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Original Article

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Investigation of SARS-CoV-2 RNA in intraoperatively collected tissue samples during coronary bypass surgery

Abstract

Aim: This study aimed to investigate the presence of SARS-CoV-2 RNA in atherosclerotic plaque and tissue samples obtained intraoperatively from patients with a history of COVID-19 who underwent coronary artery bypass grafting (CABG).
Material and Methods: This retrospective study included 235 patients with a documented history of COVID-19 who underwent CABG. Tissue samples were placed in tubes containing an RNA stabilization solution, incubated at 4–8°C for 8–12 hours, and then stored at −80°C until analysis. Reverse transcription and denaturation were performed at 55°C for 20 minutes and 95°C for 2 minutes, respectively. Amplification was conducted using the manufacturer's recommended thermal cycling protocol: 95°C for 15 seconds, 55°C for 45 seconds, and 72°C for 15 seconds. Samples with at least one target gene showing a Ct value below 45 were considered positive.
Results: SARS-CoV-2 RNA was detected in tissue samples from six patients. The Ct values of the positive samples ranged from 34 to 40. Our findings suggest that SARS-CoV-2 RNA may persist in peripheral vascular tissues beyond the pulmonary system in patients with a history of COVID-19.
Conclusion: This observation may have prognostic implications regarding the systemic effects of the disease. The results highlight the need for further large-scale and long-term studies to elucidate the clinical significance of SARS-CoV-2 persistence in extrapulmonary tissues.

Keywords: Severe acute respiratory syndrome coronavirus 2, COVID-19, coronary artery bypass grafting, vascular tissue, RNA detection, RT-PCR

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, has resulted in a serious global health problem by affecting not only the respiratory system but also multiple organ systems. Although the virus primarily targets the respiratory epithelium, studies in recent years have demonstrated that it can also directly or indirectly affect extrapulmonary tissues, primarily the cardiovascular system (1,2). Cardiovascular complications have emerged as a leading cause of COVID-19-related morbidity and mortality. Complications such as myocarditis, arrhythmias, acute coronary syndromes, and thromboembolic events frequently arise due to endothelial dysfunction, systemic inflammation, and cytokine storm (3). Studies reporting myocardial injury, elevated cardiac biomarkers, and vascular involvement even in patients with mild respiratory symptoms suggest a broader pathophysiological impact of the disease (4).

The cardiovascular system is susceptible to SARS-CoV-2 due to the expression of angiotensin-converting enzyme 2 (ACE2), the viral entry receptor. ACE2 is widely expressed on endothelial

cells, cardiomyocytes, and vascular smooth muscle cells. This facilitates viral entry into cells and can lead to tissue damage (5,6). Furthermore, it has been shown that viral invasion of endothelial cells causes destruction, thereby promoting a prothrombotic state and predisposing to microvascular dysfunction (7). Beyond acute infection, the long-term cardiovascular effects of COVID-19 have become an increasingly concerning issue.

Persistent myocardial inflammation and fibrosis have been reported in individuals who have recovered from the disease, raising concerns about underlying tissue damage and potential sequelae in the subsequent period (8). Autopsy studies revealing the presence of viral RNA in cardiac tissues post-recovery support the notion of persistent viral reservoirs in the long term (9). Surgical patient groups, particularly those undergoing cardiac operations such as coronary artery bypass grafting (CABG), are more vulnerable to COVID-19-related complications. The perioperative period is characterized by significant physiological stress, and prior infection may have adverse effects on endothelial function, inflammation, and postoperative recovery (10).

Consequently, intraoperatively harvested tissue samples provide a valuable opportunity to investigate the persistence of SARS-CoV-2 in cardiovascular structures, even months after the initial infection. While autopsy studies offer crucial insights into viral tropism, postmortem tissue changes may complicate the interpretation of viral presence. Therefore, intraoperative molecular analyses obtained from living patients enable the detection of residual viral RNA, offering important information regarding the long-term effects of COVID-19 and its potential implications for surgical outcomes (11). The aim of this study is to investigate the effects of SARS-CoV-2's continued interaction with cellular systems, even in the early postoperative period, on cardiac surgery and tissue healing.

