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COVID-19 Cardiac Manifestations and Scent Perception Genes in Hearts of SARS-Cov-2 Infected Patients: A Meta-Analysis of Gene Expression Data

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Abstract

Background: COVID-19 induced cardiac events are reported by many papers, while psychophysiology of association of the COVID-19 and cardiac attacks are not fully understood yet. **Materials and Methods:** Here, we compared gene expression levels of heart autopsies of SARS-Cov-2 infected patients with the cardiac organoid model of human myocardial infarction and controlled healthy cardiac organoids to identify differentially expressed genes (DEGs). Gene Ontology (GO) biological processes were enriched in DEGs. **Results:** Results showed that smell perception genes were down-regulated in SARS-COV2 compared to myocardial infarction samples; while showing upregulated genes related to the immune system process in contrast to control healthy heart organoids. Our results agree with theories of immune system reactions in COVID-19 infected patients' hearts, while our analysis indicates different patterns of heart gene expression from myocardial infarction models. **Conclusion:** our study suggests that there may be other pathways involved in MI appearance in COVID-19 patients rather than classic is known atherosclerotic and inflammatory pathways. **[GMJ.2021;10:e2250]**

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Keywords: COVID-19; SARS-Cov-2; Myocardial Infarction; Cardiac; Heart

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Introduction

The prevalence of cardiovascular (CVD) events in COVID-19 patients is unknown, but pre-existing cardiovascular disease is linked with more severe infection with COVID-19 [1,2]. Systemic severe inflammation raises the risk of disruption of atherosclerotic plaque and acute myocardial infarction [3,4], which could explain the link between the COVID-19 and cardiac events. The mechanism of acute myocardial damage triggered by SARS-CoV-2 infection could be linked to ACE2. ACE2 is commonly distributed not only in the lungs but also in the cardiovascular system, so ACE2-related signaling mechanisms can, therefore, have a potential role in cardiac injury [4,5]. Thus, COVID-19 may be considered severe systemic inflammation and contribute to acute myocardial infarction or other CVD events.

So, evaluate the genetic pathways that are getting altered after SARS-COV2 infection. This issue is required to understand the cardio-pathogenic role of the SARS-COV2 fully. This type of data would help us identify potential medication that could help to prevent CVD events after COVID-19. So, we aimed at comparing a genomic model of SARS-COV2 infected heart with normal and myocardial infarction experiencing heart.

Materials and Methods

We conducted a meta-analysis of Gene Expression Omnibus (GEO) data on COVID-19 patients' hearts. Through a search in GEO, datasets of COVID-19 patients were quarried with COVID-19, Sars-Cov-2, new Coronavirus keywords. GEO databases were selected from 25 available sources. Inclusion criteria were the evaluation of gene expression in COVID-19 patients' hearts. Control datasets were quarried based on similarity to selected COVID-19 datasets.

Read data for autopsy heart samples of patients who died from SARS-Cov2 infection was returned from the GSE150316 dataset. Cardiac datasets of GSM4546580, GSM4546585, GSM4546587 identifiers were retrieved. Dataset of the cardiac organoid model of healthy and infarcted human myocardium was used as control (GSE113871). While most similar control datasets were in heart organoids, it may have some bias on the study's results as organoids may have different gene expression statuses with real samples; unfortunately, these organoid datasets were the most matching datasets to GSE150316. The differential expression analysis for each transcript was determined using the DESeq / EdgeR [6] method as part of the iDEP R-Shiny program. iDEP is an R programming language software application developed to manipulate genetic data. Principal analysis indicated that the differences between replicates were very limited in SARS-CoV2 vs. MI samples and fairly reasonable in SARS-CoV2 vs. Control samples, demonstrating the suitable overall composition of the examined dataset.

There was a significant disparity between the SARS-CoV2 and the MI samples, starting with the first prominent factor, which describes 96 percent of the variance and the main variable, explaining 74 percent of the variance between the SARS-CoV2 and the control samples.

