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Original Article / *Özgün Makale*

Cardiac surgery with cardiopulmonary bypass markedly lowers SARS-COV-2 antibody titer

Kardiyopulmoner baypas ile kardiyak cerrahi SARS-COV-2 antikor titrelerini belirgin düzeyde düşürür

Mustafa Şimşek[1], M. Şeyda Velioğlu Öcalmaz[2], Murat Başтopçu[3], Murat Sargın[3], Sebahat Aksaray[4]

Institution where the research was done:
Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Türkiye

Author Affiliations:
[1]Department of Anesthesiology and Reanimation, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Türkiye
[2]Department of Infectious Disease, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Türkiye
[3]Department of Cardiac Surgery, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Türkiye
[4]Department of Microbiology, University of Health Sciences, Hamidiye Medical Faculty, Istanbul, Türkiye

ABSTRACT

Background: This study aims to investigate the effect of cardiopulmonary bypass on antibody titers in patients vaccinated against the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) undergoing cardiac surgery with cardiopulmonary bypass.

Methods: Between October 2021 and October 2022, a total of 70 patients (44 males, 26 females; mean age 59.9±10.3; range, 26 to 79 years) who completed their recommended COVID-19 vaccinations and underwent elective cardiac surgery with cardiopulmonary bypass were prospectively included. Serum samples for antibody titer measurements were taken at anesthesia induction and the end of cardiopulmonary bypass after decannulation. The SARS-CoV-2 total immunoglobulin antibodies against N-protein were measured. The antibody titer measurements at anesthesia induction and at the end of cardiopulmonary bypass were compared in all patients.

Results: The median levels after cardiopulmonary bypass were lower than the preoperative levels (1,739.0 *vs*. 857.0, respectively; p<0.001). There was a drop of 40.0% (21.2%-62.6%) in the antibody titers among all patients. The decrease in antibody titers was consistent regardless of the number of vaccine doses or whether the last dose was received within the last three months. Among the studied factors, no parameter was significantly associated with a lesser or higher decrease in antibody titers.

Conclusion: Cardiac surgery with cardiopulmonary bypass causes a decrease in SARS-CoV-2 antibody titers at the end of cardiopulmonary bypass. Revaccination after cardiac operations may be considered in this patient group that is highly vulnerable due to their comorbidities and lowered antibody levels.

Keywords: Antibody, cardiac surgery, cardiopulmonary bypass, SARS-CoV-2.

ÖZ

Amaç: Bu çalışmada kardiyopulmoner baypas ile kalp cerrahisi geçiren şiddetli akut solunum yolu sendromu koronavirus 2 (SARS-CoV-2) aşılarını olmuş hastalarda kardiyopulmoner baypasın antikor düzeylerine etkisi araştırıldı.

Çalışma planı: Ekim 2021 - Ekim 2022 tarihleri arasında kardiyopulmoner baypas ile elektif kalp cerrahisi geçiren ve önerilen COVID-19 aşılarını tamamlayan toplam 70 hasta (44 erkek, 26 kadın; ort. yaş 59.9±10.3; dağılım, 26-79 yıl) prospektif olarak çalışmaya alındı. Antikor düzey ölçümleri için kan örnekleri anestezi indüksiyonunda ve dekanülasyon sonrası kardiyopulmoner baypas sonunda alındı. SARS-CoV-2 N-proteinine karşı toplam immünoglobülin antikor düzeyi ölçüldü. Tüm hastalarda anestezi öncesi ve kardiyopulmoner baypas sonundaki antikor düzeyleri karşılaştırıldı.

Bulgular: Kardiyopulmoner baypas sonlanımındaki medyan düzeyler, ameliyat öncesi düzeylere kıyasla daha düşüktü (sırasıyla 857.0'a kıyasla 1739.0; p<0.001). Tüm hastalarda antikor düzeylerinde %40.0 (%21.2-%62.6) oranında düşüş izlendi. Antikor düzeylerindeki düşme aşı doz sayısı veya son üç ay içerisinde aşı olma durumuna göre değişiklik göstermedi. İncelemeye alınan faktörler arasında, parametrelerin hiçbiri antikor düzeylerindeki düşme üzerinde etkili bulunmadı.