MATERIAL AND METHODS

Participants

This study included a total of 235 patients who underwent surgical intervention for coronary artery disease at our hospital between February 2021 and April 2023 and had a documented history of COVID-19 infection. Patients for whom surgery was contraindicated or who had no prior history of COVID-19 infection were excluded from the study. Demographic data, comorbid systemic diseases, and intraoperatively collected tissue samples were thoroughly recorded for all participants (Table 1).

In this study, the presence of viral genomic material in tissue samples obtained from individuals previously diagnosed with COVID-19 or found to be infected with SARS-CoV-2 through molecular analysis was investigated using the polymerase chain reaction (PCR) method. The study was conducted on a voluntary basis, and postoperative complications were also documented. This is an observational study incorporating both retrospective and prospective design elements. The study was approved by the Ethics Committee of Namık Kemal University Faculty of Medicine (Approval No: E-150147, Date: 08.04.2022).

Sample Collection, Transport, and Storage

During surgery, tissue samples including aortic plaques, pleural tissue, pericardium, and auricular endothelium were collected from the 235 patients enrolled in the study. Tissue samples were placed in tubes containing an RNA stabilization solution. They were then incubated at 4–8°C for 8–12 hours and subsequently stored at −80°C until analysis. All specimens were transported to the Microbiology Laboratory under appropriate cold chain conditions immediately after collection.

mRNA Extraction and Real-Time Polymerase Chain Reaction (RT-PCR)

Sample Preparation and Preservation

Tissue samples were placed in tubes containing a fixative RNA stabilization reagent (Fix RNA, EURx®, Poland). The samples were incubated at 4–8°C for 8–12 hours and then stored at −80°C until analysis.

Viral RNA Extraction

To prepare for RT-PCR analysis, total viral RNA was extracted from the samples using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany), in accordance with the manufacturer's spin column protocol. Prior to extraction, a lysis process was applied to the samples to inactivate RNase enzymes. The resulting high-purity RNA was then eluted in a specially formulated RNase-free AVE buffer.

RT-PCR Analysis

Cycle threshold (Ct) values for SARS-CoV-2 RNA were assessed using the Altona RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Altona Diagnostics GmbH, Hamburg, Germany), which targets the E and S genes through specific probes. The reverse transcription step was carried out at 55°C for 20 minutes, followed by an initial denaturation at 95°C for 2 minutes. Amplification proceeded under thermal cycling conditions recommended by the manufacturer, consisting of 95°C for 15 seconds, 55°C for 45 seconds, and 72°C for 15 seconds per cycle. To account for the potential presence of low viral loads, the reaction was extended to a total of 50 cycles. Each RT-PCR run included both positive and negative controls. A sample was considered positive for SARS-CoV-2 if at least one of the target genes yielded a Ct value below 45.

Statistical Analysis

Descriptive statistics were used to summarize the data: categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean ± standard deviation, median, and range (minimum–maximum). The normality of the distribution of continuous variables was assessed using the Shapiro–Wilk test. Comparisons between patients with and without SARS-CoV-2 RNA positivity were performed using the Mann–Whitney U test for non-normally distributed continuous

variables. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

The mean age of the 235 patients included in the study was 65.4 ± 9.1 years; 172 patients (73.2%) were male, and 63 patients (26.8%) were female. The clinical characteristics and risk factors of the participants are presented in Table 1. According to these data, 158 patients (67.2%) had hypertension (HT), 110 (46.8%) had hyperlipidemia, 55 (23.4%) had chronic obstructive pulmonary disease (COPD), 74 (31.4%) had diabetes mellitus (DM), and 102 (43.4%) had peripheral arterial disease (PAD). The rate of smoking was 61.7% (n=145), and the mean body mass index (BMI) was calculated as 26.84 ± 4.07. During the operation, tissue samples were obtained intraoperatively from the aortic plaque, atrial appendage (auricle), pleura, and pericardium of each patient, preserved under appropriate conditions, and subsequently analyzed using RT-PCR.