Results

Using the DESeq2 package, with a threshold of false discovery rate (FDR) <0.1 and fold-change >2, 7703 upregulated and 7259 down-regulated genes were identified in SARS-COV2 vs. MI comparison and 6328 upregulated and 4942 down-regulated genes in SARS-COV2 vs. control comparison. The scatter plot shows that SARS-COV2 leads to a massive transcriptomic response in the heart. The Venn diagram shows that 4875 DEGs were used as the commonality between the 3 datasets (Figure-1).

Sets of upregulated or downregulated genes were then exposed to an enrichment analysis based on the hypergeometric distribution. Some of the various genes mentioned in Table-1 can be used to evaluate specific hypotheses.

In SARS-COV2 vs. MI contrast, up-regulated genes are related to the metabolic cycle, and down-regulated genes are linked to Sensory perception of scent, Identification of chemical stimuli involved in sensory perception of

Table 1. Enriched GO Terms in Up and Down-Regulated Genes

Direction	SARS-COV2 vs. control			SARS-COV2 vs. MI		
	P	Number	Pathways	P	Number	Pathways
Up-regulated	1.96E-49	697	Small molecule metabolic process	5.37E-20	157	Organic acid transport
	2.38E-38	376	Oxidation-reduction process	1.25E-19	204	Organic anion transport
	7.48E-38	438	Carbohydrate derivative metabolic process	2.18E-19	543	Transmembrane transport
	6.73E-36	153	Energy derivation by oxidation of organic compounds	1.15E-13	193	Detection of chemical stimulus involved in sensory perception of smell
	9.36E-33	406	Oxoacid metabolic process	2.54E-15	77	Organic acid transmembrane transport
	9.36E-33	116	Cellular respiration	2.05E-13	394	Organophosphate metabolic process
	3.65E-32	409	Organic acid metabolic process	1.13E-14	387	Ion transmembrane transport
	4.04E-32	220	Generation of precursor metabolites and energy	1.51E-14	205	Sensory perception of smell
	4.91E-32	233	Ribonucleotide metabolic process	3.53E-13	53	Amino acid transmembrane transport
	1.24E-31	278	Nucleoside phosphate metabolic process	2.05E-13	388	Cation transport
Down-regulation	4.02E-87	1085	Immune system process	4.86E-96	1188	Regulation of gene expression
	2.51E-71	581	Cell activation	1.49E-91	1099	Regulation of nucleobase-containing compound metabolic process
	5.95E-69	821	Immune response	2.75E-85	1072	Regulation of macromolecule biosynthetic process
	3.87E-66	524	Leukocyte activation	2.75E-85	1026	Regulation of RNA metabolic process
	1.47E-51	611	Regulation of immune system process	1.18E-84	1045	Regulation of cellular macromolecule biosynthetic process
	4.91E-48	637	Defense response	1.66E-83	1112	Regulation of biosynthetic process
	1.19E-47	314	Lymphocyte activation	7.55E-82	1094	Regulation of cellular biosynthetic process
	1.19E-45	470	Immune effector process	2.30E-78	991	Nucleic acid-templated transcription
	3.04E-43	327	Inflammatory response	2.49E-78	995	RNA biosynthetic process
	2.66E-42	499	Biological adhesion	6.69E-77	979	Transcription, DNA-templated
	5.07E-42	731	Response to external stimulus	1.95E-76	789	Transcription by RNA polymerase II
	6.81E-42	496	Cell adhesion	7.28E-75	949	Regulation of nucleic acid-templated transcription
	2.73E-41	436	Positive regulation of immune system process	1.01E-74	951	Regulation of RNA biosynthetic process
	9.16E-38	873	Cell surface receptor signaling pathway	3.08E-73	1080	Nucleobase-containing compound biosynthetic process
	6.00E-37	363	Response to other organisms	3.10E-73	1092	Heterocycle biosynthetic process