Sonuç: Kardiyopulmoner baypas kullanılarak yapılan kalp cerrahisi, kardiyopulmoner baypas sonlanımında SARS-CoV-2 antikor düzeylerinde düşüşe neden olur. Ek hastalıklar ve düşük antikor düzeyleri nedeniyle büyük ölçüde hassas olan bu hasta grubunda kalp ameliyatlarından sonra ek doz aşı uygulaması düşünülebilir.

Anahtar sözcükler: Antikor, kalp cerrahisi, kardiyopulmoner baypas, SARS-CoV-2.

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Correspondence: Mustafa Şimşek, MD. Dr. Siyami Ersek Göğüs Kalp ve Damar Cerrahisi Eğitim Araştırma Hastanesi Anesteziyoloji ve Reanimasyon Kliniği, 34668 Üsküdar, İstanbul, Türkiye.
Tel: +90 505 - 778 99 80 e-mail: mustafasimsek73@gmail.com

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As of January 2022, the novel coronavirus 2019 disease (COVID-19) pandemic has caused more than 251 million cases of infection and claimed 5.1 million deaths.[1,2] The social and economic consequences of the pandemic have led to accelerated vaccine development efforts and their emergency use authorizations.[3] The Turkish Ministry of Health has approved CoronaVac (Synovac Life Sciences, Beijing, China), the inactivated whole virion vaccine, and Comirnaty (Pfizer-BioNTech, Mainz, Germany), the messenger ribonucleic acid (mRNA)-based vaccine for emergency use in Türkiye. Emerging variants and impermanent immunity with the vaccines have necessitated booster doses for individuals within three to six months of their last vaccine dates.

The immune response to the COVID-19 infection is complex with humoral and cellular immunity playing different roles. The neutralizing antibodies against viral proteins provide transient immunity that recedes within months. The community consequences of the receding antibody titers have not been fully elucidated, as cellular immunity may provide a level of protection after the period of decreased neutralizing antibody titers, while individuals may be susceptible to an infection a certain time after vaccination or an infection.[4,5]

Despite the overwhelming burden of the COVID-19 pandemic, cardiovascular diseases remain a major cause of mortality. Cardiovascular deaths have increased during the pandemic, a major portion of which is not COVID-related, but due to delayed treatments.[6] Cardiac surgery patients cannot be delayed indefinitely and often require immediate or early attention despite the pandemic. Cardiopulmonary bypass (CPB) remains the mainstay of cardiac operations and has diverse effects on the immune system, with the release of both proinflammatory and anti-inflammatory cytokines and attenuation of host defenses.[7] The literature is lacking in the effects of CPB on the levels of antibodies produced as a result of vaccinations. One study on congenital heart disease patients undergoing cardiac surgery with CPB showed a decrease in antibody titers of childhood vaccines, but not below immunization thresholds.[8] Such a decrease in severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) neutralizing antibody titers in vaccinated individuals may make cardiac surgery patients prone to COVID-19 infection in the postoperative period.

There are currently no data on the effects of CPB on SARS-CoV-2 antibody titers. Surgery with CPB causes macro and microcirculatory changes in permeability and fluid dynamics, affecting body fluid compositions. Therefore, changes in antibody titers may be evident after a period on CPB. The lowest margin of antibody levels necessary for protection against SARS-CoV-2 infection has also not been studied. Considering the complex pathophysiological mechanisms of CPB, the primary question that needs evidence is the amount of change antibody titers after cardiac surgery.

In the present study, we aimed to investigate the effect of CPB on antibody titers in patients vaccinated against the SARS-CoV-2 virus undergoing cardiac surgery with CPB with measurements of antibody levels before and after CPB.

PATIENTS AND METHODS

This single-center, prospective study was conducted at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Departments of Anesthesiology and Cardiovascular Surgery between October 4th, 2021 and October 22nd, 2022. A total of 70 patients aged (44 males, 26 females; mean age 59.9±10.3; range, 26 to 79 years) who completed their recommended COVID-19 vaccinations and underwent elective cardiac surgery under CPB were included. Patients with operative mortality were excluded from the study.

All patients were monitored with arterial catheterization, five-lead electrocardiography, central venous catheterization, peripheral oxygen saturation, and bispectral index (Covidien - BIS Vista, Mansfield, MA, USA). Anesthesia was induced with propofol, fentanyl, and rocuronium and maintained with propofol, fentanyl, rocuronium, and sevoflurane per routine protocol.

