desmosomes mechanically integrate cells within tissues and thereby function to resist mechanical stress. Desmosome dysfunction and the production of autoantibodies against desmosomes have been implicated in many diseases. Autoantibodies to desmoglein (Dsg)2 have been associated with arrhythmic right ventricular cardiomyopathy and familial dilated cardiomyopathy. In this study, the research team from the United Kingdom investigated the presence of anti-Dsg2 autoantibodies in sera from patients with acute COVID-19 and convalescents who have recovered after severe COVID-19.

Desmosomes are composed of proteins from three families: the cadherin, armadillo, and plakin family. The desmosomal cadherin family, desmogleins (Dsg), and desmocollins mediate calcium-dependent cell-cell adhesion. The expression of Dsg 1 and 3 is restricted to stratified epithelia.

However, Dsg2 is widely expressed in epithelia of pulmonary, gastrointestinal, renal, and myocardial tissues. In myocardial tissue, desmosomes connect cardiomyocytes at their intercalated discs. Dsg2 is not necessary for cardiac development, it is required for mechanical integrity. The importance of desmosomes in tissue integrity is highlighted by human diseases caused by mutations in desmosomal genes, autoantibody attacks of desmosomal cadherins, and bacterial toxins that selectively target desmosomal cadherins.



About the Study and *Results*

The authors investigated the presence of anti-Dsg1, Dsg2, and Dsg3 autoantibodies in sera from patients with acute COVID-19 and those who have recovered from severe COVID-19. To analyze the relevance of the anti-Dsg2 autoantibodies for cardiac damage, they performed the histopathological examination of *postmortem* cardiac tissue from patients who died from COVID-19.

They also investigated whether anti-Dsg2 autoantibodies are disease-specific by recruiting three comparison groups: one with severe influenza infection, a healthy control cohort, and a cohort of patients with cardiac disease not associated with SARS-CoV-2 infection.

The results showed that individuals with acute SARS-CoV-2 infection had skeletal, cardiac, and epidermal autoantibodies, with rates of 23%, 8%, and 46%, respectively. These high levels of autoantibodies were also detected in COVID-19 convalescents, in whom positivity increased to 30% skeletal, 40% cardiac, and 52% epidermal autoantibodies. By contrast, only 6% of non-COVID-19 patients had cardiac autoantibodies. Low levels were also observed in influenza patients.

The levels of anti-Dsg2 IgG autoantibodies were significantly elevated in sera from both groups, patients suffering from acute COVID-19 and the group of convalescents who have recovered after severe COVID-19. The levels of anti-Dsg2 autoantibodies in sera of patients who have recovered from severe COVID-19 were comparable to those found in patients with cardiac disease not associated with SARS-CoV-2 infection.

Anti-Dsg2 autoantibodies were not elevated in sera from COVID convalescents who had mild disease, patients recovered from influenza infection, and healthy controls.

The histopathological examination of *postmortem* cardiac tissues from patients who died from COVID-19 showed structural changes and disruption of the intercalated discs between cardiomyocytes. According to the authors, the intercalated disc disruption leads to increased fat deposition and scar tissue, and ultimately, to an impaired capacity of cardiac action potentials to spread through cardiac tissue. This results in cardiac conduction delay and ventricular arrhythmias.

Conclusion

This study has shown that autoimmunity to Dsg2 might contribute to unexpected pathologies associated with COVID-19. The anti-Dsg2 autoantibodies are potentially pathogenic and have been associated with arrhythmogenic right ventricular cardiomyopathy and familial dilated cardiomyopathy.

According to the authors, the possible association of anti-desmoglein 2 autoantibodies and post-COVID-19 cardiac sequelae can identify Dsg2 autoantibodies as a new biomarker for cardiac damage after SARS-CoV-2 infection.

This article was published in the Clinical and Experimental Immunology.

Journal Reference

Ward KE et al. SARS-CoV-2 infection is associated with anti-desmoglein 2 autoantibody detection, *Clinical and Experimental Immunology*, 2023. (Open Access). https://academic.oup.com/cei/advance-article/doi/10.1093/cei/uxad046/7140487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