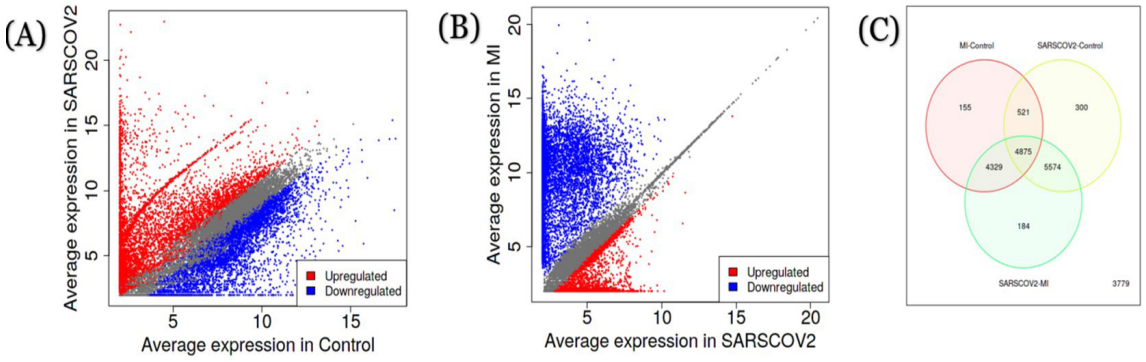

Figure 1. Summary plots for differentially expressed genes analysis. (**A**) Scatter plot of SARS-COV-2 infected patients' DEGs vs. control hearts. (**B**) scatter plot of SARS-COV-2 infected patients' DEGs vs. myocardial infarction heart models. (**C**) Venn diagram.

scent, Organic acid, and movement of ions. In SARS-COV2 vs. control comparison, up-regulated genes were linked with the immune system mechanism and reaction to certain species, and down-regulated genes were related to the metabolic process. In comparing the 20 DEGs listed in Table-1 between the 3 groups, in the case of SARS-COV2 vs. control DEGs, there was a noticeable higher rate of variety between groups compared to SARS-COV2 vs. MI DEGs that could help to synthesis various hypothesizes (Figure-2).

Discussion

Our results indicated the possible role of the smell perception genes and immune system process sets of genes in the pathophysiology of SARS-COV2 in the heart. Still, interpreting these results gets hard as this is a simulation study. But this study provides multiple hypothesizes to be tested in real-world studies; until now, the only available real-world findings show that cardiac complications in COVID-19 patients are possible, and it seems that cardiac events are not rare [7,8].

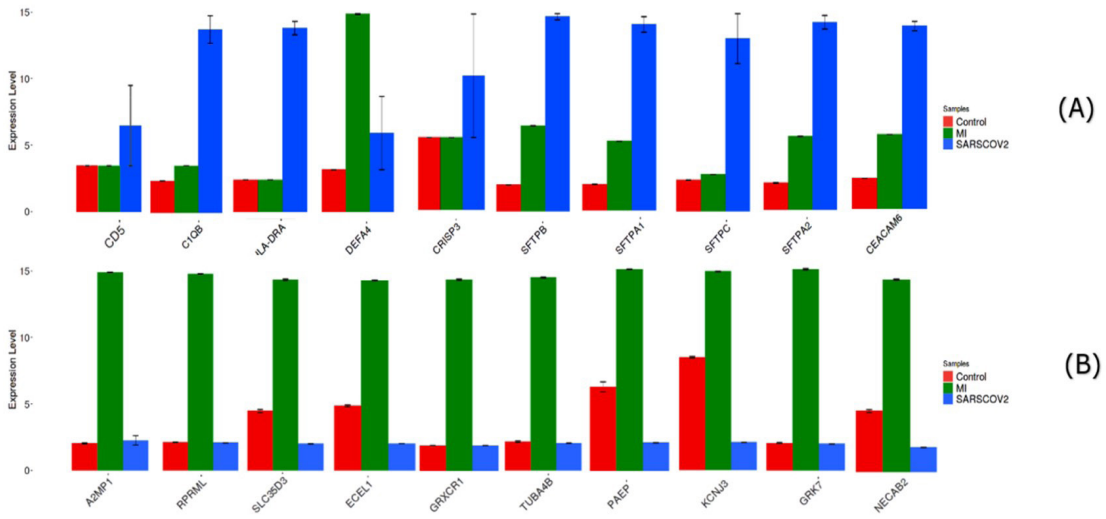

Figure 2. (**A**) SARS-COV2 vs. control top DEGs. (**B**) SARS-COV2 vs. MI top DEGs.