Table 1. Demographic and clinical characteristics

Features	Mean ± SD / n (%)
Age (years)	65.4 ± 9.1
Sex (Male)	172 (73.2%)
Body Mass Index (kg/m²)	26.8 ± 4.1
Hypertension	158 (67.2%)
Hyperlipidemia	110 (46.8%)
Peripheral Arterial Disease (PAD)	102 (43.4%)
Chronic Obstructive Pulmonary Disease	55 (23.4%)
Diabetes Mellitus	74 (31.4%)
Smoking	145 (61.7%)
Time Since COVID-19 Infection (days)	198 ± 61
Preoperative PCR Positivity	6 (2.6%)

RT-PCR Results and Overall Distribution

RT-PCR analysis revealed the presence of SARS-CoV-2 RNA in 6 out of 235 patients, corresponding to a positivity rate of 2.6%, while the remaining 229 patients (97.4%) were found to be negative. The Ct values of the positive samples ranged from 34 to 40. These findings suggest that SARS-CoV-2 can still be detected in tissue specimens despite low viral loads (Table 2).

Table 2. SARS-CoV-2 RNA results

Result	Number (n=235)	Percentage (%)
Positive	6	2.6%
Negative	229	97.4%
Ct Range (Positive)	34-40	-
Number of Positive Genes	1 gene in 4 patients, 2 genes in 2 patients	-

The clinical characteristics, detected genes, and Ct values of the six SARS-CoV-2-positive cases are detailed in Table 3. Among these patients, only a single gene (either N or ORF1ab) was detected in four cases, while both genes were positive in two cases. Ct values ranged from 34.2 to 40.0. Of the positive cases, three were male and three were female, with a mean age of 66.7 ± 4.2 years.

Figure 1 Detected Genes and Ct Values in SARS-CoV-2 RNA Positive Patients.

The following bar chart illustrates the types of SARS-CoV-2 genes detected and their respective Ct values in the six patients who tested positive by RT-PCR. Patient numbers are presented on the horizontal axis, and Ct values are shown on the vertical axis. N gene and ORF1ab gene detections are color-coded. Cases with both genes detected are represented with grouped bars.

Table 3. Clinical characteristics and Ct values of SARS-CoV-2 positive cases

Patient No	Age	Sex	Comorbidities	Time Since COVID-19 Diagnosis (days)	Detected Gene(s)	Ct Value(s)
1	61	Male	HT, DM	150	N gene	36.5
2	68	Male	HT	180	N + ORF1ab	34.2 / 35
3	70	Female	DM	210	ORF1ab	38.1
4	63	Male	None	172	N gene	39.0
5	66	Male	HT, COPD	200	N + ORF1ab	34.8 / 36
6	72	Female	HT, DM	190	ORF1ab	40.0

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease

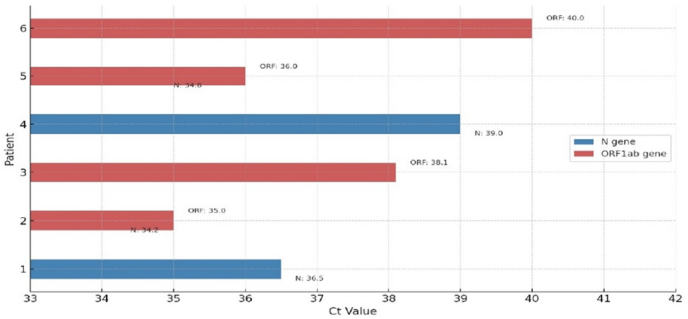

Figure 1. Detected Genes and Ct Values in SARS-CoV-2 RNA Positive Patients. The bar chart shows the cycle threshold (Ct) values of N and ORF1ab genes detected in SARS-CoV-2 RNA positive tissue samples collected intraoperatively from six patients undergoing coronary bypass surgery

Statistical Comparisons

No statistically significant differences were observed between the SARS-CoV-2 positive and negative groups with respect to age, sex, hypertension, diabetes mellitus, or smoking history ($p > 0.05$). The average time elapsed since a prior COVID-19 diagnosis was 183 ± 24 days in the positive group and 198 ± 61 days in the negative group, a difference that did not reach statistical significance ($p=0.51$). A detailed summary of the comparative findings is presented in Table 4.