Operations were performed with median sternotomy. The patients were anticoagulated with 300 to 400 IU/kg of heparin before cannulation via ascending aorta and atrial or bicaval venous cannulation. The CPB was initiated with activated clotting time >450 sec. Operations were performed at 28 to 32°C of hypothermia, on-pump with cross-clamping of the aorta. Blood cardioplegia was administered every 20 min. At the end of CPB, heparin was neutralized with protamine at a 1:1 ratio.

Serum samples for antibody titer measurements were taken at anesthesia induction and the end of CPB after decannulation. During CPB, hemoglobin levels were targeted above 7 to 8 g/dL, and patients were transfused with red blood cells when lower levels were detected. Patients were not transfused with other blood products for minimal interference with antibody titers.

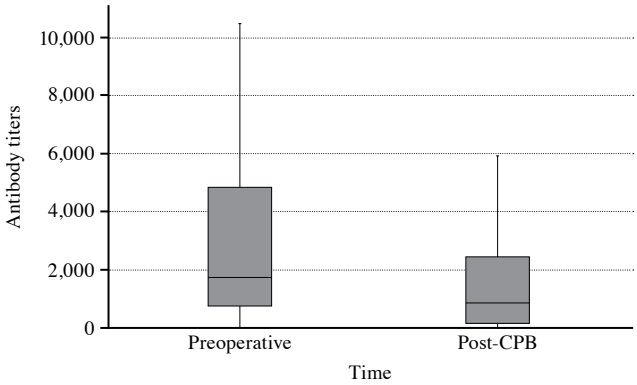

Figure 1. Preoperative and post-CPB antibody titers.
CPB: Cardiopulmonary bypass.

Other necessary transfusions were given after sampling at the end of CPB. Samples were centrifuged at 1,500 g at room temperature. The supernatant serum was separated and stored at -80°C before transport to another laboratory. After transport, the samples were thawed and underwent a two-stage quality control process. The SARS-CoV-2 total immunoglobulin (Ig) antibodies against N-protein were measured using Cobas e801 (Roche Diagnostics, Mannheim, Germany) which uses the electrochemiluminescence technique. The antibody titer measurements at anesthesia induction and at the end of CPB were compared in all patients. Patient factors affecting the change in antibody titers were also analyzed.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. For analysis of antibody levels, the Wilcoxon signed-rank test was applied to all patients and subgroups. Change in antibody levels according to patient factors was tested using Spearman's rank-order correlation for continuous variables and Mann-Whitney U test for categoric variables. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 71 patients underwent coronary artery bypass grafting (CABG) under CPB during the study period. However, one patient experienced operative mortality and was excluded. The study was completed with 70 patients. The baseline characteristics of the study patients are summarized in Table 1.

All patients were sampled for antibody titer measurement before the operation and at the end of CPB. The levels after CPB were lower than the preoperative levels (preoperative median 1,739.0 vs. post-CPB median 857.0, p<0.001) (Figure 1). There was a drop of 40.0% (21.2-62.6%) in the antibody titers among all patients. The decrease in antibody titers was consistent regardless of the number of vaccine doses or whether the last dose was received within the last three months (Table 2).

Considering the potential effect of fluid balance on the concentration or dilution of serum proteins, the patients were grouped according to fluid balance at the end of CPB.

In all subgroups, the antibody titer at the end of CPB was lower than the preoperative levels and significant relationships could be shown in near-balance and positive balance groups (Table 3). The amount of

Table 1. Baseline characteristics of study patients

	n	%	Mean±SD
Age (year)			59.9±10.3
Sex			
Female	26	37.1	
Body mass index (kg/m^2)			27.5±3.8
Hypertension	41	58.6	
Diabetes mellitus	23	31.9	
Chronic obstructive pulmonary disease	7	10.0	
Chronic renal disease	6	8.6	
History of cerebrovascular event	1	1.4	
Left ventricular ejection fraction			54.1±9.2

SD: Standard deviation.