In a report, among 138 patients admitted with COVID-19, 16.7% had arrhythmias, and 7.2% had acute heart attacks [7].

There was a higher risk of increased Troponin I in severe COVID-19 patients [7]. Imazio *et al*. stated in their study that cardiac troponin levels are significantly higher in patients with more severe infections, patients admitted to intensive care units, or those who have died [8].

While the exact pathophysiological process underlying the myocardial injury triggered by COVID-19 is not well known, a previous study indicated that 35 percent of patients with severe acute coronavirus syndrome (SARS-CoV) infection or SARS disease, the SARS-CoV genome was positively identified in the heart [9].

But the study providing the GSE150316 dataset based on the autopsies of COVID-19 patients stated that isolated hearts were negative for detectable SARS-CoV-2 by RNA-ISH [10].

Previous studies about SARS and MERS show the possibility of direct virus disruption to cardiomyocytes [9]. At the same time, there has been no report of the presence of SARS-COV-2 in the heart till now. But, SARS-CoV-2 may share the exact mechanism with SARS-COV. The two viruses are closely homologous in the genome [11], and the direct effect could not be fully rolled out as our study also revealed upregulated pathways of response to other organisms in the heart. Our study showed downregulation of sensory perception of smell in COVID-19 affected the heart.

This is consistent with evidence showing the presence of Odor smell genes in the heart. A study by Drutel *et al*. showed that the Rat OL1 gene was expressed in the nose and the heart. This unusual cardiac activity was developmentally controlled, being maximum at the early postnatal level but barely observable at the adult stage. This transient cardiac expression indicates the role of smell sensory genes in cardiac morphogenesis and cardiac cell development [12].

Olfactory and gustatory dysfunctions are seen in patients with COVID-19 [13], and findings on smell perception genes show possible interactions of COVID-19 with olfactory genes that may contribute to altered immune system activities. A correlational study showed that variation in the genotype of smell or taste perception genes might be associated with different susceptibility to severe COVID-19 [14].

In our research, Surfactant Protein (SFTP) C and B genes were upregulated in COVID-19 affected heart. In contrast, a study by Islam *et al.* [15] SFTPC genes was downregulated, whereas SFTPB was upregulated in our study. These genes are responsible for the alveolar surface tension in the lung [16]; the relationship of the Surfactant Proteins is widely evaluated in heart failure patients as a diagnostic factor [17], but its association with the SARS-COV2 effect on the heart remains unclear. But an exciting hypothesis might come to mind as researchers have attributed alveolar membrane damage in heart failure to be associated with the alternation in serum levels of surfactant-derived proteins [18].

There might be a cardiopulmonary association between the COVID-19 affected heart and lung. Also, our study showed upregulated CRISP3 gene following SARS-COV2 infection. Some researchers have worked on the CRISP system's role in the Diagnostics and Therapeutics of COVID-19 [19], but the definitive relationship is still unclear due to limited studies.

The C1QB gene was upregulated in COVID-19 in Daamen *et al*.'s study [20], like our investigation, while it was downregulated in Shaath *et al*.'s study [21]. But there are many differences among these mentioned studies making this comparison unreliable. Other significant genes of our study were not reported in the literature to be associated with COVID-19.

Conclusion

It seems that systemic inflammatory response seen as a cytokine storm is a possible source of late-scale myocardial damage, typically correlated with acute respiratory distress syndrome, multi-organ failure, and mortality in COVID-19.

Our results are consistent with hypotheses

of immune system reactions in the heart of COVID-19 infected patients, so our analysis shows different patterns of expression of heart genes from models of myocardial infarction, suggesting possible immunopathological rather than atherosclerotic pathways.Further studies are needed to indicate the pathophysiology of cardiac attacks of COVID-19 patients.

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Conflict of Interest

There are no conflicts of interest in this study.

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