PCR Procedure and Quality Control

The RT-PCR protocol used in this study is presented in Table 5. For each run, both positive and negative control samples were included. Technical adequacy of the assays was ensured by verifying signal detection in the internal control (HEX) channels, thereby confirming the reliability of the PCR processes.

Sample placement on the RT-PCR test plate is illustrated in Table 6. Among these samples, those with positive SARS-CoV-2 detection are indicated with bolded Cq values. SARS-CoV-2 RNA was detected in three aortic, two pleural, and one atrial appendage (auricular) tissue samples. In the RT-PCR analysis, a Ct value < 45 was considered positive, and based on this criterion, these six tissue samples were recorded as positive cases.

Figure 2 Distribution of Positive SARS-CoV-2 RT-PCR Cq Values by Sample and Tissue Type.

Table 4. Comparison of patients with and without SARS-CoV-2 RNA positivity by RT-PCR

Features	Positive (n=6)	Negative (n=229)	p-value
Age (mean±SD)	66.7 ± 4.2	65.3 ± 9.3	0.72
Male sex (%)	4 (66.7%)	168 (73.4%)	0.70
Hypertension (%)	5 (83.3%)	153 (66.8%)	0.39
Diabetes Mellitus (%)	4 (66.7%)	108 (47.2%)	0.42
Smoking History (%)	3 (50.0%)	92 (40.2%)	0.68
Time since COVID-19 diagnosis (days, mean±SD)	183 ± 24	198 ± 61	0.51

Table 5. RT-PCR protocol used in the study

Reagent / Component	Volume (µl)	Step	Cycle	Temperature (°C)	Time
2x Prime Script Mix	10	Reverse Transcription	1	55	20 minutes
		Denaturation	1	95	2 minutes
		Amplification (Cycle Start)	50	95	15 seconds
				55	45 seconds
				72	15 seconds
CVD Di Oligo Mix	5	—	—	—	—
Nucleic Acid (RNA)	5	—	—	—	—
Total Reaction Volume	20 µl	Detect (Read)	—	—	ORF1ab+N (FAM-Green) / RNase P (HEX-Yellow)

Table 6. SARS-CoV-2 Test sample layout (Content – Sample – Cq)

Sample	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10
Content	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium
Cq	N/A	N/A	**36.5**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sample	E13	E14	E15	E16	E17	E18	E19	E20	A1	A2
Content	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Endotelium	Aorta	Aorta
Cq	**34.2**	N/A	N/A	N/A	N/A	N/A	**38.1**	N/A	**39.0**	N/A
Sample	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14
Content	Aorta	Aorta	Aorta	Aorta	Aorta	Aorta	Aorta	Aorta	Aorta	Aorta
Cq	N/A	**34.8**	N/A	N/A	**40.0**	N/A	N/A	N/A	N/A	N/A
Sample	A17	A18	A19	A20	A21	N1	N2	P1	P2	1
Content	Aorta	Aorta	Aorta	Aorta	Aorta	Neg Ctrl	Neg Ctrl	Pos Ctrl	Pos Ctrl	NTC
Cq	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**22.66**	**23.15**	N/A

Sample: Internal laboratory code for the specimen, Content: Tissue type (e.g., Aorta, Pleura, Auricle, Pericardium), Cq (or Ct): Quantification cycle, Bold values indicate Cq < 45, N/A: Not Applicable, NTC: No Template Control

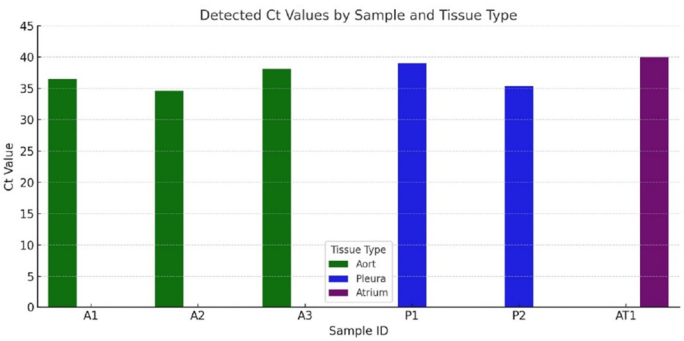

Figure 2. Distribution of Cq values of tissue samples found positive for SARS-CoV-2 RNA by RT-PCR