Table 2. Antibody levels before and after cardiopulmonary bypass

	Preoperative antibody titers		Antibody titers after CPB		
	Median	IQR	Median	IQR	*p*
All patients	1,739.0	713.0-4,848.0	857.0	149.0-2,473.0	<0.001
By vaccination status					
2 Doses (n=33)	1,637.0	771.0-4,848.0	888.0	380.0-2,475.0	<0.001
>2 Doses (n=37)	1,757.0	520.0-4,766.0	656.0	90.6-1,847.0	<0.001
By vaccination time					
Last dose <3 months	2,456.0	1,108.5-5,542.0	1,283.0	1,108.5-5,542.0	<0.001
Last dose >3 months	1,338.0	318.5-3,101.5	680.0	129.0-1,291.5	<0.001

CPB: Cardiopulmonary bypass; IQR: Interquartile range.

Table 3. Subgroup analysis of antibody titers according to CPB fluid balance

	Preoperative antibody titers		Antibody titers after CPB		Decrease (%)		
Fluid balance (mL)	Median	IQR	Median	IQR	Median	IQR	*p*
≤500 (n=7) (negative balance group)	3,013.0	1,355.5-7,205.0	680.0	219.5-3,560.5	45.7	66.0-0.1	0.063
-500 + 500 (n=27) (near-balance group)	2,148.0	856.0-3,836.5	888.0	477.0-1,702.0	33.6	43.1-18.0	**<0.001**
> +500 (n=36) (positive balance group)	1,593.0	475.0-5,195.5	844.0	81.2-2,474.0	44.1	56.9-25.2	**<0.001**

CPB: Cardiopulmonary bypass; IQR: Interquartile range.

decrease was similar in all subgroups ranging between 33.6% and 45.7% (p=0.273).

Among the studied factors, no parameter was significantly associated with a lesser or higher decrease in antibody titers. To investigate whether patient factors influenced the decrease in antibody titers, the amount of decrease was compared across demographic, laboratory, and operative factors. Among the studied factors, no parameter was significantly associated with a lesser or higher decrease in antibody titers (Table 4).

DISCUSSION

Our study showed that SARS-CoV-2 antibody titers substantially decrease after cardiac surgery using CPB. The decrease in antibody titers was not affected by patient or operative factors. To the best of our knowledge, this is the first study that demonstrates the effect of CPB on SARS-CoV-2 titers.

Along with community precautions, immunization remains the preeminent measure against the spread of the disease and the associated mortality. The mRNA and inactivated SARS-CoV-2 vaccines produce an antibody response within days of vaccination.[9,10] While a high antibody count does not forego the risk of infection, higher titers correlate with better protection from COVID-19 disease.[11] On the other hand, as SARS-Cov-2 IgG antibody levels decrease, there is an increase in avidity maturation that plays a different role in long-term immunity and may allow increased neutralization potency against different variants.[12,13] With the connection between antibody titers and immunity from infection yet to be completely illuminated, evidence from recovering COVID-19 patients suggests that higher antibody levels may provide better protection from reinfection. Patients with severe COVID-19 disease have higher peak antibody levels after disease and have higher remaining antibody levels after six months, while patients with milder disease demonstrate an immune response with lower antibody levels which decay faster to lower levels, making these individuals more susceptible to reinfection.[14] All in all, higher antibody levels appear to be more protective against reinfection.[15]

Table 4. Patient factors and decrease in antibody titers

	Percent decrease (%)			
	Correlation coefficient	Median	IQR	*p*
Age	0.132			0.277
Sex				0.780
Male		39.5	55.2-20.7	
Female		40.4	52.6-21.2	
Body mass index	0.162			0.180
LVEF	-0.095			0.432
LVEF category				0.093
<40		30.3	39.8-6.5	
>40		40.8	58.6-21.5	
DM				0.925
None		40.2	51.1-21.5	
Present		39.0	54.0-17.1	
Hypertension				0.407
None		40.7	60.1-24.2	
Present		39.1	51.9-19.7	
CRD				0.518
None		40.2	54.0-23.0	
Present		30.3	51.5-5.4	
COPD				0.512
None		40.1	52.2-23.0	
Present		39.0	50.9-6.2	
Total vaccine doses				0.362
2 Doses		40.1	50.5-25.0	
3 Doses		39.4	51.7-7.8	
4 Doses		57.6	62.6-52.6	
Days since last vaccine	0.188			0.120
Type of operation				0.512
CABG		39.5	60.5-24.5	
CABG + valve		8.4	2.6-19.4	
Valve		43.8	53.4-30.6	
Aortic		43.2	44.2-23.2	
Preoperative hemoglobin (g/dL)	-0.103			0.397
Hemoglobin during CPB (g/dL)	0.047			0.700
Hemoglobin at the end of CPB (g/dL)	0.140			0.246
Cross-clamp duration	0.105			0.388
CPB duration	0.131			0.279

IQR: Interquartile range; LVEF: Left ventricular ejection fraction; DM: Diabetes mellitus; CRD: Chronic renal disease; COPD: Chronic obstructive pulmonary disease; CABG: Coronary artery bypass graft; CPB: Cardiopulmonary bypass.

The effect of CPB on antibody titers may have important clinical implications. Cardiac surgery with CPB prompts a state of immune dysfunction in the early postoperative period with increasing tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10).[16] Coupled with decreasing SARS-Cov-2 antibodies, the cardiac surgery patient is at an increased risk for a severe infection. Pediatric patients undergoing CPB were previously studied for postoperative levels of childhood vaccines and Bordatella and hepatitis B antibodies were lowered in the postoperative period and not below the immunization thresholds.[8] Follow-up

nationwide studies are necessary to illuminate the connection between lowered antibody titer and clinical susceptibility to COVID-19 disease. With these future studies, a sound recommendation can be made if patients undergoing cardiac surgery require an additional booster dose to remain sufficiently immune against the disease, bearing in mind that most cardiac surgery patients are older and have more comorbidities than the general population. A booster dose is recommended in individuals who have received their last vaccine dose longer than six months before. The rationale follows the decrease in antibodies of vaccinated individuals.[17] This recommendation has recently been revised to three months considering the burden of a new wave of disease emerging with a novel variant. How the declining antibody levels correlate with immunity against new disease is uncertain, while booster shots protect both the vaccinated individual and recovered patients.[18] After waning antibody levels, a single booster dose raises antibody levels to protective levels.[19] With the same rationale, patients undergoing cardiac surgery may require an additional booster or their booster dose may be timed after a planned operation. Nationwide studies can better analyze the additional risk of COVID-19 infection in patients who undergo cardiac surgery and the benefit of postoperative revaccination.

Surgery under CPB is associated with hemodilution and lowered concentration of plasma proteins.[20] Priming with crystalloid solutions and some loss of blood to outside the CPB circuit. To investigate whether the drop in antibody titers is influenced by hemodilution, a subgroup analysis was performed with patients at positive, near-zero, and negative balance at the end of CPB. All subgroups were similar in the amount of drop in antibody levels, although there was a decrease also in the positive balance group with a lower median at the end of CBP, the difference was not significant due to the low number of patients in this subgroup.

There are certain limitations to our study. The CPB has numerous effects on the immune and hematological systems which may not be observed in other cardiac or non-cardiac surgeries. Therefore, our results may not be generalized to all surgical patients. In addition, there are different methods available for the measurement of antibody levels, which may yield different results.[21] Cardiac surgery patients are in a state of hypervolemia and hemodilution at the end of CPB. The fluid shift in the early postoperative days may affect the plasma concentrations of Ig and the concentrations of SARS-CoV-2 antibodies may vary over time. Future studies with antibody titers measured at different time points in the postoperative period can better portray the effects of fluid shift on serum SARS-CoV-2 antibody levels.

In conclusion, during the pandemic, a booster dose has been recommended for all individuals after two doses of vaccination regardless of the level of decrease in antibodies. Our study shows that cardiac surgery with cardiopulmonary bypass may cause a decrease in antibody titers at the end of cardiopulmonary bypass. Based on this evidence, the recommendation of early or postoperative booster vaccination for cardiac surgery patients can be evaluated by the authorities. In particular, a recommendation for a booster dose after cardiac operations may be considered in this patient group that is highly vulnerable due to their comorbidities and lowered antibody levels.

Ethics Committee Approval: The study protocol was approved by the Dr. Siyami Ersek Research and Training Hospital Academic Board (E-28001928-604.01.01) and the associated local ethics committee (HNEAH-KAEK 2021/252-3115). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, control, data collection, analysis, literature review - M.Ş., M.Ş.V.Ö., M.B., M.S., S.A.

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