DISCUSSION

This pioneering study investigates the presence of SARS-CoV-2 RNA in intraoperatively collected peripheral vascular and adjacent tissue samples from patients with a prior COVID-19 diagnosis undergoing CABG. RT-PCR analyses of 235 patients revealed SARS-CoV-2 RNA in 6 cases (2.6%). The detection of viral RNA in vascular and perivascular structures including the aorta (n=3), pleura (n=2), and atrium (n=1) suggests that the virus may persist not only within the pulmonary or systemic circulation, but also directly within the vascular wall and neighboring tissues. Ct values ranged between 34 and 40, indicating low-level viral RNA. Despite the absence of active infection symptoms, the identification of SARS-CoV-2 RNA months after initial diagnosis implies potential tissue-level persistence (12,13). Previous studies have demonstrated that SARS-CoV-2 can be detected in various extrapulmonary tissues, including vascular, cardiac, and pleural tissues (14). Autopsy findings frequently identify viral RNA in endothelial and myocardial tissues, supporting the view that the cardiovascular system is a direct target for viral involvement (15). However, intraoperative sampling from living patients as performed in our study provides an opportunity to investigate viral persistence unaffected by postmortem tissue alterations (16). The detection of viral RNA in the aorta and atrium aligns with studies demonstrating the expression of ACE2 and TMPRSS2 receptors in vascular and myocardial tissues, which facilitate viral cell entry (17). Additionally, SARS-CoV-2 has been reported to cause endotheliitis, thrombosis, and vascular inflammation, effects that may persist even after systemic infection resolution (18). In our study, the positive pleural samples are consistent with imaging studies and autopsy reports revealing pleural thickening, effusions, and localized inflammation (19). Some studies report SARS-CoV-2 RNA persistence for weeks or months after symptom resolution, particularly in regions with reduced vascularity (20). Although the detected RNA may not indicate active viral replication, it could trigger immune responses, fibrosis, or endothelial dysfunction (21,22). Our findings support this evidence and suggest that low-level RNA persistence in cardiovascular tissues may influence long-term recovery trajectories or postoperative outcomes. A critical observation in our cohort is that all six RNA-positive patients had a confirmed history of COVID-19 at least three months prior to surgery. This finding corroborates studies showing delayed viral RNA clearance in extrapulmonary tissues (23,24). While the clinical implications of such persistence remain unclear, some research proposes that residual viral antigens may be associated with post-acute sequelae of COVID-19 (PASC), particularly cardiovascular and pulmonary manifestations (25,26). The

low viral load (Ct 34–40) in our study aligns with findings in convalescent individuals, indicating that these RNA signals likely represent non-infectious remnants. Nevertheless, the presence of these remnants in critical cardiovascular structures like the aorta and atrium raises significant questions regarding potential effects on vascular healing, endothelial damage, or bypass graft patency (27).

Study Limitations

SARS-CoV-2 RNA detection relied solely on RT-PCR without sequencing or immunohistochemical validation. Despite these limitations, our findings contribute to the growing body of evidence advocating for long-term tissue monitoring of post-COVID-19 pathological changes, particularly in surgical cohorts.

CONCLUSION

The central premise of our study emphasizes that assessing SARS-CoV-2 interactions with the vascular system necessitates extending the focus beyond the symptomatic acute phase to a broader subclinical timeframe. We demonstrate persistent SARS-CoV-2 RNA detection in cardiovascular and thoracic tissues long after systemic infection resolution. These findings hold potential significance for cardiac surgical planning, tissue healing dynamics, and understanding long-term post-COVID complications. Consequently, this study confirms the presence of SARS-CoV-2 genetic material in peripheral vascular and perivascular tissues, illuminating the virus's impact on the systemic vascular bed. Further large-scale investigations are warranted to clarify the clinical implications of these findings and advance our understanding of their influence on long-term cardiovascular outcomes.

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Ethics Committee Approval: This study was approved by the Ethics Committee of Namık Kemal University Faculty of Medicine (Approval No: E-150147, Date: 08.04.2022).

Informed Consent: Informed consent was waived by the ethics committee due to the nature of the study.

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